

The effect of inspiratory muscle training on clinical outcomes and health-related quality of life in children with neuromuscular disease and respiratory muscle weakness.



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DECLARATION

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Anri Human (HMNANR001)

Date

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"No country can claim to have achieved universal healthcare if it has not adequately and equitably met the needs of those with rare diseases"

Rare Diseases SA.

Last, but not least, I would like to thank the ultimate source of Breath and Life, for the privilege to be part of a greater plan:

"As long as there's breath in me, Lord there will always be, one more song for You"

Casting Crowns



My red balloon family

My muscles are aching
And I don't really know why
At school, I can't keep up
During playtime, everyone passes me by...

Getting up from the floor, a challenge for me
Gower's sign the doctor says
What will that be?
I get so tired and have to catch my breath...

My mom says I'm a hero
Because I never give up and always get by
Forget about Superman and all the rest!
But, I surely don't feel like one...
Wish I can put my cape on and fly!

One day, very soon
I want to be there to hear it too
A cure for my lack of dystrophin
And hope for the future
Please join me, won't you?
A red balloon, especially for me,
to raise awareness about Duchenne muscular dystrophy
If all of us can work together as a family
We can improve our lives...
and create a beautiful tapestry
of hearts weaved together

with one goal in mind
To make a breakthrough
and a cure to find!

So next time when you see a red balloon,
Don't just pass it by
Spare a thought for each one of us
who bravely stand up and face this giant every day...

But for now, I will dream of running
kicking a ball and play...
Tomorrow again
I will fight once more-
Because I *am* going to do life *my* way!

08/09/2018

Anri Human

ABSTRACT

Background: Progressive respiratory muscle weakness and ineffective cough contributes to pulmonary morbidity and mortality in children with neuromuscular disease. Inspiratory muscle training aims to preserve or improve respiratory muscle strength, reduce respiratory complications and improve health-related quality of life. **Objectives:** To describe South African physiotherapists' knowledge and respiratory management strategies and determine the safety, viability, acceptability and efficacy of inspiratory muscle training for children 5-18 years with neuromuscular disease. **Methods:** Four studies were conducted: i) a quantitative descriptive survey; ii) a systematic review using Cochrane methodology; iii) a prospective, pre-experimental observational study and iv) a prospective, cross-over randomised controlled trial using a standardised 12-week inspiratory muscle training intervention. **Results:** i) South African physiotherapists (n=64) reported being aware of international clinical practice recommendations, however they favoured manual airway clearance techniques. The use of inspiratory muscle training in chronic management was well supported by South African physiotherapists. ii) Results of the systematic review (seven included studies; n=168) suggested that inspiratory muscle training may be effective in improving inspiratory muscle strength. There was insufficient evidence for an effect on patient morbidity or health-related quality of life. iii) The pre-experimental, pilot study (n=8) suggested that a six-week inspiratory muscle training programme was safe, viable, acceptable and associated with a significant increase in inspiratory muscle strength. iv) The cross-over randomised controlled trial (n=23) did not show evidence of a difference in the primary outcome measures (number of hospitalisations and respiratory tract infections) between intervention and control periods. There were no adverse events related to inspiratory muscle training. Inspiratory muscle strength (Pimax) and peak expiratory cough flow increased by 14.57 (± 15.67)cmH₂O and 32.27 (± 36.60)L/min respectively during the intervention period compared to a change of 3.04 (± 11.93)cmH₂O (p=0.01) and -16.59 (± 48.29)L/min (p=0.0005) during the control period. There was no evidence of change in spirometry, functional ability or total health-related quality of life scores following the intervention. Overall participant satisfaction with inspiratory muscle training was high and adherence was good. **Conclusions:** Inspiratory muscle training in children with neuromuscular disease is well tolerated, appears to be safe and is associated with significant improvements in inspiratory muscle strength and cough efficacy.

Keywords: Inspiratory muscle training, neuromuscular disease, children, respiratory muscle weakness, health-related quality of life.

TABLE OF CONTENTS

DECLARATION	ii
ACKNOWLEDGEMENTS.....	iii
ABSTRACT	vi
TABLE OF CONTENTS	vii
LIST OF FIGURES	xv
RESEARCH OUTPUTS OF THIS THESIS AT THE TIME OF SUBMISSION	xx
ABBREVIATIONS	xxi
OPERATIONAL DEFINITIONS	xxvi
Chapter 1: LET ME INTRODUCE YOU TO NEUROMUSCULAR DISEASES	1
Overview, pulmonary pathophysiology, problem statement, purpose and significance of the study	1
1.1 Background and introduction	1
1.1.1 Neuromuscular disease healthcare management in South Africa	2
1.1.2 Pulmonary pathophysiology and clinical implications in neuromuscular diseases..	4
1.1.3 The importance of the cough mechanism in neuromuscular diseases	5
1.1.4 Management strategies in neuromuscular diseases	9
1.2 Problem statements	19
1.3 Purpose and objectives of the study	20
1.3.1 Aims and objectives.....	20
1.4 Significance of the study	23
1.5 Outline of the thesis	24
1.6 Conclusion.....	26
Chapter 2: WHAT DO THE PHYSIOTHERAPISTS HAVE TO SAY?.....	27
A South African survey about acute and chronic respiratory management of children with neuromuscular disease.....	27
2.1 Background and introduction	27
2.2 The role of physiotherapy in patients with neuromuscular disease within the South African healthcare context	28
2.3 Aims and objectives of the survey.....	30
2.4 Significance of the study	30
2.5 Methodology.....	31
2.5.1 Research design.....	31

2.5.2 Sample and participants	31
2.5.3 Development of questionnaire and input from an expert panel	32
2.5.4 Procedure.....	36
2.5.5 Pilot study	37
2.5.6 Ethical considerations and permissions obtained.....	40
2.5.7 Data collection	41
2.5.8 Data analysis	41
2.6 Results	42
2.6.1 Survey response rate	42
2.6.2 Section A: Vocational background of participants	43
2.6.3 Section A: Years of experience of participants	44
2.6.4 Section B: Acute care of patients with neuromuscular disease.....	44
2.6.5 Section C: Chronic care of patients with neuromuscular disease	51
2.6.6 Section D: South African management of patients with neuromuscular disease..	57
2.6.7 Associations between variables	60
2.7 Discussion	63
2.7.1 Respondent background: A South African context	63
2.7.2 Response rate.....	64
2.7.3 Vocational background and years of experience	65
2.7.4 General respiratory management, mechanical ventilation and support during acute and chronic management	66
2.7.5 Secretion mobilisation techniques (peripheral ACT) for acute and chronic management	71
2.7.6 Cough augmentation techniques (proximal ACT) for acute and chronic management	75
2.7.7 Respiratory muscle training in chronic management.....	82
2.7.8 Limitations of the South African standard of care survey	83
2.7.9 Recommendations for clinical practice	84
2.7.10 Recommendations for future research	85
2.8 Conclusion.....	87
Chapter 3: WHAT DOES THE LITERATURE SAY?.....	88
Inspiratory muscle training for paediatric and adolescent patients with neuromuscular disease: a systematic review.....	88
3.1 Background and introduction	88

3.2 Description of how inspiratory muscle training might work	88
3.3 Rationale and significance of the study	89
3.4 Objectives	90
3.5 Methods.....	90
3.5.1 Criteria for considering studies for this review.....	91
3.5.2 Search methods for identification of studies.....	93
3.5.3 Data collection and analysis.....	94
3.6 Results	97
3.6.1 Description of studies and search results	97
3.6.2 Included studies	100
3.6.3 Participants	100
3.6.4 Inspiratory muscle training interventions (training programmes).....	105
3.6.5 Risk of bias	110
3.6.6 Effects of interventions.....	113
3.6.7 Meta-analysis (effect size)	118
3.6.8 Other reported outcome measures	119
3.7 Discussion	120
3.7.1 Summary of main results	120
3.7.2 Applicability of evidence.....	121
3.7.3 Respiratory morbidity and adverse events.....	125
3.7.4 Methodological quality and bias of included studies.....	125
3.7.5 Possible learning/training effect	126
3.7.6 Alternative measures of inspiratory muscle strength	127
3.8 Clinical implications, recommendation and limitations of the study	128
3.9 Conclusion.....	130
Chapter 4: HOW TO TRAIN YOUR DIAPHRAGM	131
The methods, outcome measures, inspiratory muscle training protocol and ethical considerations	131
4.1 Introduction	131
4.2 Overview of methodology	131
4.2.1 Research settings and population	131
4.2.2 Study designs	133
4.2.3 Eligibility criteria.....	133
4.2.4 Sample size.....	135

4.2.5 Recruitment procedure	136
4.3 Outcome measures	137
4.3.1 Introduction	137
4.3.2 Anthropometric measures.....	142
4.3.3 Pulmonary function	144
4.3.4 Functional ability (level of ambulation and upper limb function).....	153
4.3.5 Health-related quality of life (PedsQL)	158
4.3.6 OMNI scale.....	161
4.4 Study process and procedures	162
4.4.1 Randomisation for pre-experimental study.....	162
4.4.2 Randomisation for cross-over RCT	163
4.4.3 Inspiratory muscle training protocol	163
4.4.4 Data collection procedure for pre-experimental and cross-over randomised controlled trial	168
4.4.5 Data analysis	169
4.5 Ethical considerations.....	170
4.5.1 Autonomy	170
4.5.2 Beneficence.....	171
4.5.3 Justice	174
4.5.4 Ethical clearance and permissions obtained for data collection.....	175
4.6 Funding	176
4.7 Conclusion.....	176
Chapter 5: TESTING, TESTING 1,2,3...	177
Pre-test post-test IMT pre-experimental, pilot study	177
5.1 Introduction	177
5.2 Study design.....	177
5.3 Methods.....	178
5.4 Adverse events related to inspiratory muscle training	178
5.5 Pulmonary function	178
5.6 Functional ability (level of ambulation and upper limb function).....	179
5.7 Health-related quality of life	179
5.8 Inspiratory muscle training programme and participant adherence	179
5.9 Analysis	179
5.10 Results.....	180

5.10.1 Bio-demographic description of participants.....	180
5.10.2 Home programme of participants.....	182
5.10.3 Adverse events, hospitalisations, respiratory tract infections and precautionary measures	182
5.10.4 Pulmonary function	183
5.10.5 Functional ability, level of ambulation and upper limb function	187
5.10.6 Health-related quality of life	189
5.10.7 Inspiratory muscle training adherence, intensity, power and volume.....	191
5.10.8 Feedback from participants and physiotherapists	196
5.11 Discussion.....	198
5.11.1 Bio-demographic description of participants.....	198
5.11.2 Adverse events and precautionary measures.....	199
5.11.3 Pulmonary function	200
5.11.4 Functional ability (level of ambulation and upper limb function).....	206
5.11.5 Health-related quality of life	208
5.11.6 Participant adherence and satisfaction	210
5.12 Limitations of study and recommendations for future research	210
5.12.1 Limitations	210
5.12.2 Recommendations for future research	211
5.12.3 Lessons learned from the pre-experimental, pilot study	212
5.13 Conclusion.....	213
Chapter 6: LET’S TRAIN: TAKE A DEEP BREATH!	214
Inspiratory muscle training cross-over randomised controlled trial.....	214
6.1 Introduction	214
6.2 Sample size.....	214
6.3 Eligibility criteria	214
6.4 Recruitment, allocation and follow-up.....	215
6.5 Data analysis	217
6.6 Results	218
6.6.1 Bio-demographic description of participants	218
6.6.2 Adverse events, hospitalisations, respiratory tract infections, change in medications and safety measures	225
6.6.3 Pulmonary function	229
6.6.4 Functional ability (level of ambulation and upper limb function).....	239

6.6.5	Associations/correlations	240
6.6.6	Health-related quality of life (PedsQL)	240
6.6.7	Home programme of participants.....	242
6.6.8	Adherence with the inspiratory muscle training programme and feedback from participants and parents/caregivers and physiotherapists	243
6.7	Discussion	247
6.7.1	Participant characteristics	247
6.7.2	Adverse events, hospitalisations and respiratory tract infections and safety measures	250
6.7.3	Pulmonary function	252
6.7.4	Change in functional ability (level of ambulation and upper limb function) and health related quality of life and participant adherence and satisfaction.	258
6.8	Limitations of the cross-over RCT.....	261
6.9	Recommendations for clinical practice based on the cross-over RCT results	263
6.10	Recommendations for research based on the cross-over RCT results.....	264
6.11	Conclusion.....	265
Chapter 7:	MAKE EVERY BREATH COUNT!	266
	Discussion, recommendations, limitations of the study and conclusions.....	266
7.1	Introduction	266
7.2	Respiratory management strategies including the use of IMT for children with NMD: What did South African physiotherapists have to say?	266
7.3	The use of inspiratory muscle training in children with neuromuscular disease: What does the literature say?	268
7.4	Inspiratory muscle training in children with neuromuscular disease: To train or not to train?	268
7.4.1	Adverse events, hospitalisations and respiratory tract infections	269
7.4.2	Pulmonary function: lung volumes and flow	269
7.4.3	Pulmonary function: inspiratory muscle strength.....	270
7.4.4	Pulmonary function: cough ability	271
7.4.5	Functional ability, health-related quality of life (PedsQL), perceived exertion (OMNI), participant adherence and participant/parent/caregiver/clinician feedback	272
7.5	Recommendations for clinical practice in children with neuromuscular disease	273
7.5.1	Implementation of cost-effective and safe respiratory management strategies such as inspiratory muscle training and cough augmentation	273

7.5.2 Evidence-based practice and education for improved respiratory management for children in South Africa	275
7.6 Recommendations for future research	276
7.6.1 Pulmonary function	276
7.6.2 Functional ability, health-related quality of life and addressing the needs of patients and their families	278
7.7 Strengths of the study	279
7.8 Limitations	280
7.9 Conclusion.....	281
REFERENCES	282
APPENDICES	308
Appendix Ai: Information letter and informed consent for validation of standard of care questionnaire.....	308
Appendix Aii: Physiotherapy experts in the field of Respiratory physiotherapy to provide input in standard of care questionnaire.....	311
Appendix Aiii: South African physiotherapy survey: feedback provided by expert panel and pilot study participants.....	313
Appendix Aiv: Letter of confirmation of questionnaire to expert panel	323
Appendix Av: Standard of care questionnaire	325
Appendix Avi: Information letter and informed consent for pilot study	336
Appendix Avii: Pilot study participants and feedback on South African survey on standard of care	339
Appendix Aviii: Survey Monkey opening statement and consent	341
Standard of Care Questionnaire: Chest physiotherapy practice (ACT) in paediatric and adolescent patients with neuromuscular disease.	341
Appendix Aix: Response rate on Survey Monkey	344
Appendix Ax: Additional responses/data from survey participants (standard of care): Section A-D	345
Appendix Axi: International clinical practice guidelines and publications on respiratory management of children with neuromuscular disease or respiratory muscle weakness	371
Appendix Bi: Search strategies (in alphabetical order)	372
Appendix Bii: Data extraction form.....	403
Appendix Biii: Excluded studies	409

Appendix Ci: Types of neuromuscular disease included in the study and confirmation of diagnosis	411
Appendix Cii: Research personnel and colleagues involved in the inspiratory muscle training study	412
Appendix Ciii: Information leaflets to be distributed at the NMD clinics.....	413
(IMT cross-over study).....	413
Appendix Civ: Inspiratory muscle training data collection sheet.....	415
Appendix Cv: PedsQL (self/child-reported)	423
Appendix Cvi: PedsQL (proxy/parent report)	426
Appendix Cvii: Information leaflet and informed consent for parent(s)/caregiver(s)/legal guardians	429
Appendix Cviii: Information leaflet for patients and assent form (11-17 years)	440
Appendix Cix: Information leaflet for patients and assent form (Intervention II) (7-10 years)	448
Appendix Di: Ethical clearance certificate	455
Appendix Dii: Mapi Trust translation agreement and permission to use PedsQL	457
Appendix Diii: Permission to conduct a pre-experimental, six-week pilot study	466
Appendix Div: Permission for cross-over randomised controlled trial (Western Cape) ...	468
Appendix Dv: Permission for cross-over randomised controlled trial (Gauteng)	471
Appendix Ei: Additional results from the pre-experimental, pilot (Chapter 5) and cross-over randomised controlled trial (Chapter 6).....	474

LIST OF FIGURES

Figure 1. 1 (a-c): Cough mechanism (inspiration, glottic closure and expiration).	7
Figure 1.2: Peripheral and proximal airway clearance techniques including cough augmentation. ...	10
Figure 1.3: Influence of progressive respiratory muscle weakness in neuromuscular disease and the potential role of inspiratory muscle training.	15
Figure 1.4: Function of dystrophin in the muscle.....	16
Figure 1.5: The clinical effect of the absence of dystrophin/non-functional dystrophin.	17
Figure 1.6: Outline of thesis chapters.....	24
Figure 2.1: Procedure for a standard of care survey conducted among South African physiotherapists.	36
Figure 2.2: Flow chart of combined responses for the pilot study and Survey Monkey.....	43
Figure 2.3: Years of experience in patients with neuromuscular disease.	44
Figure 2.4: Acute respiratory management in patients with neuromuscular disease.	45
Figure 2.5: Chronic respiratory management in patients with neuromuscular disease.	52
Figure 2.6: South African acute respiratory management in children with neuromuscular disease...	58
Figure 2.7: South African chronic respiratory management in children with neuromuscular disease.	59
Figure 2.8: Airway clearance techniques (peripheral and proximal).	71
Figure 3.1: Flow diagram of study selection and results	99
Figure 3.2: Summary of risk of bias of included studies.	111
Figure 3.3: Effect size of the change in inspiratory muscle strength (Pimax).	119
Figure 4.1: Data collection procedure pre-experimental study.....	140
Figure 4.2: Inspiratory muscle training: randomised cross-over data collection process.	141
Figure 4.3: Ulna length conversion table.....	143
Figure 4.4: Pulmonary function outcome measures.	145
Figure 4.5: Outcomes for general function and mobility.	154
Figure 4.6: OMNI scale for perceived exertion.	162
Figure 4.7: Duration of participation in cross-over randomised controlled trial based on group allocation.	163
Figure 4.8: Powerbreathe K3 ® device	165

Figure 5.1: Change in mean inspiratory muscle strength (Pimax) throughout intervention.....	184
Figure 5.2: Change in mean inspiratory muscle strength (SNIP) throughout intervention.	185
Figure 5.3: Change in mean peak inspiratory flow (PIF) values throughout intervention.	186
Figure 5.4: Change in mean strength-index (S-index) values throughout intervention.	187
Figure 5.5: Upper limb function and coordination (MFM) pre-post inspiratory muscle training.	189
Figure 5.6: Change in mean inspiratory muscle training intensity (load) throughout the intervention period (weeks).....	191
Figure 5.7: Change in mean inspiratory muscle training intensity (load) over the intervention period	193
Figure 5.8: Change in mean power (Watts) over the intervention period.	194
Figure 5.9: Change in mean volume (L) over the intervention period.	195
Figure 5.10: Change in mean training index (%) over the intervention period.	196
Figure 6.1: Group allocation for the cross-over randomised controlled trial.....	215
Figure 6.2: Summary of inspiratory muscle training cross-over randomised controlled trial methodology.....	216
Figure 6. 3: Clinical assessments during the study period (Group 1: ce).....	217
Figure 6.4: Clinical assessment during the study period (Group 2: ec).	217
Figure 6.5: Patient recruitment and data collection process (CONSORT framework).	219
Figure 6.6: Change in inspiratory muscle strength (mean Pimax) over the intervention period.	233
Figure 6.7: Change in inspiratory muscle strength (mean SNIP) over the intervention period.....	234
Figure 6. 8: Change in inspiratory muscle strength (mean strength-index)throughout intervention.	236
Figure 6. 9: Change in mean peak inspiratory flow (PIF) throughout intervention.	237
Figure 6.10: Change in mean cough ability (PECF) throughout intervention.	238

LIST OF TABLES

Table 1.1: The role of the inspiratory and expiratory muscles in breathing.....	8
Table 1.2: Airway clearance techniques to enhance the cough mechanism.	11
Table 2.1: Development and revision of the questionnaire.....	38
Table 2.2: Vocational background of eligible participants indicated as frequencies and percentages.....	43
Table 2.3: Summary of suggested treatment duration and frequencies for peripheral and proximal airway clearance techniques (acute care).....	48
Table 2.4: Summary of suggested repetitions and frequencies per day for respiratory muscle training, lung compliance and airway clearance techniques (chronic care).....	55
Table 2.5: Summary of preferred techniques in acute and chronic management of children with neuromuscular disease.....	57
Table 2.6: Overview of respiratory management techniques used per work-setting for acute management of children with neuromuscular disease.....	60
Table 2.7: Overview of respiratory management techniques used per work-setting for chronic management of children with neuromuscular disease.....	61
Table 2.8: Overview of respiratory management techniques used in the acute management of children with neuromuscular disease and years of experience.....	62
Table 2.9: Overview of respiratory management techniques used in the chronic management of children with neuromuscular disease and years of experience.....	63
Table 3.1: Systematic literature review: Included studies.....	101
Table 3.2: Respiratory muscle training (RMT) programmes and devices used.....	107
Table 3.3: Outcomes of muscle strength and endurance training.....	116
Table 4.1: Primary outcome measures: inspiratory muscle training programme.....	138
Table 4.2: Secondary outcome measures: inspiratory muscle training programme.....	138
Table 4.3: Brooke scale (upper limb function).....	155
Table 4.4: Vignos scale (Lower limbs).....	155
Table 4.5: Selected Motor Function Measure (MFM) items for upper limb function and coordination.....	157
Table 4.6: PedsQL™ Generic Core Scales translations for South Africa.....	160
Table 4.7: Inspiratory muscle training protocol for the pre-experimental, pilot study.....	166

Table 4.8: Inspiratory muscle training protocol for the cross-over randomised controlled trial.....	167
Table 5.1: Baseline bio-demographic data, mobility levels and pulmonary function.....	181
Table 5.2: OMNI scale averages during two-week intervals of inspiratory muscle training.....	182
Table 5.3: Pre-post variables for pulmonary function and inspiratory muscle training load.....	183
Table 5.4: Mobility and upper limb function and coordination.....	188
Table 5.5: Health-related quality of life measurements: total scores, subdomains for child and proxy.....	190
Table 5.6: Proxy PedsQL scores.....	190
Table 5.7: Open-text verbatim responses from participants and physiotherapists about inspiratory muscle training.....	197
Table 6. 1: Bio-demographic data and functional ability of participants.....	221
Table 6.2: Bio-demographic and pulmonary function baseline data at recruitment based on recruitment site and group allocation.....	223
Table 6.3: Respiratory tract infections and hospitalisations during training and non-training periods.....	226
Table 6.4: Respiratory tract infections and hospitalisations during the non-training/control period only, per recruitment site and group allocations.....	226
Table 6.5: Respiratory tract infections and hospitalisations during the training period only, per recruitment site and group allocations.....	227
Table 6.6: OMNI scores over the intervention period.....	228
Table 6.7: Pulmonary function during training and non-training periods.....	230
Table 6.8: Spirometry values pre-post intervention (IMT) and post monitoring.....	231
Table 6.9: Inspiratory muscle strength values (Pimax; SNIP) pre-post intervention and post monitoring.....	232
Table 6.10: Pulmonary function measured by Powerbreathe K3 ® during training period.....	235
Table 6.11: Pre-post training and post-monitoring variables for cough ability (PECF).....	238
Table 6.12: Change in Brooke, Vignos and upper limb function and coordination (MFM) during training and non-training periods.....	239
Table 6.13: Functional ability (ambulation) and upper limb function and coordination.....	240
Table 6.14: Health-related quality of life measurements: total scores, subdomains for child and proxy (training vs non-training).....	241

Table 6.15: Health-related quality of life measurements: total scores, subdomains for child and proxy (intervention period).....	242
Table 6.16: Open-text responses from participants and parents/caregivers/physiotherapists about inspiratory muscle training.....	245

RESEARCH OUTPUTS OF THIS THESIS AT THE TIME OF SUBMISSION

Presentations:

International congresses:

- Two poster presentations at the World Confederation of Physical Therapists (WCPT) international congress (2017):

“Inspiratory muscle training for children and adolescents with neuromuscular diseases: a systematic review.”

“Respiratory care in children and adolescents with neuromuscular diseases: a South African perspective.”

- A poster presentation at the International Congress for Neuromuscular diseases (ICNMD) in Austria (2018):

“Breathing is life! Inspiratory muscle training in children and adolescents living with neuromuscular diseases.”

- An oral presentation at the World Confederation of Physical Therapists (WCPT) international congress (2019):

“Every breath counts! Inspiratory muscle training in children with neuromuscular diseases: a cross-over study.”

- An oral presentation at the TREAT-NMD international congress (2019):

“Take a deep breath and cough! Inspiratory muscle training and cough assistance in NMD.”

National congresses:

- A poster presentation at the Child Health Priorities Conference: Beyond Survival (University of Pretoria):

“Inspiratory muscle training in severe spinal muscular atrophy: a case study”

- An oral presentation at the national congress of the South African Society of Physiotherapy (2018):

“Inspiratory muscle training in children and adolescents living with neuromuscular diseases: a pre-experimental study”

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ABBREVIATIONS

AAD:	Assisted autogenic drainage
ACBT:	Active cycle of breathing technique
ACOB:	Active cycle of breathing
ACT:	Airway clearance techniques
AD:	Autogenic drainage
ADHD:	Attention deficit hyperactivity disorder
ADL:	Activities of daily living
AFO:	Ankle foot orthosis
ALS:	Amyotrophic lateral sclerosis
ANOVA:	Analysis of variance
ATS:	American Thoracic Society
BiPAP:	Bi-level positive airway pressure
BMD:	Becker muscular dystrophy
BMI:	Body mass index
BTS:	British Thoracic Society
CMD:	Congenital muscular dystrophy
COPD:	Chronic obstructive pulmonary disease
CPAP:	Continuous positive airway pressure
CPRG:	Cardiopulmonary rehabilitation group
CPT:	Chest physiotherapy
CV:	Closing volume
DBE:	Deep breathing exercises
DGMAH:	Doctor George Mukhari Academic Hospital

DM:	Myotonic dystrophy
DMD:	Duchenne muscular dystrophy
DoH:	Department of Health
EBP:	Evidence-based practice
ERS:	European Respiratory Society
EVC:	Slow vital capacity measured on expiration
FET:	Forced expiratory time
FEV₁:	Forced expiratory volume in one second
FRC:	Functional residual capacity
FVC%p:	Forced vital capacity percentage predicted
FVC:	Forced vital capacity
GPB:	Glossopharyngeal breathing
HFA:	Height for age
HFCWO:	High frequency chest wall oscillation
HMV:	Home mechanical ventilation
HPCSA:	Health Professions Council of South Africa
HR:	Heart rate
HREC:	Human Research Ethics Committee
HRQoL:	Health-related quality of life
IMT:	Inspiratory muscle training
IPPB:	Intermittent positive pressure breathing
IPV:	Intrapulmonary Percussive Ventilation
IQR:	Interquartile range

KAFO:	Knee ankle foot orthosis
LGMD:	Limb girdle muscular dystrophy
LRTI:	Lower respiratory tract infection(s)
LVR:	Lung volume recruitment
MAC:	Manually assisted cough
MDG:	Millenium Development Goals
MDN:	Median
MFM:	Motor Function Measure
MIC:	Maximum insufflation capacity
MicroRPM:	Electronic handheld mouth pressure meter
MI-E:	Mechanical insufflation-exsufflation
MND:	Motor neuron disease/disorder
MVV:	Maximum voluntary ventilation
NIV:	Non-invasive ventilation
NMD:	Neuromuscular disease(s)/disorder(s)
NPPV:	Non-invasive positive pressure ventilation
OMNI:	Visual modified Borg scale (patient's perceived level of exertion)
PD:	Postural drainage
Pdi:	Transdiaphragmatic pressure (difference between gastric and oesophageal pressures)
Pdimax:	Transdiaphragmatic pressure (measured during a maximal sniff manoeuvre)
PECF:	Peak expiratory cough flow

PedsQL:	Pediatric Quality of Life Inventory/Questionnaire
PEF:	Peak expiratory flow
Pemax:	Maximum expiratory mouth pressure
PEP:	Positive expiratory pressure
Pes:	Oesophageal pressure
Pesmax:	Oesophageal pressure measured during a maximal sniff manoeuvre
Pga:	Gastric pressure
PIF:	Peak inspiratory flow
Pimax:	Maximum inspiratory mouth pressure
RCT:	Randomised controlled trial(s)
RCWMCH:	Red Cross War Memorial Children's Hospital
RLP:	Respiratory load perception
RMT:	Respiratory muscle training
ROM:	Range of motion/movement
RPE:	Rating of perceived exertion
RR:	Respiratory rate
RV:	Residual volume
SA:	South Africa/South African
SASP:	South African Society of Physiotherapy
SD:	Standard deviation
SDG:	Sustainable development goals
S-index:	Strength-index
SMA:	Spinal muscular atrophy

SMN-1:	Survival Motor Neuron 1
SMU:	Sefako Makgatho Health Sciences University
SNIP:	Sniff nasal inspiratory pressure
SOC:	Standard of care
SpO₂:	Oxygen saturation as measured by pulse oximetry
T_E:	Endurance time
TLC:	Total lung capacity
TREAT-NMD:	Translational Research in Europe- Assessment & Treatment of NMD
URTI:	Upper respiratory tract infection
V/Q:	Ventilation/perfusion
VAS:	Visual analogue scale (or faces pain scale)
VC:	Vital capacity
V_E:	Minute ventilation
WCPT:	World Confederation of Physical Therapy
WFA:	Weight for age
WFH:	Weight for height
WHO:	World Health Organisation
WOB:	Work of breathing

OPERATIONAL DEFINITIONS

The following definitions of terms are used for this thesis:

Active cycle of breathing

This is an airway clearance technique consisting of breathing control, thoracic expansion exercises and forced expiration to mobilise secretions from peripheral to proximal airways (Bhowmik, Chahal, Austin & Chakravorty, 2009).

Adherence

Adherence with treatment is broadly defined as “the extent to which a person’s behaviour – taking medication, following a diet or home pulmonary rehabilitation program, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider”

(World Health Organisation (WHO), 2003). If patient adherence with treatment is less than 80%, it is defined as low or poor adherence (Mäkelä, Backer, Hedegaard & Larsson, 2013).

Adolescent

The definition of adolescence is variable, including age ranges between 10 and 25 years (Kliegman, Behrman, Jenson & Stanton, 2007; Williams, Thomson, Seto, Contopoulos-Ioannidis, Ioannidis, Curtis et al. 2012). The South African (SA) Department of Health defines adolescence as being from 12 to 17 years of age (Department of Health, 2015). For this thesis, patients are considered as adolescents if they are between the age of 13 and 17 completed years (Ratcliffe, 1998). Pre-adolescence and adolescence (10-18 years) is usually the time when a pulmonary functional decline becomes evident in people with Duchenne Muscular Dystrophy (DMD) (Mayer, Leinonen, Rummey, Meier & Buyse, 2017; Meier, Rummey, Leinonen, Spagnolo, Mayer, Buyse et al. 2017).

Airway clearance techniques

Airway clearance techniques (ACT) are physiotherapy modalities aimed at clearing the airways of obstructive secretions to enhance airway patency, reduce the work of breathing, and improve gas exchange (McCool & Rosen, 2006; De Boeck, Vermeulen, Vreys, Moens & Proesmans, 2008). Airway clearance techniques in the management of patients with neuromuscular diseases (NMD) can be subdivided into secretion mobilisation (peripheral ACT) and cough augmentation (proximal ACT) (McCool & Rosen, 2006; Piper & Moran, 2006; Finder, 2010; Chatwin, Toussaint, Gonçalves, Sheers, Mellies, Gonzales-Bermejo et al. 2018; Toussaint, Chatwin, Gonzales, Berlowitz, Berlowitz, Lacombe et al. 2018):

Peripheral ACT includes manual techniques such as percussions, vibrations, high frequency chest wall oscillation or compression, intrapulmonary percussive ventilation and chest wall strapping.

Proximal ACT refers to the assistance of inspiration (single and stacked breaths), expiration (manually assisted cough or mechanical exsufflation) or both inspiration and expiration (MI-E), to improve or simulate a patient's cough effort.

Ambulation

A patient is described in this thesis as being ambulant if they were able to walk independently; partially ambulant if the child was able to walk, but needed support such as holding on to a railing, person or using orthoses or mobility assistive devices; and non-ambulant describes children who were unable to walk with assistance and used a wheelchair (Meier et al., 2017).

Autogenic drainage

Autogenic drainage is an active, self-drainage airway clearance technique, which assists in mobilising secretions from the peripheral to central airways by controlled exhaling from different lung volumes (from low to high volumes) (McCool & Rosen, 2006; Bhowmik et al., 2009).

Becker muscular dystrophy

Becker muscular dystrophy (BMD) is a NMD caused by either deletions or mutations in the X-chromosome, similar in presentation to, but less common than Duchenne muscular dystrophy (DMD). In BMD a less severe mutation in the dystrophin gene results in the production of less or abnormal dystrophin causing a milder phenotype and later onset than DMD (Ballo, Viljoen & Beighton, 1994; Gozal, 2000; McDonald, 2012; Kerr, Robinson, Essop & Krause, 2013; Boentert, Wenninger & Sansone, 2017).

Body mass index

Body Mass Index (BMI) is an indication of relative weight for height and associated with total body fat content. It is calculated as the ratio of weight in kilograms (kg) divided by the square of height in meters (kg/m^2). The BMI Z-scores are used to describe a participant's BMI with statistical reference to the population average for their age and sex. In children, body weight classifications differ from those of adults because body composition varies greatly as a child develops, and varies between boys and girls primarily owing to differences in sexual development and maturation.

The categories used for the description of weight (Z-scores and absolute BMI) are underweight, normal, overweight and obese. A BMI of $> 30 \text{ kg/m}^2$ is classified as general obesity and $> 40 \text{ kg/m}^2$ as extremely obese (Nici, Donner, Wouters, Zuwallack, Ambrosino, Bourbeau et al. 2006; Hruby & Hu, 2015; Purnell, 2018).

Breath-stacking (also known as air stacking/lung volume recruitment)

Breath-stacking is a technique used by patients with NMD to recruit lung volume (increase inspiratory capacity), maintain chest wall and lung compliance and/or augment cough flow (Anderson, Hasney & Beaumont, 2005; Bach, Bianchi, Vidigal-Lopes, Turi & Felisari, 2007; Birnkrant, Bushby, Bann, Alman, Apkon, Blackwell et al. 2018; Castrillo, Lacombe, Boré, Vaugier, Falaize, Orlikowski, Lofaso et al. 2019; Katz, Momoli, Barrowman, Bijelic, Mah, McMillan & McKim, 2019).

This technique is performed by taking sequential voluntary or applied breaths, without allowing exhalation between consecutive breaths (using glottic closure or a one-way valve), until maximum inspiratory capacity is reached

(Bach et al., 2007; Ishikawa, Bach, Komaroff, Miura & Jackson-Parekh, 2008; Toussaint, Boitano, Gathot, Steens & Soudon, 2009; McKim, Katz, Barrowman, Ni & LeBlanc, 2012;

Farrero, Antón, Egea, Almaraz, Masa, Utrabo et al. 2013; Chatwin et al., 2018; Toussaint et al., 2018). Breaths may be delivered manually with a resuscitation bag or using mechanical positive pressure ventilation, via face mask or mouthpiece interfaces

(Ishikawa et al., 2008; Jenkins, Stocki, Kriellaars & Pasterkamp, 2014; Castrillo et al., 2019;

Katz et al., 2019; Birnkrant et al., 2018; Toussaint et al., 2018).

Breath-stacking/air stacking can be done either voluntarily/unassisted/independently or with the assistance of a caregiver or family member

(Bach et al., 2007; Ishikawa et al., 2008; Jenkins et al., 2014; Castrillo et al., 2019).

Caregiver

A caregiver is defined in South Africa (SA) as “a person who factually cares for a child” (s1 Children’s Act, 38 of 2005); a caregiver is obliged (in terms of s 32(1)) to safeguard the child’s “health, well-being and development; and to protect the child from abuse and other harms”.

In addition, a caregiver may provide consent to medical examination or treatment of a child (in terms of s 32(2))(Department of Health, 2015).

Congenital muscular dystrophies

Congenital muscular dystrophies are a group of rare autosomal recessive myogenic disorders. Patients present with hypotonia and weakness at birth or early infancy, as well as progressive muscle weakness with variable distribution and severity due to an absence or defect in dystrophin which affects function and mobility (Emery, 2002; Aboussouan, 2009; Wang, Bonnemann, Rutkowski, Sejersen, Bellini, Battista et al. 2010; Yilmaz & Sechtem, 2012).

Congenital myopathies

The term “congenital myopathy” refers to a group of genetically inherited primary myopathies characterised by “non-dystrophic” changes. Unlike muscular dystrophies, these congenital myopathies tend to be relatively non-progressive (static) or otherwise slowly progressive conditions presenting in infancy with hypotonia, delayed milestones, diffuse weakness of the limbs, slow progression of symptoms and sometimes dysmorphic features (Darin & Tulinius, 2000; Iwabe, Nucci, Pfeilsticker & Magna, 2014).

In general, patients tend to have a good prognosis as compared to other NMD regarding lifespan, but congenital myopathies may be associated with respiratory and cardiac failure (Iwabe et al., 2014.).

Duchenne muscular dystrophy

Duchenne muscular dystrophy (DMD) is a rare (1 in every 3000-6000 live male births), inherited X-linked recessive neuromuscular disease, clinically characterised by progressive muscle weakness and wasting, affecting all body muscles including the respiratory muscles and heart. The onset of first symptoms is usually seen between two to five years of age whilst loss of ambulation and respiratory muscle weakness usually become apparent at approximately 10 years of age (Boentert et al., 2017; Birnkrant et al., 2018). In DMD, the gene mutation (deletion or duplication) is on the Xp21 locus causing a lack of dystrophin in the muscle (Gozal, 2000; Emery, 2002; Finder, Birnkrant, Carl, Farber, Gozal, Iannaccone et al. 2004; Guglieri & Bushby, 2011; Bladen, Salgado, Monges, Foncuberta, Kekou, Kosma et al. 2015).

Patients present with increased serum creatine kinase (CK) (Emery, 2002; Guglieri & Bushby, 2011; Landfeldt Lindgren, Bell, Schmitt, Guglieri, Straub & Bushby, 2015) and muscle fibres show variation in sizes, areas of necrosis and as the disease progresses increased fat and connective tissue which manifests as pseudohypertrophy (Emery, 2002).

Male children usually present with early signs of muscle weakness including difficulty in running, hopping, getting up from the floor (Gower's sign), climbing stairs or abnormal (toe) walking due to proximal muscle weakness

(Emery, 2002; Guglieri & Bushby, 2011; Bendixen, Senesac, Lott & Vandeborne, 2012).

Although recognition of such problems is most common between two and five years of age, motor and speech developmental delays can assist with earlier diagnosis (Guglieri & Bushby, 2011; van Ruiten, Straub, Bushby & Guglieri, 2014). In the natural disease course, ambulation is usually lost by 12 years of age, most patients die in their early twenties due to respiratory and/or cardiac failure and only a few patients survive to their thirties (Kerr, Robinson, Essop & Krause, 2013; van Ruiten et al., 2014; Yilmaz, Yildirim, Yilmaz, Kara, Taylan, Demir, Yilmaz et al., 2016). However, if patients are managed with steroid treatment, nocturnal ventilation and cardiac support as outlined in the DMD Care Standards, they have a good chance of survival into their thirties (Finder et al., 2004; Mercuri, McDonald, Mayhew, Florence, Mazzone, Bianco & Vroom, 2012; Goemans & Buyse, 2014; van Ruiten et al., 2014).

Behavioural problems and cognitive impairments have also been described as common in DMD (Petrof, 1998; Guglieri & Bushby, 2011; van Ruiten et al., 2014; Chiang, Mehta & Amin, 2018).

Dystrophin

Dystrophin is a large structural rod-shaped cytoskeletal protein linking the actin cytoskeletal components to the cell membrane to provide stability to the muscle cell

(Koenig, Monaco & Kunkel, 1988; Cossu & Sampaolesi, 2007; Aboussouan, 2009; Kerr et al., 2013).

Forced vital capacity

A spirometric value (expressed in litres) that determines the total amount of air that can be moved through the lungs while breathing with maximal effort (maximum exhalation after maximum inhalation), which indicates both inspiratory and expiratory muscle function (Mayer, Finkel, Rummey, Benton, Glanzman, Flickinger & Meier, 2015; Kinane, Mayer, Duda, Lowes, Moody & Mendell, 2018). Normal lungs can generally empty more than 80 percent of their volume in six seconds or less (Barreiro & Perillo, 2004).

Functional Residual Capacity

The volume of air (litres) in the lungs at resting end expiration during normal tidal breathing (Barreiro & Perillo, 2004; Chiang et al., 2018).

Glossopharyngeal breathing

This breathing technique, also known as “frog-breathing”, consists of a series of approximately six to 10 pumping strokes (gulps) produced by the lips, tongue, soft palate, pharynx and larynx that aims to enhance lung insufflation by gulping sequential boluses of air into the lungs, closing the glottis in-between each inspiration until maximum insufflation capacity (MIC) is reached

(Dohna-Schwake, Ragette, Teschler, Voit & Mellies, 2006; Bach et al., 2007; Wang et al., 2010; Hull, Aniapravan, Chan, Chatwin, Forton, Gallagher et al. 2012; Chatwin et al., 2018; Toussaint et al., 2018; Castrillo et al., 2019).

Health

The World Health Organisation (WHO) defines health as a state of physical, mental and social well-being and not merely the absence of disease and infirmity (WHO (constitution): <https://www.who.int/about/who-we-are/constitution>). A person’s “health state” is a broader term defined as the combination of various health concepts that describes the patient’s health-related quality of life which can either encompass multiple attributes (holistic) or contain a single domain/construct (Patrick & Erickson, 1993).

Health-related quality of life

Health-related quality of life (HRQoL) is a comprehensive term that is multi-dimensional and focuses on capturing subjective experiences of health and well-being, including the patients’ satisfaction regarding physical, psychological (emotional), social and school domains (Eiser & Morse, 2001; Bastiaansen, Koot, Bongers, Varni & Verhulst, 2004; Boyer, Morrone, Laffont, Dizien, Etienne & Novella, 2006; Gold, Mahrer, Yee, & Palermo, 2009; Hull et al., 2012; Fayers & Machin, 2013). This valuable outcome measurement describes the functional and holistic effect of an illness and its consequent therapy on a patient, as perceived by the specific patient (Schipper, Clinch & Olweny, 1996; Boyer et al., 2006; Gold et al., 2009; Clary, Vander Wal & Titus, 2010; Spuijbroek et al., 2011).

In children, HRQOL incorporates concepts of illness, functional status, mental health and comfort, but also parental impact and family functioning (Finder et al., 2004; Vargus-Adams, 2005).

Children value the ability to participate in peer groups and keep up with developmental activities (Grootenhuys, De Boone & Van der Kooi, 2007), but HRQoL has received less attention in children compared to adult populations (Eiser & Morse, 2001).

Incidence

This indicates the number of new cases of a condition/disease in a specified period (Verhaart Robertson, Wilson, Aartsma-Rus, Cameron, Jones & Lochmüller, 2017).

Inspiratory capacity

The maximal volume of air (litres) inhaled from a resting expiratory level (passive end tidal expiration or functional residual capacity (FRC)) to total lung capacity (TLC), with a closed glottis, and is influenced by oropharyngeal and laryngeal muscle strength. Inspiratory capacity is therefore the difference between TLC and FRC (Kang & Bach, 2000; Barreiro & Perillo, 2004; Miller, Hankinson, Brusasco, Burgos, Casaburi, Coates, et al. 2005; Toussaint et al., 2018).

Inspiratory muscle training

Inspiratory muscle training can be defined as the training of muscles that act to expand the chest wall for air to flow into the lungs and enhance ventilation, through improved respiratory coordination, strength and endurance (Bissett, Leditschke, Paratz & Boots, 2012; Xiao, Luo, Wang & Luo, 2012; Wenninger, Greckl, Babačić, Stahl & Schoser, 2019). The loads for IMT can either be flow, threshold or resistive (Weiner, Magadle, Beckerman, Weiner & Berar-Yanay, 2004; Koppers, Vos, Boot & Folgering, 2006; Houston, Mills & Solis-Moya, 2008) and types of IMT devices include non-targeted, targeted, threshold or normocapnic hyperventilation (Geddes, O'Brien, Reid, Brooks & Crowe, 2008).

Inspiratory muscle training involves progressive resistance loading of the inspiratory muscles in order to strengthen them (Bissett et al., 2012; Wenninger et al., 2019). For threshold IMT, patients must create a certain threshold pressure to open the valve which then initiates inspiratory flow, improving both inspiratory muscle strength and the ability to create airflow (McCool & Tzelepis, 1995).

Lung function

Refer to spirometry and pulmonary function.

Manually assisted cough

Manually assisted cough is a cough augmentation technique in which external manual compression is applied to the chest, abdomen or both (thoracic and/or abdominal thrusts or compressions), in synchrony with the patient's cough effort, to increase intra-thoracic and intra-abdominal pressure and enhance peak expiratory cough flow (PECF) (Finder et al., 2004; Boitano, 2006; McCool & Rosen, 2006; Panitch, 2006; Finder, 2010; Farrero et al., 2013; Bianchi, Carrara, Khirani & Tuccio, 2014; Panitch, 2017; Toussaint et al., 2018).

Manually assisted cough can be used independently or in combination with techniques that augment inspiratory volume (Finder et al., 2004; Hull et al., 2012; Panitch, 2017).

Maximum inspiratory pressure

Refer to Pimax.

Maximum insufflation capacity

Maximum insufflation capacity is the maximum, tolerable inspiratory lung volume (litres) maintained with a closed glottis and requires oropharyngeal and laryngeal muscle strength and control (Kang & Bach, 2000; Finder et al., 2004; Bach et al., 2007; Chatwin et al., 2018).

Maximum expiratory pressure

Maximum static expiratory pressure (P_{max}/MEP), expressed in cmH₂O, can be defined as the greatest negative pressure measured at the mouth and sustained for at least one second (Fauroux & Aubertin, 2007; Kinane et al., 2018). Performing a maximal expiratory effort is volitional, but a relatively simple and readily available way to determine expiratory muscle strength (European Respiratory Society (ERS), 2002; Fauroux & Aubertin, 2007; Caruso, Albuquerque, Santana, Cardenas, Ferreira, Prina, et al. 2015; Boentert et al., 2017; Gogou, Giannopoulos, Eboriadou, Hatzistylianou & Haidopoulou, 2017; Kinane et al., 2018).

Based on respiratory muscle strength guidelines, and aligned with most studies, P_{max} is measured from total lung capacity (TLC) (ERS, 2002; Verma, Chiang, Qian & Amin, 2019).

Maximum static inspiratory pressure

Maximum static inspiratory pressure (Pimax/MIP) can be defined as the greatest negative pressure (cmH₂O) obtained at the mouth and sustained for at least one second, and is an easily accessible way of gauging inspiratory muscle strength (ERS, 2002; Huang, Martin & Davenport, 2003; Fauroux & Aubertin, 2007; Ratnovsky, Elad & Halpern, 2008; Caruso et al., 2015; Kinane et al., 2018).

This test is a non-invasive volitional global indicator of inspiratory muscle strength, especially diaphragmatic strength (ERS, 2002; Boentert et al., 2017; Kinane et al., 2018). Although Pimax measures muscle strength by the force created, it is also dependent on lung volumes: the greatest pressures are achieved near functional residual capacity (FRC) and residual volume (RV). This relationship between pressure and volume indicates the diaphragm's force-length properties and mechanical coupling with the chest wall (McCool, 1992; Ratnovsky et al., 2008).

Based on convention and standardisation of assessment, Pimax was measured at RV for all participants (Fauroux & Aubertin, 2007).

Mechanical insufflation-exsufflation

Mechanical insufflation-exsufflation (MI-E) involves the delivery of positive pressure to the airways via nose, mouth or tracheostomy to promote maximal lung inflation (insufflation) followed by a rapid switch to negative pressure to the upper airway (exsufflation), thus simulating a cough and removing secretions from the airways (Gómez-Merino, Sancho, Marin, Servera, Blasco, Belda & Bach, 2002; Anderson et al., 2005; Fauroux, Guillemot, Aubertin, Nathan, Labit, Clément & Lofaso, 2008; Farrero et al., 2013; Morrow, Zampoli, van Aswegen & Argent, 2013; Auger, Hernando & Galmiche, 2017; Chatwin et al., 2018; Chiang et al., 2018; Toussaint et al., 2018).

The rapid change from positive to negative pressure (expressed in cmH₂O) aims to simulate the flow changes that occur during a cough, hence assisting proximal airway clearance (Chatwin, Ross, Hart, Nickol, Polkey & Simonds, 2003; Toussaint et al., 2018). Although various interfaces can be used for MI-E, including a mouthpiece, mask or via a tracheal tube, when bulbar involvement is severe, the efficacy of MI-E could be limited and safety might be a concern (Chatwin et al., 2003; Wang, Finkel, Bertini, Schroth, Simonds, Wong et al. 2007; Farrero et al., 2013).

Maximum voluntary ventilation

Maximum voluntary ventilation (MVV) is a measure of the maximum volume of air that can be inhaled and exhaled within one minute, indicative of respiratory muscle endurance (Winkler, Zifko, Nader, Frank, Zwick, Toifl & Wanke, 2000; Koessler, Wanke, Winkler, Nader, Toifl, Kurz & Zwick, 2001). Measurements of hard and fast breathing are taken over a 12 (12sMVV) or 15 second period (15sMVV) and then extrapolated to 60 seconds (reported as litres per minute)

(DiMarco, Kelling, DiMarco, Jacobs, Shields & Altose, 1985; Vilozeni, Bar-Yishay, Gur, Shapira, Meyer & Godfrey, 1994; Barreiro & Perillo, 2004).

Maximum voluntary ventilation is approximately equal to baseline $FEV_1 \times 40$ and low MVV values are commonly seen in patients with restrictive pulmonary disorders (Barreiro & Perillo, 2004).

Neuromuscular diseases/disorders

Neuromuscular diseases (NMD) are a group of heterogeneous neurological disorders that include pathology of the muscle (myopathies, muscular dystrophies), neuromuscular junction, peripheral nerves and motor neurons (anterior horn cell), with potentially severe and devastating consequences (Emery, 1991; Jensen, Abresch, Carter & McDonald, 2005; Cup, Pieterse, Jessica, Munneke, van Engelen, Hendricks & Oostendorp, 2007; Yang & Finkel, 2010; Benditt & Boitano, 2013; Iwabe et al., 2014). Based on the area of involvement, neuromuscular diseases are divided into five main groups: anterior horn cell disease, peripheral neuropathies, neuromuscular junction disorders, muscular dystrophies as well as congenital and metabolic myopathies (Ambrosino, Carpena & Gherardi, 2009).

In this study neuromuscular diseases refer to conditions affecting the neurological system including the spinal cord (anterior horn cells), motor nerves and muscles (Benditt & Boitano, 2013). Traumatic spinal cord lesions are excluded.

Non-invasive ventilation

Non-invasive ventilation is mechanical ventilation applied using a non-invasive interface such as a nasal mask, nasal pillow, cuirass, mouthpiece or face mask (Hull et al., 2012).

Overweight and obesity

Obesity is defined as excess body weight for height due to excess fat accumulation (regionally, globally or both), which increases the risk of morbidity and burden of disease for patients and healthcare systems, especially in developing countries (Hruby & Hu, 2015; Purnell, 2018).

Decreased activity due to immobility and lean body mass can reduce resting energy expenditure, increasing the risk of children with NMD becoming obese. For this reason, a healthy diet needs to be implemented as soon as possible after diagnosis, to prevent malnutrition and obesity and assist in bone health (Wang et al., 2007; Goemans & Buyse, 2014). Weight can also be classified based on BMI: underweight ($<21 \text{ kg/m}^2$), normal weight ($21\text{-}25 \text{ kg/m}^2$), overweight ($25\text{-}30 \text{ kg/m}^2$) and obese ($>30 \text{ kg/m}^2$) (Nici et al., 2006).

Paediatric patient

Definitions for “paediatric” are variable, but the term generally refers to infants and children up until adolescence (Williams et al., 2012). Within the umbrella term, different age categories include: newborn/neonate, infant, toddler, pre-school age (3-4 years), early school age (5-8 years) and later school age (9-12 years) (Ratcliffe, 1998). In this study, a paediatric patient is defined as a newborn up to 13 years of age, after which they are classified as adolescents. Children in this study encompass all patients younger than 18 years old (Department of Health, 2015).

Peak expiratory flow

A maximum or peak flow produced during exhalation, with maximum effort (Mayer et al., 2015), expressed as litres per minute (L/min). This maximum expiratory effort may be used as a surrogate measure for expiratory muscle strength (Meier et al., 2017).

Peak expiratory cough flow

Peak expiratory cough flow (L/min) is the maximum airflow (usually 360-1200L/min) generated during the expulsive phase of a cough, resulting from the sudden release of high intrapleural and thoraco-abdominal pressures when the glottis opens and is used to objectively determine cough efficacy (Anderson et al., 2005; Gauld, 2009; Mayer, Henricson, McDonald & Buyse, 2017). Cough efficacy, as measured by PECO, is determined by inspiratory and expiratory muscle strength, and the ability to close the glottis to generate sufficient pressure to clear debris from the airways (Park, Kang, Lee, Choi & Kim, 2010; Kang & Bach, 2000; Avendaño & Güell, 2003; Bianchi & Baiardi, 2008; Toussaint et al., 2009; Park et al., 2010; Gogou et al., 2017; Chatwin et al., 2018).

Peak inspiratory flow

Peak inspiratory flow (PIF) as a function of inspiratory muscle strength, refers to the amount of airflow that can be created when taking a deep breath, relating to the force-velocity relationship of the inspiratory muscles (Powerbreathe: <https://www.powerbreathe.com/powerbreathe-k3>; McCool, 1992; Gozal, 2000).

Postural drainage

Postural drainage, including head down tilt/Trendelenburg positioning, is hypothesised to enhance secretion mobilisation through the use of gravity and positioning the bronchi more vertically (Houtmeyers, Gosselink, Gayan-Ramirez & Decramer, 1999).

Prevalence

The number of living persons with a certain condition at a certain time (Verhaart et al., 2017).

Pulmonary function

[Also refer to FRC, FVC, MVV, Pemax, PEF, Pimax, SNIP, Spirometry and VC].

In this study pulmonary function refers to the patient's ability to ventilate (move air in and out of the lungs) expressed as relaxed and forced spirometry (volume and flow), volitional respiratory muscle strength tests (Pimax, SNIP) (Caruso et al., 2015) as well as the patient's cough ability (PECF) (Aslan, Gurses, Issever & Kiyan, 2013; Finkel, Mercuri, Meyer, Simonds, Schroth, Graham et al. 2018).

Although spirometry is most commonly used in standard practice, helium dilution technique may also be used if available, for example, to determine FRC (DiMarco et al., 1985; ERS, 2002; Wang et al., 2007).

The following lung volumes (expressed in litres) are relevant to this study of patients with NMD (Eagle, 2002; Barreiro & Perillo, 2004; Miller et al., 2005; Aslan et al., 2013; Chiang et al., 2018):

- Forced vital capacity (FVC): The maximum volume of air exhaled during a maximal forced expiratory effort, after maximum inhalation (TLC).
- Forced expiratory volume in one second (FEV₁): The maximum volume of air exhaled in the first second during a forced expiration, after a maximal inhalation (TLC).
- FEV₁/FVC ratio: The percentage (%) or proportion of the FVC (volume of air) expired in one second.

- Expiratory reserve volume (ERV): The maximum volume of air that can be forcibly exhaled from the end-expiratory level during tidal breathing.
- Inspiratory reserve volume (IRV): The maximal volume of air inhaled with a maximum inspiratory effort from end inspiration (tidal volume).
- Vital capacity (VC): The largest volume measured on complete exhalation after a full inspiration (EVC) or the maximum volume of air measured on complete inhalation after a full expiration (IVC). Vital capacity is also be expressed as the difference between total lung capacity (TLC) and residual volume (RV) or a combination of tidal, inspiratory and expiratory reserve volumes.
- Residual volume (RV): The volume of air remaining in the lungs after a maximal exhalation.
- Tidal volume (TV): The volume of air inhaled or exhaled during each respiratory cycle (during normal inspiration and expiration).

This study did not include expiratory muscle strength testing (Pemax) or maximum voluntary ventilation (MVV) as part of the pulmonary function assessment.

Pulmonary rehabilitation

Pulmonary rehabilitation is a multi-disciplinary, evidence-based approach for patients with symptomatic pulmonary disease and impaired ability to perform activities of daily living.

Pulmonary rehabilitation aims to minimise symptoms, maximise functional capacity and participation as well as reduce healthcare costs by stabilising or reversing the manifestations of pulmonary disease (Avendaño & Güell, 2003; Nici et al., 2006; Rosiere, Vader, Cavin, Grant, Larcinese, Voellinger & Fitting, 2009). The main components of pulmonary rehabilitation include muscle training, education and airway clearance techniques, adapted according to individual patient presentation (Nici et al., 2006; Rous, Lobato, Trigo, Vélez, San Miguel, Cejudo, et al. 2014; Castrillo et al., 2019; Toussaint et al., 2018). Pulmonary rehabilitation has both physiological and psychosocial benefits for patients living with chronic disease, but is frequently underutilised (Avendaño & Güell, 2003; Rochester, Vogiatzis, Holland, Lareau, Marciniuk, Puhan, et al. 2015).

Respiratory exacerbation

An exacerbation is defined as a change in any of the three cardinal respiratory features, namely symptoms, sputum colour and shortness of breath, for more than 48 hours (Bourbeau, Saad, Joubert, Ouellet, Drouin, Lombardo & Lebel, 2013).

Respiratory failure

Respiratory failure is described as the inability to provide oxygen along with the removal of carbon dioxide at a rate that matches the body's metabolic demand (Hammer, 2013). Indications of respiratory failure and the need for ventilatory support non-invasive or invasively via an artificial airway include an increase in severity of dyspnoea, tachypnoea followed by bradypnoea, poor air entry, tachycardia, cyanosis, hypoxia, respiratory dysfunction or symptoms of hypoventilation and evidence of fatigue (orthopnoea) as well as reduced level of consciousness and responsivity (Farrero et al., 2013; Pflieger & Eber, 2013; Bourke, 2014; Birnkrant et al., 2018).

Sniff nasal inspiratory pressure

This is a non-invasive volitional measure of dynamic inspiratory respiratory muscle strength, with high rates of change in pressure and is expressed in cmH₂O. A maximal effort is needed from the participant by performing a sharp, short voluntary inspiratory manoeuvre (SNIP) through the nostril (ERS, 2002; Caruso et al., 2015; Boentert et al., 2017).

Spinal muscular atrophy (SMA)

Spinal muscular atrophy (SMA), an autosomal recessive neuromuscular disease, is one of the most common NMD affecting the paediatric population (Gozal, 2000) and can range from severe to mild phenotypes (Verhaart et al., 2017). Spinal muscular atrophy is caused by a mutation in the SMN-1 or VAPB genes on chromosome five (Bach, Niranjan & Weaver, 2000; loos, Mrad, Barois, Estournet-Mathiaud et al. 2004; Chatwin, Bush & Simonds, 2011; Verhaart et al., 2017). This is a progressive degenerative disease of the motor neurons in the spinal cord (anterior horn), brainstem (motor nuclei) and some cranial nerves (V, VII, IX, XII). The clinical picture includes progressive general muscle weakness (proximal more severe than distal and lower limbs more affected than upper limbs), respiratory muscle weakness and decreased deep tendon reflexes. Respiratory insufficiency caused by recurrent pulmonary infections and atelectasis is a common occurrence in SMA (loos et al., 2004; Sharma, 2009).

Spinal muscular atrophy can be categorised into three types (some literature state four which includes adult SMA), based on time of onset, severity and clinical picture. Phenotypes can be seen more as a continuum than distinct subtypes of SMA.

Patients with severe forms of SMA present with both inspiratory and expiratory muscle weakness caused predominantly by intercostal muscle weakness, with relative diaphragmatic sparing (Gozal, 2000; Bach et al., 2000; loos et al., 2004; Wang et al., 2007). This distribution of muscle weakness leads to the development of a bell-shaped chest wall deformity and a paradoxical intercostal breathing pattern is common (loos et al., 2004; Wang et al., 2007; Bourke, 2014). Furthermore, as the condition progresses and children age, progressive muscle weakness leads to decreased forced vital capacity (FVC), increasing the risk of pulmonary complications (loos et al., 2004).

A description of the different types of SMA is provided below (Bach et al., 2000; Gozal, 2000; Tangsrud, Carlsen, Lund-Petersen & Carlsen, 2001; loos et al., 2004; Wang et al., 2007; Chatwin et al., 2011; Verhaart et al., 2017):

SMA I (Werdnig-Hoffmann disease)

This is the most severe form of SMA, with early onset (< 6 months of age). Infants present with severe hypotonia, decreased reflexes, decreased head control, swallowing problems and the tongue might show atrophy and fasciculation. Patients present with progressive muscle weakness and many of them with floppiness at birth. These children cannot sit without support and never attain independent sitting. Without mechanical respiratory support, children have a poor prognosis, due to respiratory failure causing morbidity and mortality, and most do not live beyond two years of age.

SMA II (Dubowitz disease)

SMA type II is the intermediate form, with the onset of symptoms between the ages of six and 18 months. Children with type II SMA can usually sit independently, but cannot walk without assistance. Children present with swallowing problems and poor weight gain (Wadman, De Amicis, Brusa, Battezzati, Bertoli, Davis, et al. 2020) and tend to develop deformities such as scoliosis and contractures. Patients also present with periods of respiratory failure during early childhood that can cause death, but have a better prognosis than type I. Expected life span is two to 30 years, but the majority of patients now live into their twenties.

SMA III (Kugelberg-Welander/juvenile disease)

This type of SMA is mild and has a later onset of disease (18 months to adulthood). These patients attain the ability to walk without assistance. Some lose the ability to walk during childhood, while others remain ambulant until adolescence or adulthood. Scoliosis can develop at a later stage and nocturnal hypoventilation is less than in type II. These patients have a good prognosis with most having a normal lifespan.

SMA IV (Adult disease)

This is the least severe, adult type of SMA, with onset during the twenties or thirties (late adolescence or adulthood) and a slow progression. Patients can still walk during their adulthood years and the age of death might be similar to those without the disease. Mild motor impairment can be seen and patients usually do not present with respiratory or gastro-intestinal complications (Wang et al., 2007).

Spirometry

[Also refer to Pulmonary Function, FRC, FVC and VC].

Spirometry measures the volume and flow changes during breathing (Barreiro & Perillo, 2004) and includes static and dynamic lung volumes as well as maximum flow (ERS, 2002; Mayer et al., 2015).

Total lung capacity

The volume of air in the lungs (litres) at maximal inflation (Barreiro & Perillo, 2004) consists of the sum of vital capacity (VC) and residual volume (RV) (Chiang et al., 2018). Total lung capacity usually starts decreasing when inspiratory muscle strength falls below 50% predicted value (Eagle, 2002).

Vital capacity

Vital capacity is the maximum amount of air (litres) that can be expired after full inspiration (Barreiro & Perillo, 2004).

Chapter 1: LET ME INTRODUCE YOU TO NEUROMUSCULAR DISEASES

Overview, pulmonary pathophysiology, problem statement, purpose and significance of the study

1.1 Background and introduction

Neuromuscular diseases (NMD) refer to a heterogeneous group of disorders that include pathology of the muscle (myopathies, muscular dystrophies), neuromuscular junction, peripheral nerves and motor neurons (anterior horn cell), with potentially severe and devastating consequences due to progressive muscle weakness (Emery, 1991; Yang & Finkel, 2010; Benditt & Boitano, 2013; van Ruiten et al., 2014). Clinical presentation of NMD depends on the specific anatomical structures affected (Gozal, 2000; Benditt & Boitano, 2013; Deenen, Horlings, Verschuuren, Verbeek & van Engelen, 2015). Neuromuscular diseases can be categorised as either inherited or acquired NMD, depending on the onset of symptoms (Yang & Finkel, 2010; McDonald, 2012). The most common types of NMD seen in childhood are Duchenne muscular dystrophy (DMD), Becker muscular dystrophy (BMD), spinal muscular atrophy (SMA) and congenital myopathies. Muscular dystrophies, such as DMD and BMD, are inherited myogenic disorders characterised by progressive general muscle weakness and wasting in varying degrees, including cardiac and respiratory muscles (Emery, 2002; Avendaño & Güell, 2003; Wang et al., 2010; Guglieri & Bushby, 2011; Goemans & Buyse, 2014; Boentert et al., 2017).

Duchenne muscular dystrophy is the most common paediatric muscle condition affecting one in every 3000 to 6000 live male births, caused by a mutation in the dystrophin gene (Koenig et al., 1988; Finder et al., 2004; Nicot, Hart, Forin, Boulé, Clément, Polkey & Fauroux, 2006; Yang & Finkel, 2010; Guglieri & Bushby, 2011; Boentert et al., 2017). Global prevalence for DMD and BMD has been estimated at 1.7 to 4.2 or 0.70-4.7 per 100 000 and 0.4 to 3.6 or 0.07-3.65 per 100 000 respectively (Theadom, Rodrigues, Roxburgh, Balalla, Higgins, Bhattacharjee & Feigin, 2014; Deenen et al., 2015). In some African countries such as Libya (DMD: 6/100 000) and Egypt (DMD: 7.7/100 000; BMD: 3.8/100 000), the prevalence was higher (Theadom et al., 2014). On the contrary, lower muscular dystrophy prevalence has been reported in South Africa (SA) (Theadom et al., 2014), with a minimum overall prevalence of one per 100 000 for DMD and one per 755 000 for BMD (n=163) (Ballo et al., 1994).

A lower incidence of DMD among the black African population (1/250 000) as compared to other European countries such as the United Kingdom (1/40 000) has been reported, but statistics in SA are limited (Ballo et al., 1994; Theadom et al., 2014;

Esterhuizen, Greenberg, Ballo, Goliath & Wilmshurst, 2016; Verhaart et al., 2017; Jalloh, Mathiassen, Wessels, Ndondo & Wilmshurst, 2018).

Spinal muscular atrophy is a neurodegenerative disease affecting the alpha motor neurons in the anterior horn cells of the spinal cord, which also presents with progressive muscle weakness and atrophy (Wang et al., 2007; Verhaart et al., 2017). Spinal muscular atrophy occurs due to a mutation or deletion of the Survival Motor Neuron 1 (SMN-1) caused by a defect on chromosome five and the clinical manifestations and prognosis depends on the severity or type of SMA (loos et al., 2004; Wang et al., 2007). Spinal muscular atrophy is not as common as muscular dystrophies, with an estimated incidence of one in 10 000 live births for all types of SMA; SMA type I accounting for the majority (60%) of cases (Verhaart et al., 2017). A recent review indicated a median prevalence for SMA of 2 (1.3-3.2) per 100 000 (Deenen et al., 2015). However, most NMD prevalence studies have been performed in small populations, primarily in European countries and before widespread genetic testing (Verhaart et al., 2017). Possible reasons for the observed difference in the prevalence of NMD in SA, compared to other countries, could be ascribed to the heterogeneity of the conditions, the small number of SA prevalence studies available, differences in mutations between regions and certain ethnicities, decreased sensitivity of available tests and poor healthcare access for certain population groups (Ballo et al., 1994; Theadom et al., 2014; Bladen et al., 2015; Esterhuizen et al., 2016; Verhaart et al., 2017; Jalloh et al., 2018).

Despite the differences in pathophysiology and severity, common complications among children with NMD are caused by underlying skeletal and/or respiratory muscle weakness that affects gross motor, speech, behaviour, physical and cardiopulmonary function and ultimately health-related quality of life (HRQoL) (Avendaño & Güell, 2003; Servera, Sancho & Zafra, 2003; Kohler, Clarenbach, Böni, Brack, Russi & Bloch, 2005; Yeldan, Gurses & Yuksel, 2008; Yang & Finkel, 2010; Guglieri & Bushby, 2011; McDonald, 2012; van Ruiten et al., 2014; Voet, van der Kooi, van Engelen & Geurts, 2019). The focus of management in children with NMD is to prevent and/or ameliorate these unpleasant symptoms in order to optimise quality of life.

1.1.1 Neuromuscular disease healthcare management in South Africa

South Africa is a country characterised by a high burden of disease, including diseases associated with poverty and underdevelopment, emphasising the need for health-related research that can advance services in our country (Department of Health, 2015). Research focusing on prevalence and burden of NMD among children in SA is limited and there are no data available on South African (SA) physiotherapists' knowledge, expertise and practice in this field.

In addition, the adherence of SA physiotherapists to NMD clinical practice guidelines and the respiratory management strategies used in this context is unknown. This information is however necessary to inform both research and clinical practice, as well as optimise resource utilisation in the context of a resource-constrained African country, as envisioned by the White Paper on Transformation of Health Services and Sustainable Development Goals (SDG) (Department of Health, 1997; Sachs, 2012). The success of SDG requires an integrative approach among social, economic and environmental sectors (Sachs, 2012; Bircher & Kuruvilla, 2014). The provision of healthcare services to improve efficiency and optimise the use of limited resources is therefore essential (Woolf, Grol, Hutchinson, Eccles & Grimshaw, 1999; Auger et al., 2017; Finkel et al., 2018; HMI, 2019; Stander, Grimmer & Brink, 2020).

The SA national health system includes both public and private healthcare sectors. The government manages the public sector, which serves about 84% of the general population, while private sector healthcare access depends on an individual's ability to pay for these services. The majority of the SA population of approximately 57.7 million (Standar, Grimmer & Brink, 2019) are living in rural areas and most households (approximately 70%) make use of public health care facilities as their first point of access (WHO (case study): <https://www.who.int>; Standar et al., 2019). South Africa consists of nine provinces with varying economic status and development/infrastructure, employment rates and access to healthcare (Standar et al., 2019). Statistics SA (2017) report that only 17% of the population have private medical insurance (Department of Health: <https://www.gov.za/about-sa/health>). In the next decade, the SA government plans to implement a national health insurance (NHI) programme that will incorporate both public and private healthcare sectors to provide health services for all citizens, irrespective of socio-economic status (Department of Health: <https://www.gov.za/about-sa/health>). Healthcare recommendations should therefore be contextualised regarding the planned implementation of NHI (Health Market Inquiry (HMI), 2019).

Research in children with NMD is essential to understand how service delivery, alignment with clinical practice guidelines and outcomes can be improved in this vulnerable population (Landfeldt et al., 2015). With this in mind, it would be important to assess SA physiotherapists' knowledge and implementation of clinical practice guidelines for the management of children with NMD. Furthermore, identifying appropriate, effective, low-cost and simple physiotherapy interventions that could be applied across the healthcare and socio-geographic spectrum should be prioritised, to optimise care and ultimately improve HRQoL for SA children living with NMD.

1.1.2 Pulmonary pathophysiology and clinical implications in neuromuscular diseases

Children with NMD may experience reduced activity levels and participation due to delays in milestones, frequent falls and hypotonia caused by their underlying skeletal muscle weakness (Avendaño & Güell, 2003; McDonald, 2012).

Participation and HRQoL may further be affected by respiratory, orthopaedic, feeding/swallowing and, in some NMD, cardiac complications (Gozal, 2000; Piper & Moran, 2006; Goemans & Buyse, 2014; van Ruiten et al., 2014; Landfeldt et al., 2015; Wadman et al., 2020). In addition to skeletal muscle weakness, inspiratory and/or expiratory muscle weakness develops over time in many NMD, leading to the deterioration of pulmonary function, with increased risk of respiratory morbidity and mortality (Rochester & Arora, 1983; Hill, 2002; Laghi & Tobin, 2003; Servera et al., 2003; Boitano, 2006; Dohna-Schwake et al., 2006; Kirk, 2006; Boentert et al., 2017; Panitch, 2017; Morrow et al., 2019). The degree and rate of pulmonary dysfunction in children with NMD might differ due to the type of NMD, the severity of the disease, respiratory muscle involvement, co-morbidities and individual patient differences (Kirk, 2006; Boentert et al., 2017; Finkel et al., 2018).

As children with NMD grow older and their condition progresses, pulmonary function, including lung volumes such as forced vital capacity (FVC), vital capacity (VC) and total lung capacity (TLC) declines. This regression increases the risk for pulmonary complications, hospitalisations, post-operative respiratory insufficiency and prolonged ventilatory support, nocturnal ventilation and ultimately necessitating full-time ventilation, if this is available (loos et al., 2004; Bushby, Bourke, Bullock, Eagle, Gibson & Quinby, 2005; Wang et al., 2007; Sharma, 2009; Takaso, Nakazawa, Imura, Okada, Fukushima, Ueno et al. 2010; Mayer et al., 2017; Chiang et al., 2018). Low tidal volumes can further lead to alveolar hypoventilation with ventilation-perfusion (V/Q) mismatch; secretion retention, leading to recurrent lower respiratory tract infections; dyspnoea; sleep disturbances (nocturnal hypoxia and hypercapnia); restrictive lung disease and decreased exercise tolerance (Benditt, 2006; Kirk, 2006; Nicot et al., 2006; Piper & Moran, 2006; Sharma, 2009; Yang & Finkel, 2010; McDonald, 2012; Panitch, 2017; Chiang et al., 2018; Toussaint et al., 2018). Respiratory muscle strength also decreases with age; in the case of DMD, this decline is most notable around ten years of age when many patients become non-ambulant (Guglieri & Bushby, 2011; Boentert et al., 2017). An annual decline in inspiratory muscle strength (Pimax) percentage predicted value of 3.8% and expiratory muscle strength (Pemax) of 2.7% has been observed in patients with DMD (7-15 years) (Kinane et al., 2018).

Progressive muscle weakness in NMD, combined with limited sigh capacity, is associated with shortening, weakness and atrophy of inspiratory muscles over time with concomitant poor ventilation, recurrent infections and functional consequences (Panitch, 2009; Toussaint et al., 2009; Kinane et al., 2018). Intercostal and diaphragmatic muscle weakness contributes to the development of postural deformities (Panitch, 2009) and may lead to fibrosis of the chest wall muscles, decreased chest expansion and the development of progressive, restrictive pulmonary disease (Kohler et al., 2005; Kirk, 2006; Fauroux, Guillemot, Aubertin, Nathan, Labit, Clément & Lofaso, 2008; Bento, Gonçalves, Silva, Pinto, Marinho & Winck 2010; Guglieri & Bushby, 2011; Birnkrant et al., 2018). Vital capacity could also be disproportionately reduced according to the presence and severity of scoliosis (Alman, Raza & Biggar, 2004; Wang et al., 2007). However, Bushby et al. (2005) suggested that scoliosis is unlikely to have a significant effect on respiratory function in DMD, with pulmonary function decline more likely attributed primarily to intrinsic respiratory muscle weakness.

Many patients present with respiratory complications due to progressive inspiratory muscle weakness causing decreased ability to take a deep breath (decreased ventilation), and reduced secretion clearance due to a poor cough (Ambrosino, Carpené & Gherardi, 2009; Boentert et al., 2017; Panitch, 2017; Morrow, Angelil, Forsyth, Huisamen, Juries & Corten, 2019), which may ultimately lead to respiratory failure (Farrero et al., 2013; Mayer et al., 2017).

1.1.3 The importance of the cough mechanism in neuromuscular diseases

Coughing is an important respiratory defense mechanism responsible for removing debris and secretions from the airways (Chatwin et al., 2003; Servera et al., 2003; Chiang et al., 2018). Patients with NMD may present with progressive inspiratory and secondary expiratory muscle weakness and decreased bulbar/oro-motor control, which leads to an ineffective cough and increases the risk of broncho-aspiration (Perrin, Unterborn, Ambrosio & Hill, 2004; Bourke, 2014; Toussaint et al., 2018; Wadman et al., 2020). An ineffective cough leads to secretion retention and the potential for further infection, airway obstruction, and increased work of breathing (Dohna-Schwake et al., 2006; Sharma, 2009; Chatwin et al., 2018; Finkel et al., 2018; Morrow et al., 2019). In many cases, cough insufficiency rather than hypoventilation is responsible for respiratory morbidity and mortality among patients with NMD (Finder, 2010). In patients with NMD, the inability to produce an effective cough can be caused by decreased VC, bulbar function impairment and expiratory muscle weakness (Dohna-Schwake et al., 2006; McCool & Rosen, 2006; Nicot et al., 2006).

The cough mechanism consists of inspiration, compression (increased intra-thoracic pressure) and expiration (Panitch, 2006; Toussaint et al., 2009; Finder, 2010; Bourke, 2014). In order to produce an effective cough, a deep inspiratory breath (ranging from 60-90% of TLC or 80-90% of VC), followed by glottic closure (for approximately 0.2s) to contain the inspired air, is needed (Kang & Bach, 2000; Bianchi & Baiardi, 2008; Gauld, 2009; Sharma, 2009; Finder, 2010; Toussaint et al., 2018). The compressive phase of the cough mechanism is subsequently followed by an expulsive phase where a maximum contraction of the expiratory muscles and subsequent forceful glottis opening create turbulent airflow (peak expiratory cough flow (PECF)) that can effectively expel secretions (360L/min-1200L/min) (Servera et al., 2003; Dohna-Schwake et al., 2006; Panitch, 2006; Farrero et al., 2013; Panitch, 2017) (Figure 1.1 a-c).

The lowest normative value for an effective cough in adults (PECF=400L/min) is only reached at 12 or 13 years of age, while the PECF threshold value at which cough augmentation is recommended, in children and adults older than 12 years of age, is less than 270L/min (Finder et al., 2004; Hull et al., 2012; Farrero et al., 2013; Chiang et al., 2018; Toussaint et al., 2018). Even if PECF values are greater than 270L/min in a healthy individual with NMD, a further decline in lung function, respiratory muscle strength and PECF are commonly observed during acute respiratory infections (Bach, Ishikawa & Kim et al., 1997; Poponick, Jacobs, Supinski & DiMarco, 1997; Gómez-Merino et al., 2002; Sejerson & Bushby, 2009; LoMauro, Romei, D'Angelo & Aliverti, 2014; Finkel et al., 2018).

The threshold PECF values for an effective cough and indicating cough augmentation in children is currently unknown (Bianchi & Baiardi, 2008; Hull et al., 2012) and warrants further investigation.

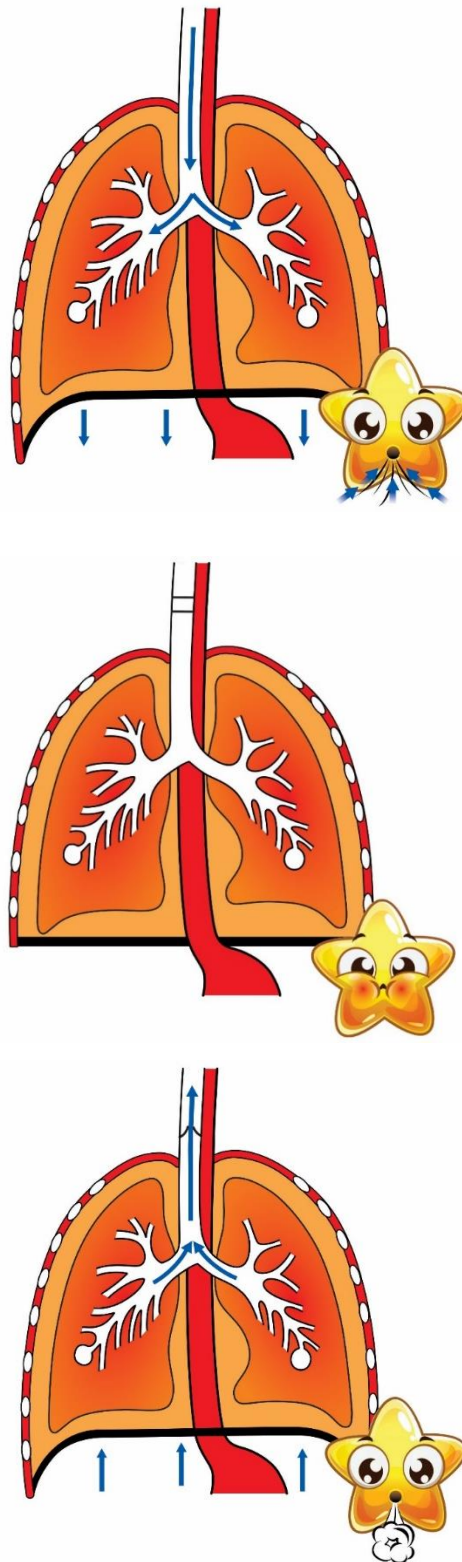


Figure 1. 1 (a-c): Cough mechanism (inspiration, glottic closure and expiration).

The ability to achieve adequate expiratory cough flows (>270L/min in adults) in order to expel secretions effectively is at least in part determined by achieving sufficient volumes (VC) during the inspiratory phase (>1.5L in adults) (Bach et al., 1997; Toussaint et al., 2009; Chatwin et al., 2018).

Expiration is predominantly a passive process relying on elastic recoil, however, in some disease processes and during coughing, expiration becomes active and forced. Inspiratory muscles contribute mostly to ventilation, while expiratory muscles assist with forced expiratory flow and expulsion of secretions while the bulbar muscles mainly stabilise and protect the airway (Ratnovsky & Elad, 2005; Panitch, 2006; Aboussouan, 2009; Xiao et al., 2012; Toussaint et al., 2018). Decreased speed and strength of expiratory muscle contraction leads to a decrease in peak expiratory flow (Dohna-Schwake et al., 2006; Panitch, 2006; Farrero et al., 2013; Meier et al., 2017), affecting the patient's cough ability (Table 1.1). Patients with expiratory muscle weakness can present with an increase in residual volume (RV) resulting in a decreased TLC, while poor inspiratory muscle strength also reduces TLC (Eagle, 2002; Chiang et al., 2018). Although inspiratory and expiratory muscle weakness in DMD co-incide, a steeper gradient of regression in the expiratory muscles have been reported (Nicot et al., 2006).

The respiratory muscles are responsible for moving air into and removing air from the lungs, which is the mechanism of ventilation (Ratnovsky et al., 2008). Inspiratory muscles and especially the diaphragm, increase the cranio-caudal, lateral (transverse) and anterior-posterior (A-P) diameter of the chest when contracting, hence reducing intra-thoracic pressure allowing air to flow into the lungs (Ratnovsky & Elad, 2005; Nicot et al., 2006; Aboussouan, 2009; Bissett et al., 2012; Xiao et al., 2012) (Table 1.1).

Table 1.1: The role of the inspiratory and expiratory muscles in breathing.

Inspiratory muscles (Resting breathing)	Expiratory muscles
Diaphragm	Abdominals (rectus abdominus, external and internal oblique)
External intercostals	Internal intercostals (resting breathing)
Parasternal muscles	
Scalene muscles, sternomastoid, trapezius (accessory muscles)	
Inspiratory muscles (Forced inspiration)	Expiratory muscles (Forced expiration)
Serratus posterior superior	Transversus thoracis
	Pectoralis muscles (fixated shoulder girdle)

(Ratnovsky & Elad, 2005; Xiao et al., 2012)

Patients with both inspiratory and expiratory muscle weakness can have a more profound reduction in VC (Eagle, 2002). Progressive inspiratory and expiratory muscle weakness, fatigue, and/or lung and airway co-morbidities such as mucus plugging can further affect lung volumes (VC, FVC) (ERS, 2002) and cough ability (PECF) (Bushby et al., 2005; Nicot et al., 2006; Farrero et al., 2013; Boentert et al., 2017; Panitch, 2017).

This may be exacerbated during inter-current respiratory infections when respiratory muscle strength and lung volumes further decrease, adding to the burden of disease of NMD (PoPONICK et al., 1997; Boitano, 2006; Wang et al., 2007; Finder, 2010; Benditt & Boitano, 2013; Panitch, 2017; Chatwin et al., 2018; Finkel et al., 2018).

1.1.4 Management strategies in neuromuscular diseases

Currently, commonly used interventions such as gluco-corticosteroids in DMD might delay the onset of pulmonary functional loss and in some cases slow pulmonary function decline (Yang & Finkel, 2010; Jalloh et al., 2018; McDonald & Mercuri, 2018).

Novel therapies for NMD such as Idebenone (ubiquinone/Coenzyme Q10, Santhera Pharmaceuticals), Eteplirsen (Exondys 51, Sarepta Therapeutics), Ataluren (Translarna, PTC Therapeutics), and Nusinersin (Spinraza, Biogen) show promise as they may slow respiratory deterioration and improve HRQoL (Ho, Cardamone & Farrar, 2015; Boentert et al., 2017; Mayer et al., 2017; Verhaart et al., 2017; Kinane et al., 2018). These therapies may change the natural history of NMD and drive change in clinical outcomes and patient expectations (McDonald & Mercuri, 2018). Unfortunately, these gene modification therapies are not readily available to SA patients with NMD, owing to cost implications and regulatory constraints. Clinical trials are also needed to determine safety, efficacy and cost effectiveness in the SA context (McCool & Rosen, 2006; Guglieri & Bushby, 2011; Boentert et al., 2017). Despite the possibility of new drug therapies changing the course of the disease and respiratory function over time, adequate symptomatic and preventative management strategies in NMD are still strongly recommended (Yang & Finkel, 2010; Guglieri & Bushby, 2011; Boentert et al., 2017; Finkel et al., 2018), particularly in the context of resource-limited countries.

Although considerable advances in the management of NMD have been made, there is still no cure available (Goemans & Buyse, 2014; Theadom et al., 2014; Ho et al., 2015). Many of the symptoms and pulmonary complications can, however, be prevented, delayed and/or managed through regular pulmonary function assessment and early multi-disciplinary intervention targeting distressing symptoms and improving HRQoL (Gozal, 2000; Finder et al., 2004; loos et al., 2004; Boitano, 2006; Wang et al., 2007; Sejerson & Bushby, 2009; Yang & Finkel, 2010; Birnkrant et al., 2018).

1.1.4.1 Cough augmentation in neuromuscular diseases

Respiratory management strategies in NMD aim to improve or maintain pulmonary function, functional ability and ultimately HRQoL (Kirk, 2006; Nici et al., 2006; Rous et al., 2014).

Airway clearance techniques are indicated in patients whose muco-ciliary escalator, mucus rheology, structural defects and/or poor cough mechanics (caused by muscle weakness) compromise their secretion mobilisation and expectoration (Houtmeyers et al., 1999; Finder, 2010; Farrero et al., 2013; Volsko, 2013; Morrow et al., 2019).

Airway clearance techniques can be divided into peripheral (secretion mobilisation) and proximal (cough augmentation) airway clearance techniques (ACT) (Chatwin et al., 2018; Toussaint et al., 2018) (Figure 1.2). Secretion mobilisation forms part of ACT and includes manual techniques such as percussions, vibrations and postural drainage (McCool & Rosen, 2006; Wang et al., 2007; Bhowmik et al., 2009; Auger et al., 2017; Chatwin et al., 2018; Toussaint et al., 2018) (Figure 1.2).

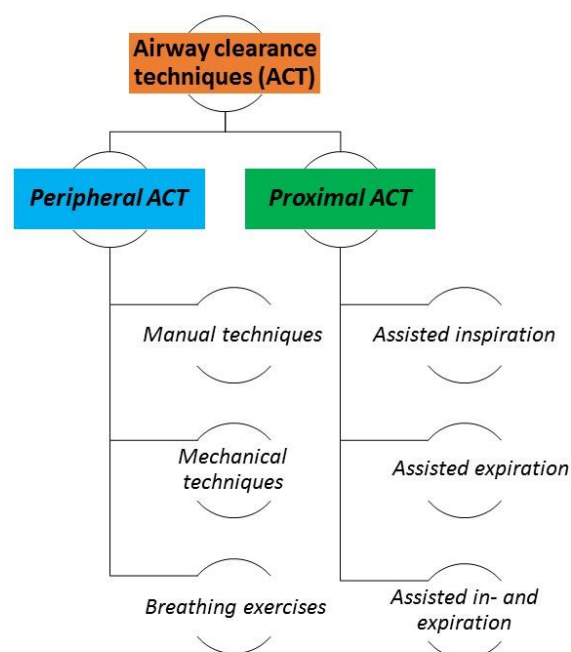


Figure 1.2: Peripheral and proximal airway clearance techniques including cough augmentation

[Adapted from Chatwin et al., 2018].

Proximal ACT aim to assist to clear the airways by assisting or augmenting a cough in order to clear mucus from the larger airways (Chatwin et al., 2018). Patients with impairment of inspiratory and/or expiratory muscle strength, with or without the ability to close the glottis, will present with decreased cough ability and reduced PEF (Gómez-Merino et al., 2002; Chiang et al., 2018; Finkel et al., 2018). Although there are no threshold values available for young children, the adult PEF value of <270L/min is used to indicate the need for proximal ACT (cough augmentation) (Bach et al., 1997; Sejerson & Bushby, 2009; LoMauro et al., 2014; Chatwin et al., 2018).

Cough augmentation (proximal ACT) includes assisting inspiration, expiration or both phases of the cough mechanism through a variety of manual and/or mechanical techniques (Finder et al., 2004; Gauld, 2009; Toussaint et al., 2009; Finder, 2010; Toussaint et al., 2018) (Table 1.2) and is preferred over techniques such as deep suctioning and bronchoscopy during acute pulmonary exacerbations in patients with NMD (Wang et al., 2007).

Table 1.2: Airway clearance techniques to enhance the cough mechanism.

Assisted inspiration	Assisted expiration	Assisted in- and expiration
<u>Single breath:</u> Mechanical insufflation; Non-invasive ventilation; Intermittent positive pressure breathing	Manually assisted cough	Any combination of assisted inspiratory and expiratory techniques
<u>Stacked breaths:</u> Air stacking; Glossopharyngeal breathing; Volume cycled non-invasive ventilation; Lung volume recruitment (e.g. resuscitation bag)	Mechanical exsufflation	Mechanical insufflation-exsufflation

(Volsko, 2013)

Cough augmentation (assisting expiration)

Expiration can be augmented with manual or mechanical methods such as manually assisted cough (MAC) or mechanical devices (mechanical exsufflation) (Figure 1.2). Assisted expiration techniques aim to aid the weakened expiratory muscles by changing intra-thoracic and/or abdominal pressure in order to create sufficient expiratory flows (Anderson, Hasney & Beaumont, 2005; Boitano, 2006; McCool & Rosen, 2006; Chatwin et al., 2018). The paradoxical movement of weak abdominal muscles observed in severe NMD during a cough manoeuvre adds to cough insufficiency. Providing compression on the thorax or abdomen using MAC is believed to counteract this paradox and assist the patient's cough effort by increasing the PECF (Finder et al., 2004; McCool & Rosen, 2006; Panitch, 2006; Farrero et al., 2013). Although MAC can improve cough efficacy by increasing PECF, it also has some disadvantages.

Manually assisted cough cannot be performed independently (needs a caregiver) and may be poorly tolerated and ineffective, especially in patients post abdominal surgery and those with scoliosis, restrictive chest walls, osteoporosis, obesity or intra-abdominal catheters (McCool & Rosen, 2006; Nici et al., 2006; Panitch, 2006; Finder, 2010).

In addition, MAC is labour intensive, at times difficult to perform by non-professionals and requires a coordinated effort by the caregiver and patient (Vianello, Corrado, Arcaro, Gallan, Ori, Minuzzo & Bevilacqua, 2005; McCool & Rosen, 2006; Panitch, 2006). However, MAC is a highly cost effective cough augmentation technique that may be underutilised, as it is not widely taught to healthcare professionals (Chatwin et al., 2018). It is recommended that patients with DMD should be taught the use of effective airway clearance techniques, including cough augmentation, from an early age (Finder et al., 2004).

Cough assist devices (mechanical exsufflators) can be considered in patients presenting with compromised lung function (FVC), decreased PEF, difficulty with airway clearance and frequent chest infections, in order to create high effective expiratory flow rates (Guglieri & Bushby, 2011; Auger et al., 2017; Rose, McKim, Leasa, Nonoyama, Tandon, Kaminska, et al. 2018; Toussaint et al., 2018). Unfortunately, these devices are cumbersome, costly and might not be readily available in all NMD contexts (Chatwin et al., 2018; Castrillo et al., 2019).

Cough augmentation (assisting inspiration)

Augmenting and maintaining inspiratory lung volumes to achieve maximum inspiratory capacity can maintain respiratory muscle length, assist with secretion mobilisation and generate higher PEF for a more effective cough, thereby potentially decreasing respiratory morbidity and improve survival (Bach & Kang, 2000; Chatwin et al., 2003; Dohna-Schwake et al., 2006; Marques, Neves, Portes, Salge, Zanoteli & Reed, 2014; Toussaint et al., 2018; Castrillo et al., 2019). Assisted inspiration (insufflation) not only increases inspiratory lung volumes, but this improves the length-tension relationship of the expiratory muscles, therefore providing greater mechanical effectiveness or recoil for the expulsive phase of coughing (Boitano, 2006; McCool & Rosen, 2006; Finder, 2010; Chatwin et al., 2018). Sufficient insufflation together with the force created by the elastance of the chest wall and lung tissue should produce sufficiently high cough flow to clear secretions from the airways (McCool & Rosen, 2006; Toussaint et al., 2009).

Assisted inspiration can be achieved with a single breath or stacked breathing, which can be a relatively inexpensive cough augmentation technique (Table 1.2).

The patient's VC can be augmented using spontaneous breaths, glossopharyngeal breathing (GPB) or applying manual or mechanical breaths using an ambubag (of the correct size depending on age) and one way valve to prevent air leaks, non-invasive ventilation (NIV) (volume mode) or Intermittent positive pressure breathing (IPPB) (Finder et al., 2004; Wang et al., 2010; Hull et al., 2012; Benditt & Boitano, 2013; Toussaint et al., 2018; Castrillo et al., 2019; Katz et al., 2019). In patients with DMD, the ability to increase lung volume with stacked breathing was better retained than with GPB, where inspiratory volume is assisted through gulping boluses of air (Torres-Castro, Vilaró, Vera-Urbe, Vasconcello & Puppo, 2016; Toussaint et al., 2018). Both breathing manoeuvres can however increase lung volumes and PEF, while GPB can improve VC as well as delay or decrease daytime ventilator usage (Bach et al., 2007; Hull et al., 2012). Unfortunately, the use of GPB and air stacking requires good coordination, which might be difficult for children (Toussaint et al., 2018).

Some ACT might be difficult to perform if the child is young and/or unable to cooperate. As the child grows older, techniques used should be chosen according to their physical maturity and psychological adjustment (Schechter, 2007; Toussaint et al., 2018). If mastered, techniques such as GPB can be effective in improving maximum insufflation capacity (MIC) and subsequently cough ability, but at times external inspiratory support might still be needed (Bianchi et al., 2014; Torres-Castro et al., 2016; Toussaint et al., 2018). If adequate ACT is not implemented in NMD, an upper respiratory tract infection can lead to lower respiratory tract infection which increases the risk of respiratory failure (Boentert et al., 2017; Mayer et al., 2017). Few studies on the outcomes of ACT in children with NMD have been performed and findings are suggestive, but not conclusive (Schechter, 2007).

In the SA context, many people live in extremely impoverished circumstances. Health is known to be influenced by social and environmental determinants, including access to healthcare; socio-economic circumstances; geographical location (for example rural, urban or peri-urban) and access to amenities such as running water and electricity (Bircher & Kuruvilla, 2014). Therefore, certain intervention strategies recommended for NMD in well-resourced countries, such as mechanical insufflation-exsufflation (MI-E) for cough assistance, might be too costly to implement and may not be suitable for patients in rural areas of SA, especially those without reliable provision of electricity. There is a need to identify clinically and cost-effective alternative and adjunct treatment modalities that optimise pulmonary function, minimise respiratory morbidity, delay the onset of respiratory failure and improve longevity and HRQoL in children with NMD.

Cough augmentation (assisting inspiration and expiration)

The augmentation of both inspiration (preceding a cough) and expiration can be performed with manual techniques or mechanical devices to improve lung volume and PEF (Chatwin et al., 2018). Mechanical cough assistance (MI-E) involves the delivery of positive pressure to the airways via nose, mouth or tracheostomy followed immediately by negative pressure, thus simulating a cough (Gómez-Merino et al., 2002; Anderson et al., 2005; Fauroux et al., 2008; Auger et al., 2017). Despite limited evidence of treatment settings, safety and efficacy of MI-E in children with NMD (Morrow, Zampoli, van Aswegen & Argent, 2013), mechanical cough augmentation is advocated as part of standard NMD care in many European countries, although it is acknowledged that availability and implementation vary among countries (Wang et al., 2007; Rosiere et al., 2009; Boentert et al., 2017; Chiang et al., 2018; Finkel et al., 2018; Toussaint et al., 2018).

Mechanical insufflation-exsufflation with a mask interface could be of benefit in children with NMD, especially once PEF nears 160L/min and MAC becomes less effective due to scoliosis (Bach et al., 1997; Finder, 2010). Adding MAC to the exsufflation phase of MI-E in very weak patients with NMD is recommended to augment PEF further (Chatwin et al., 2018). Mechanical cough assistance has been associated with improved outcomes in NMD, including PEF, but the majority of studies have focused on adult patients and short-term effects. Some MI-E studies that included children with NMD suggested short term benefits, with improved clinical outcomes, decreased treatment failure if used in adjunct with ACT, well tolerated by patients and no serious complications or adverse events related to MI-E were reported (Finder et al., 2004; Miske, Hickey, Kolb, Weiner & Panitch, 2004; Vianello et al., 2005; Fauroux et al., 2008; Chatwin & Simonds, 2009). Conversely, in patients with severe bulbar dysfunction and previous history of pneumothorax, the use of MI-E might be inefficient and may pose a safety risk (Chatwin et al., 2018; Toussaint et al., 2018).

Manually assisted cough and lung volume recruitment (air stacking methods) in combination can also improve both maximum insufflation and PEF (Bach et al., 2007; Toussaint et al., 2009; Finder, 2010; Hull et al., 2012; Boentert et al., 2017). The combination of assisted inspiration (manual or mechanical) combined with MAC has been recommended to achieve the greatest improvement in PEF (Toussaint et al., 2009; Chatwin et al., 2018). Manual techniques are however more cost-effective than devices such as MI-E and could therefore be more applicable for the SA context.

1.1.4.2 Inspiratory muscle training: a controversial technique in neuromuscular diseases

Inspiratory muscle training in patients with NMD could potentially preserve or improve respiratory muscle strength, thus maintaining adequate lung inflation, expansion and ventilation; stabilising and/or decreasing the decline of VC, improving gas exchange and delaying the onset of respiratory muscle failure and pulmonary complications

(Koessler et al., 2001; Eagle, 2002; Avendaño & Güell, 2003; Hull et al., 2012; Aslan et al., 2013).

(Figure 1.3).

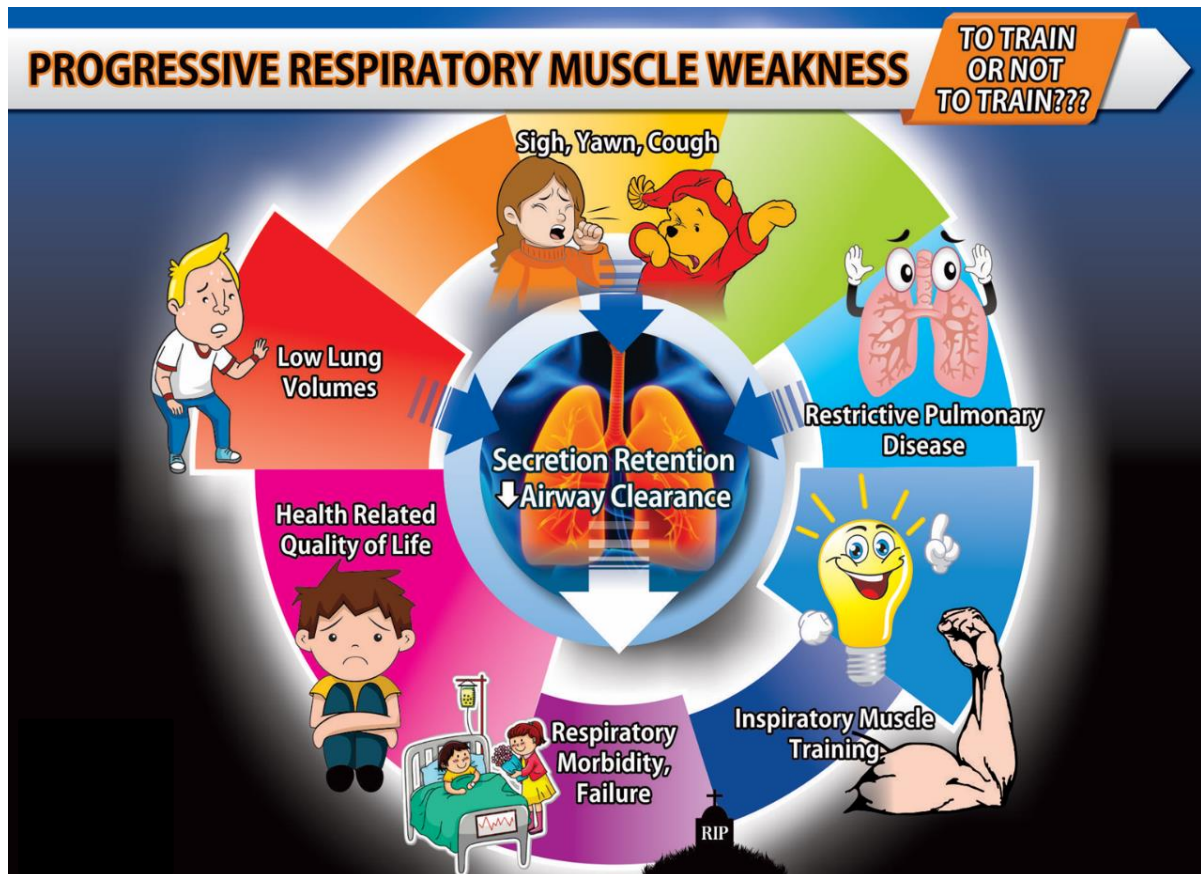


Figure 1.3: Influence of progressive respiratory muscle weakness in neuromuscular disease and the potential role of inspiratory muscle training.

Although IMT might slow the progression of muscle weakness and maintain optimal pulmonary function for longer, studies on respiratory muscle training in NMD have shown contradictory results. Some clinicians are also hesitant to use IMT owing to possible adverse effects related to defects in the protective mechanism of nitric oxide (NO) release during exercise, specifically in patients with dystrophinopathies such as DMD.

It is speculated that this defect, which may have a greater effect on fast-twitch muscles, may increase the risk of muscle damage during exercise due to decreased blood flow, decreased protection against contractile forces, increased fatigue, as well as inflammation and fibrosis (Brenman, Chao, Xia, Aldape & Bredt, 1995; Petrof, 1998; Sander, Chavoshan, Harris, Iannaccone, Stull, Thomas & Victor, 2000; Stamler & Meissner, 2001; Tidball & Wehling-Henricks, 2014).

The role of dystrophin in relation to the muscle membrane is depicted in Figure 1.4.

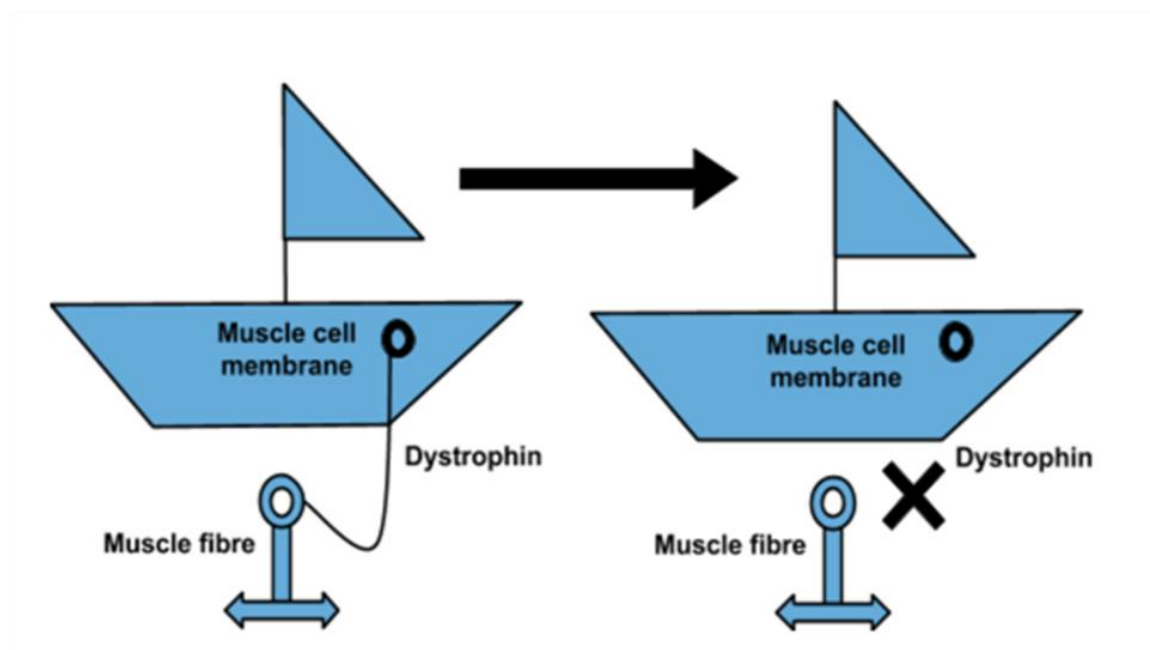


Figure 1.4: Function of dystrophin in the muscle [With permission from the author: Annemieke Aartsma-Rus; <https://www.actionduchenne.org/faqs/what-is-the-role-of-dystrophin-in-duchenne>].

The clinical effect of a lack of dystrophin/non-functional dystrophin is depicted in Figure 1.5.

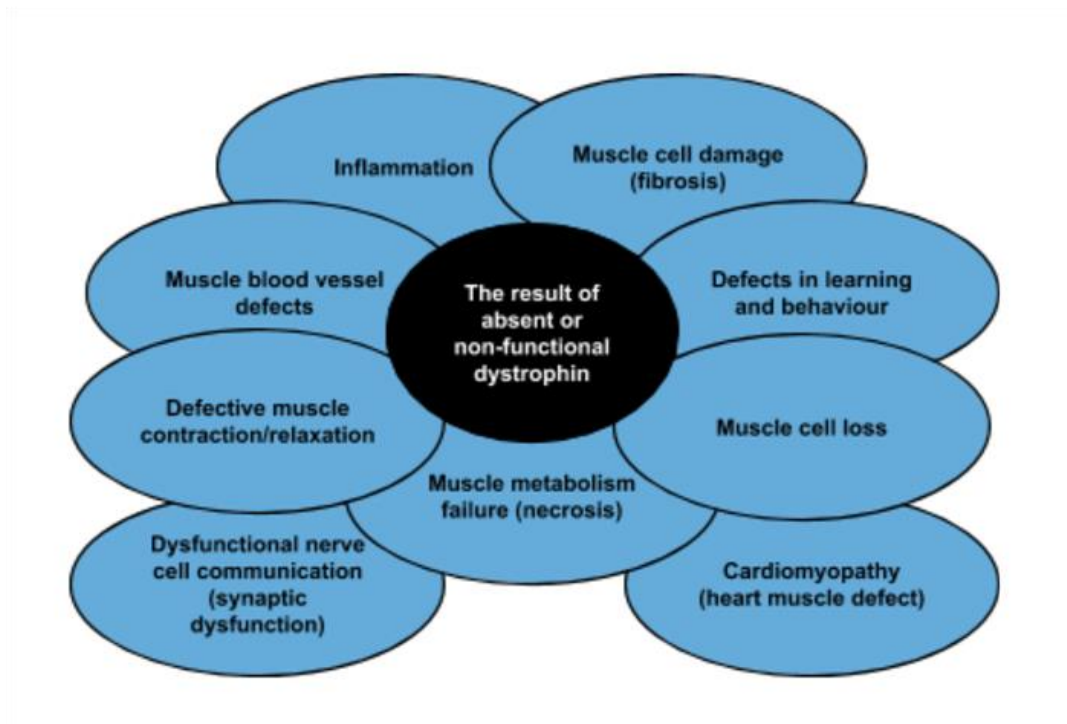


Figure 1.5: The clinical effect of the absence of dystrophin/non-functional dystrophin

[<https://www.actionduchenne.org/faqs/what-is-the-role-of-dystrophin-in-duchenne>].

Many of the NMD, particularly the dystrophinopathies, also present with associated cardiac and orthopaedic complications. Therefore, additional caution needs to be taken during respiratory muscle training, aerobic exercise and strength training (Aboussouan, 2009; Bushby, Finkel, Birnkrant, Case, Clemens, Cripe et al. 2010; Goemans & Buyse, 2014; Voet et al., 2019). Over and above the fatigue experienced during exercise, the lack of muscle membrane associated structural protein (dystrophin) in dystrophinopathies poses a risk of stretch-induced muscle damage which can result in weaker cell membranes, membrane lesions and progressive muscle fibre degeneration (Eagle, 2002; Guglieri & Bushby, 2011; Tidball & Wehling-Henricks, 2014). Various factors can contribute to patients with NMD experiencing fatigue, including the type of NMD and the severity of the condition (Aboussouan, 2009). There is also concern that IMT may accelerate fatigue and cause muscle damage in NMD as a result of overworking/overexertion, particularly in the dystrophinopathies (Finder et al., 2004; Perrin et al., 2004; Aboussouan, 2009; Goemans & Buyse, 2014; Woszezenki, Paulo Heinzmann-Filho & Donadio, 2017). However, some research findings have contradicted the opinion that exercise accelerates disease progression in DMD (Jansen, van Alfen, Geurts & de Groot, 2013).

Some studies have suggested that interventions, such as corticosteroids, disease-modifying medications and even IMT in patients with NMD may be more effective when commenced early in the disease when respiratory muscles are relatively stronger and lung volumes, including VC, are higher (Wanke, Toifl, Merkle, Formanek, Lahrman & Zwick, 1994; McCool & Tzelepis, 1995; Winkler et al., 2000; Eagle, 2002; van Ruiten et al., 2014). Unfortunately, pharmacological interventions such as corticosteroids may be associated with side effects such as weight gain (Guglieri & Bushby, 2011), which can adversely influence motor and respiratory function. The effects of respiratory muscle training in different disease conditions are highly variable, with some studies reporting significant improvement in pulmonary function while others show no or minimal improvement (Finder et al., 2004; Wenninger et al., 2019). It has been suggested that patients with rapidly progressive or advanced NMD and severe pulmonary restriction will likely not benefit from IMT (Kang & Bach, 2000; Winkler et al., 2000; Koessler et al., 2001; Finder et al., 2004; Aboussouan, 2009). Consequently, some clinicians advocate early IMT implementation, when pulmonary function is still preserved and there is less muscle damage (Wanke et al., 1994; McCool & Tzelepis, 1995; Gozal & Thiriet, 1999; van Ruiten et al., 2014; Buyse et al., 2015; Mayer et al., 2017). However, there is some suggestion that intervention at a later stage may still be of clinical value as reported in a case study of a girl with advanced SMA and severe respiratory muscle weakness who had an improvement in inspiratory muscle strength and self-reported HRQoL, after six weeks of IMT, without any intervention-related adverse events (Human, Honey & Morrow, 2019).

Some authors have also suggested that the improved respiratory outcomes observed during a course of IMT might not be maintained after IMT ceases, and improvements in inspiratory muscle strength might be attributed to a “learning effect” rather than true clinical improvements (Rodillo, Noble-Jamieson, Aber, Heckmatt, Muntoni & Dubowitz, 1989; Eagle, 2002).

Evidence for IMT in NMD is limited. Some studies suggest that endurance might improve more than strength; there is no strong evidence for improved functional outcomes, and the benefits of IMT might only be short term, without carry-over beyond the training period (Eagle, 2002). Although the American and British Thoracic Societies, both suggest that IMT could be considered as a component of pulmonary rehabilitation in respiratory muscle weakness, support for IMT in NMD is based on a low level of evidence and more research has been recommended (Nici et al., 2006; Hull et al., 2012).

1.2 Problem statements

There are marked inequalities in healthcare services and access to specialist care within the SA health system, and it is unclear what knowledge and experience SA physiotherapists have with regard to NMD clinical management guidelines in different contexts. Effective, readily available, cost-effective, and simple strategies to optimise pulmonary function in children with NMD across the socio-economic spectrum have not been investigated in the SA context. Inspiratory muscle training is a cheap and readily available modality, which could potentially minimise associated pulmonary morbidity; reduce unpleasant respiratory symptoms such as dyspnoea; improve exercise tolerance and physical activity levels; decrease the risk of intercurrent infections and improve HRQoL in patients with NMD (Wanke et al., 1994; McCool & Tzelepis, 1995; Gozal, 2000; Silva, Pedrosa, Azevedo, Forbes, Fregonezi, Junior & Ferreira, 2019).

However, the efficacy of IMT in improving these pulmonary outcomes is still not clear and effects may be dose-dependent, according to the number, frequency and intensity of training. Furthermore, the effects of IMT among individual patients may be highly variable, depending on the type of NMD and associated pathophysiology, respiratory involvement, stage and severity of disease (Nici et al., 2006; Hull et al., 2012; Boentert et al., 2017; Woszezenki et al., 2017; Finkel et al., 2018). Published research on IMT in NMD have mostly included adolescents and/or adult participants, with a variety of IMT protocols being used (DiMarco et al., 1985; Martin, Stern, Yeates, Lepp & Little, 1986; Rodillo et al., 1989; Stern, Martin, Jones, Garrett & Yeates, 1989; Wanke et al., 1994; Gozal & Thiriet, 1999; Winkler et al., 2000; Topin, Matecki, Le Bris, Rivier, Echenne, Prefaut & Ramonatxo, 2002; Yeldan et al., 2008; Wenninger et al., 2019).

Evidence from adolescent and adult research cannot necessarily be extrapolated to children, as the paediatric population has unique anatomical and physiological features indicating the need for children to be included in clinical trials (Schechter, 2007; Woszezenki et al., 2017; Toussaint et al., 2018). Furthermore, some NMD progress faster than others (e.g. SMA type I and II) and some patients might not survive until adolescence (Gozal, 2000; Piper & Moran, 2006).

In the SA context, it is of utmost importance to not waste scarce resources on management strategies that do not have an evidence-based foundation. The limited evidence base currently available for the management of paediatric patients with NMD creates a situation where this vulnerable population may receive interventions that have not been adequately tested on similar aged patients in the same socio-geographical context. There are no studies investigating the utility and clinical effectiveness of IMT for children with NMD in the SA context.

1.3 Purpose and objectives of the study

The primary purpose of this study was:

- a) to describe SA physiotherapists' knowledge and respiratory management strategies for patients with NMD; and
- b) to determine the effect of IMT on clinical outcomes and HRQoL in children with NMD and respiratory muscle weakness.

1.3.1 Aims and objectives

This thesis describes four phases of research:

Phase 1: Survey on respiratory management in children with neuromuscular disease

This phase of the study aimed to describe SA physiotherapists' perceived respiratory standard of care for the management of non-ventilated paediatric and adolescent patients with NMD in both an acute and chronic setting, using their knowledge of evidence-based care guidelines as well as clinical expertise. Furthermore, this survey aimed to describe the clinical respiratory management techniques used by SA physiotherapists, for children with NMD.

The specific objectives for the survey were:

- To describe the bio-demographic and work-related context of SA physiotherapists with a special interest and/or expertise in children with NMD.

- Using case scenarios, to describe SA physiotherapists' perceptions of optimal respiratory standards of care in non-ventilated children (5-18 years old) in an acute (hospital) and chronic (home or institution) setting, specifically regarding:
 - Ventilatory support
 - Secretion mobilisation (peripheral ACT)
 - Cough augmentation (proximal ACT)
 - Respiratory muscle training
- To describe the spectrum of respiratory management techniques used by SA physiotherapists for children with NMD in both an acute and chronic setting.

Phase 2: Inspiratory muscle training - Systematic review

A preliminary search indicated limited research available to guide clinical practice on IMT in children with NMD. The aim of this phase was therefore to perform a systematic literature review to determine the safety and efficacy of IMT using an external device (threshold, resistance or flow) on pulmonary function and HRQoL in children (5-18 years) with NMD and respiratory muscle weakness.

The specific objectives for the systematic literature review were:

- To describe the effect of IMT on morbidity including hospitalisations, respiratory infections (based on the need for antibiotics) as well as any adverse events attributed to IMT such as disease progression, desaturation, cardiac failure, muscle fatigue, muscle fibre damage, hyperinflation and barotrauma (pneumothorax) (primary outcomes).
- To describe the effect of IMT on pulmonary function including spirometry, cough ability, inspiratory muscle strength and endurance, exercise capacity, dyspnoea scores as well as the effect on HRQoL measured by any standardised measure (secondary outcomes).

Phase 3: Inspiratory muscle training - Pre-experimental, pilot study

The primary aims of this pre-experimental, pilot study of IMT in children with NMD were to establish the suitability of the proposed data collection process within the SA context, the assessment tools (such as Pimax, SNIP) and the IMT protocol; to describe and, if necessary, mitigate any adverse events associated with IMT in children with NMD and to optimise safety before the commencement of the planned cross-over clinical study.

The secondary aim of phase 3 was to describe the implementation and effects of a six-week IMT programme on clinical outcomes and HRQoL in children (5-18 years) with NMD, presenting with respiratory muscle weakness.

The specific objectives for the pre-experimental, pilot study were:

- To describe any adverse events¹, the number of hospital admissions and respiratory infections and/or complications (frequencies) that require antibiotics (confirmed by a blinded medical practitioner) during the six-week IMT intervention programme (primary outcomes).
- To describe the change over time (pre-and post-intervention) of pulmonary function measures, including spirometry (lung volumes and flow such as VC, FVC and forced expiratory volume in one second (FEV₁)), cough efficacy (PECF) and inspiratory muscle strength (Pimax; SNIP; peak inspiratory flow (PIF)); and strength-index (S-index) (secondary outcomes).
- To describe the change over time (pre-and post-intervention) of motor function, including upper limb function (Brooke scale), lower limb function or ambulation (Vignos scale) and upper limb function and coordination (Motor Function Measure (MFM)) (secondary outcomes).
- To describe the change over time of HRQoL of the participant and their caregiver (proxy) measured with the age-appropriate Pediatric Quality of Life Inventory (PedsQL) (secondary outcomes).
- To describe the association between participants' pulmonary function and motor function (upper limb function and coordination, lower limb function) (secondary outcomes).
- To describe participant and clinician (physiotherapist) satisfaction with the research process, data collection procedure and intervention (IMT).

Phase 4: Inspiratory muscle training – Cross-over randomised controlled trial

The aim of the cross-over randomised controlled trial was to determine the effects of a three-month IMT programme on clinical outcomes and HRQoL in SA children (5-18 years) with NMD, presenting with respiratory muscle weakness.

¹ Including, but not limited to, mild to moderate adverse events such as chest pain/discomfort (hyperinflation/barotrauma), nausea/vomiting, fatigue and gastric distension; severe adverse events such as pneumothorax, desaturation, bradycardia, muscle damage, disease progression/muscle deterioration, cardiac arrest, respiratory failure, bleeding and death.

The specific objectives for the randomised controlled cross-over trial were:

- To describe any adverse events related to IMT², the number of hospital admissions and respiratory infections and/or complications (frequencies) that require antibiotics (confirmed by a blinded medical practitioner) and whether there is any significant difference between the IMT intervention (experimental) and non-intervention (control) period (primary outcomes).
- To determine whether there is a change over time (pre-to post intervention) in spirometry (lung volumes and flow such as VC, FVC and FEV₁), measures of cough efficacy (PECF), and inspiratory muscle strength (Pimax, SNIP) between the intervention (experimental) and non-intervention (control) periods.
- To describe any associations between participants' pulmonary function and their upper limb (Brooke scale) and lower limb function (Vignos scale), and coordination (MFM).
- To determine if there is a significant difference in change over time in HRQoL (PedsQL) between the intervention (experimental) and non-intervention (control) periods.
- To describe the carry-over effect on pulmonary function, motor function and HRQoL over a three-month monitoring period post-intervention.

For the randomised controlled trial the following hypothesis statement was applicable:

H₀ (null) hypothesis: There is no significant difference between the intervention period (IMT) as compared to the non-intervention (control) period for the primary and secondary objectives.

H₁ (alternative) hypothesis: There is a significant difference between the intervention period (IMT) as compared to the non-intervention (control) period for the primary and secondary objectives.

1.4 Significance of the study

Clinical practice guidelines in NMD have been published since 2004, with updated recommendations published in 2010, 2012 and 2018 (Finder et al., 2004; Wang et al., 2007; Bushby et al., 2010; Wang et al., 2010; Hull et al., 2012; Birnkrant et al., 2018; Chatwin et al., 2018; Finkel et al., 2018). South African physiotherapists' knowledge and implementation of these clinical practice guidelines in children with NMD is currently unclear and warrants investigation.

² Including, but not limited to, mild to moderate adverse events such as chest pain/discomfort (hyperinflation/barotrauma), nausea/vomiting, fatigue and gastric distension; severe adverse events such as pneumothorax, desaturation, bradycardia, muscle damage, disease progression/muscle deterioration, cardiac arrest, respiratory failure, bleeding and death.

Identifying where the gaps in knowledge and practice are will inform the need for future research and the development of locally relevant clinical practice guidelines and healthcare policies. The results can also guide training needs at both under- and postgraduate levels, to improve the physiotherapy management SA children with NMD receive, and ultimately to improve the quality of life of this highly vulnerable patient group.

There are limited randomised controlled trials conducted in children with NMD (Birnkrant et al., 2018). This study will add to the body of international evidence by determining the safety, practicality, acceptability and efficacy of IMT when used as an adjunct to standard care in SA children with NMD.

1.5 Outline of the thesis

The chapters of this thesis are outlined in Figure 1.6.

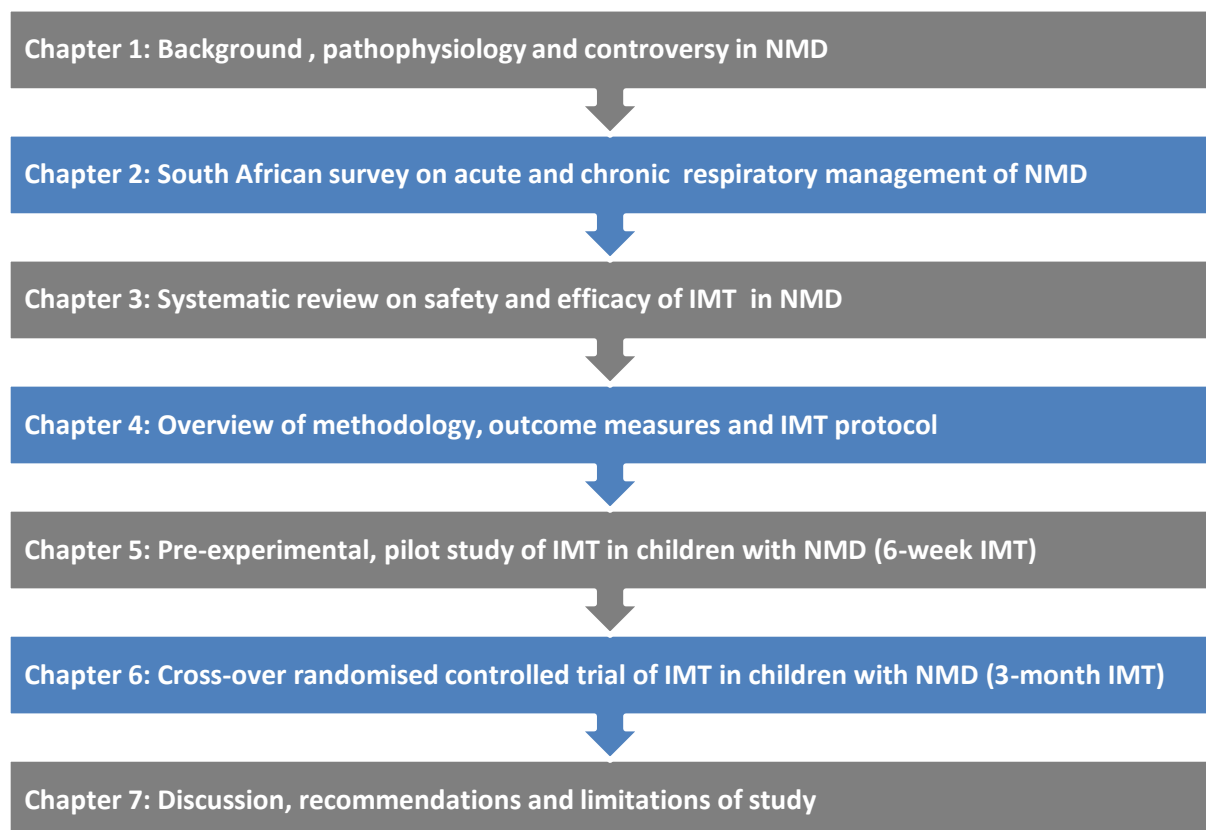


Figure 1.6: Outline of thesis chapters.

IMT=Inspiratory muscle training; NMD=neuromuscular disease.

Initially, a survey (Chapter 2), was conducted among SA physiotherapists with a special interest in cardiopulmonary rehabilitation and/or paediatric practice, to establish their opinions, based on research, knowledge and clinical experience, regarding the appropriate respiratory management of non-ventilated children with NMD in acute and chronic settings. In addition, the survey described the respiratory management techniques used by SA physiotherapists in this setting.

Although some participants recommended using IMT, those participants who reported having recently worked with children with NMD did not use these devices. Following the above survey study, a systematic review (Chapter 3), using Cochrane methodology is reported, which describes and synthesises the literature available on IMT in children and adolescents with NMD and the recommended intensity, frequency and duration for such a training protocol. Using the findings from the systematic literature review, along with clinical expertise and consultation with national and international experts, an IMT protocol was developed (Chapter 4).

To establish the practicality and acceptability of the intervention, as well as obtaining a preliminary estimate of safety and clinical effect, the IMT programme was piloted over six weeks at two schools in Pretoria (Gauteng province of SA). The effect of the six-week programme on motor function, pulmonary function and HRQoL during this pre-experimental, pilot study was reported (Chapter 5).

As no adverse events related to IMT³ occurred during the pre-experimental, pilot study and preliminary clinical findings were positive, a cross-over randomised controlled trial was implemented. Twenty-three children with NMD from Gauteng and the Western Cape participated in a multi-centre cross-over trial for either six or nine months, depending on their group allocation. The data collection period for the cross-over trial was approximately two years. The study described the safety and determined the clinical effect of a three-month IMT programme on respiratory morbidity, motor function, pulmonary function and HRQoL (Chapter 6).

Finally, Chapter 7 presents a summary of findings, conclusions, and recommendations for both clinical practice and further research arising from this series of studies.

³ Including, but not limited to, mild to moderate adverse events such as chest pain/discomfort (hyperinflation/barotrauma), nausea/vomiting, fatigue and gastric distension; severe adverse events such as pneumothorax, desaturation, bradycardia, muscle damage, disease progression/muscle deterioration, cardiac arrest, respiratory failure, bleeding and death.

1.6 Conclusion

This chapter provided an overview of NMD, the aims and objectives and the context in which this study was conducted. In this chapter, the underlying pathophysiology of NMD and how it relates to the cough mechanism was explained. Physiotherapy intervention in patients with NMD aims to reduce distressing symptoms, optimise function and participation, improve HRQoL and reduce healthcare costs (Nici et al., 2006). Factors such as time of onset of the NMD, the severity of denervation and intensity of exercise need to be considered when planning a patient's pulmonary rehabilitation programme (Aboussouan, 2009; Woszezenki et al., 2017). Chapter 2 will describe SA physiotherapists' knowledge and perceptions regarding respiratory management strategies in NMD as well as the physiotherapy techniques that are currently used for SA children living with NMD.

Chapter 2: WHAT DO THE PHYSIOTHERAPISTS HAVE TO SAY?

A South African survey about acute and chronic respiratory management of children with neuromuscular disease

This chapter describes the results from a South African (SA) survey on the knowledge and perspectives of physiotherapists with a special interest in the field of cardiopulmonary and/or paediatric practice, regarding acute and chronic respiratory management in children with neuromuscular disease (NMD). This chapter also outlines the management strategies used by physiotherapists for patients with NMD in the hospital and/or out-patient setting and describes the findings within the context of current clinical practice guidelines and other relevant literature.

2.1 Background and introduction

Evidence-based physiotherapy is informed by relevant, high quality research, patient preference and the physiotherapist's knowledge and experience (Woolf, Grol, Hutchinson, Eccles & Grimshaw, 1999; Herbert, 2005). In recent years, physiotherapy practice has changed from being based on doctor instruction, intuition and clinical expertise to the use of evidence-based practice (EBP) (Herbert, 2005). Evidence from well-performed clinical trials and rigorously developed clinical practice guidelines need to be available to implement EBP (Woolf et al., 1999; Schechter, 2007; Chatwin, Gonçalves, Gonzalez-Bermejo, Toussaint, Benditt, McKim, et al. 2020). Practice guidelines can assist healthcare practitioners and patient decision-making for appropriate healthcare, within specific clinical contexts, particularly for vulnerable and neglected populations (Woolf et al., 1999; Stander et al., 2020). The implementation of evidence-based strategies are highly valued in respiratory care, but their indications and implementation differ among various contexts (Rosiere et al., 2009). Respiratory care protocols, based on patient, process and financial outcome are essential to guide clinical practice (McCool & Rosen, 2006; Volsko, 2013). Development of standard of care guidelines and promotion of health should therefore be done in collaboration with patients, academics, regulators, policy makers as well as national and international experts (Woolf et al., 1999; HMI, 2019).

Although patients with NMD have normally functioning muco-ciliary mechanisms at birth, their cough is affected by respiratory muscle weakness and they may experience additional difficulty with airway clearance, especially during acute respiratory tract infection (Chatwin et al., 2003; Finder et al., 2004; Panitch, 2006; Gauld, 2009; Finder, 2010; Chiang et al., 2018). It is postulated that many respiratory complications leading to morbidity and mortality in children with NMD can be prevented and treated (Hill, 2002; Kirk, 2006; Finder, 2010).

Non-pharmacological respiratory management of children with NMD, presenting with respiratory muscle weakness and ineffective cough, is therefore of great importance (Balachandran, Shivbalan & Thangavelu, 2005; Farrero et al., 2013; Boentert et al., 2017; Chatwin et al., 2018). Airway clearance techniques aim to improve airway clearance, gas exchange, lung mechanics and preventing secondary complications such as atelectasis (Bhowmik et al., 2009; Finder, 2010; Finkel et al., 2018). Manual airway clearance techniques such as percussions, vibrations, postural drainage (PD), positioning and breathing exercises aim to mobilise secretions from the peripheral airways; whereas proximal ACT (cough augmentation) and suctioning can assist with removing secretions from the central airways (McCool & Rosen, 2006; Bhowmik et al., 2009; Hull et al., 2012; Auger et al., 2017; Mercuri et al., 2018; Toussaint et al., 2018).

Although approximately one in every 1200 people in SA may be affected by NMD (Morrow et al., 2019), cough assist devices such as mechanical insufflation-exsufflation (MI-E) are costly and might not be readily available because of resource constraints and variation in the implementation of respiratory management strategies (Chatwin et al., 2018; Castrillo et al., 2019). Due to the rarity and broad spectrum of clinical presentations in NMD, the availability of systematic reviews and randomised controlled trials to guide clinical practice, especially among children, remain limited (Moseley, Herbert, Sherrington & Maher, 2002; Hull et al., 2012; Straub, 2013; Woszezenki et al., 2017).

2.2 The role of physiotherapy in patients with neuromuscular disease within the South African healthcare context

South Africa is a democratic state in which human dignity, equality and advancement of human rights are respected, promoted and protected in terms of the Constitution of the Republic of SA, 1996 (Department of Health (DoH), 2015). The Bill of Rights in Section 27 of the Constitution (1996) emphasises that access to healthcare is a basic human right and the Department of Health (DoH) strives to provide a long and healthy life for all South Africans, as set out in the National Health Act (2003) (DoH: <https://www.gov.za/about-sa/health>). With this in mind, the proposed National Health Insurance (NHI) programme aims to ensure that all South Africans have access to good quality healthcare services provided by the public and private healthcare sectors (DoH: <https://www.gov.za/about-sa/health>). The management of the health workforce in SA is guided by various policies, including the White Paper on Transformation of Health Services (https://www.who.int/workforcealliance/031616south_africa_case_studiesweb.pdf?ua=1; DoH, 1997: https://www.gov.za/sites/default/files/gcis_document/201409/17910gen6670.pdf).

Once qualified, SA physiotherapists are required by law to register with a regulatory body, the Health Profession Council of SA (HPCSA)

(https://www.who.int/workforcealliance/031616south_africa_case_studiesweb.pdf?ua=1). In SA, physiotherapy training consists of a four-year degree, followed by one year of compulsory community service within the public health sector setting, after which physiotherapists can be sanctioned for independent practice

(https://www.who.int/workforcealliance/031616south_africa_case_studiesweb.pdf?ua=1).

Independent practitioners are viewed as “generalists” and can work within all fields of the profession including sport, orthopaedics, cardiopulmonary care and paediatrics. The HPCSA (Professional Board of Physiotherapy, Podiatry and Biokinetics) regulates the physiotherapy profession regarding registration, education (training), professional and ethical conduct/behaviour to ensure continued professional development and adherence to healthcare standards (DoH: <https://www.gov.za/about-sa/health>).

It is important to note that any registered physiotherapist in the SA healthcare system may provide respiratory management to patients with NMD. To remain registered with the HPCSA and practice in SA, physiotherapists need to accumulate 30 Continuous Professional Development (CPD) points per annum, of which five points must be related to ethics, human rights and medical law (World Physio: <https://world.physio/membership/south-africa>). Improved knowledge or obtaining qualifications in areas such as paediatrics and cardiopulmonary rehabilitation is dependent on an individual’s self-directed learning and attendance of CPD accredited courses. Specialisation in the physiotherapy profession is not formally recognised in SA, but post-graduate special interest courses and tertiary academic qualifications in most fields are available and advanced practice post-graduate qualifications are registerable with HPCSA (Personal communication, SASP (2019)).

Clinical practice guidelines for the standard respiratory management of children with a range of NMD are available (Finder et al., 2004; Nici et al., 2006; Wang et al., 2007; Bushby et al., 2010; Wang et al., 2010; Hull et al., 2012; Farrero et al., 2013; Birnkrant et al., 2018; Finkel et al., 2018). These guidelines provide patients, their caregivers and healthcare professionals with up to date, evidence-based information and management strategies, and may improve health-related quality of life (HRQoL) and survival (Finder et al., 2004; Guglieri & Bushby, 2011; Farrero et al., 2013; Straub, 2013; Panitch, 2017; Birnkrant et al., 2018; Finkel et al., 2018).

There is currently no system in place to ensure the implementation or use of existing NMD clinical practice guidelines in either the public or private healthcare sector in SA, and neither the familiarity physiotherapists have with these guidelines, nor the extent to which such guidelines are implemented is known.

2.3 Aims and objectives of the survey

The purpose of this survey was to describe the respiratory standard of care for acute and chronic management of non-ventilated children with NMD, based on SA physiotherapists' knowledge of evidence-based care guidelines and clinical expertise, as well as management strategies used in SA. The specific objectives are outlined in Chapter 1 (1.3.1).

2.4 Significance of the study

Consistency in implementing standard NMD clinical practice guidelines can improve the quality of health care and patient outcomes whilst decreasing ineffective management strategies, thereby potentially improving HRQoL and reducing patient morbidity and mortality (Woolf et al., 1999; Guglieri & Bushby, 2011; Mercuri et al., 2012). Although the essential role of respiratory management in NMD has been recognised by caregivers and healthcare professionals, secretion clearance management has received relatively little attention and clinical management strategies are diverse (Wang et al., 2010; Straub, 2013; Chatwin et al., 2018). This survey describes the knowledge of physiotherapists in SA regarding evidence-based respiratory management in NMD, in order to determine if these strategies correlate with international trends and existing clinical practice guidelines (Finder et al., 2004; Wang et al., 2007; Bushby et al., 2010; Wang et al., 2010; Hull et al., 2012; Birnkrant et al., 2018; Chatwin et al., 2018; Finkel et al., 2018).

This survey aimed to establish the current respiratory “standard of care” for children with NMD in SA so that gaps in knowledge/clinical practice can be identified to guide future clinical trials in this subgroup of patients (Chapter 5 and 6).

Results from this survey may be used to inform healthcare managers and policy makers, in planning appropriate and equitable access to high quality healthcare, under the new SA healthcare system (NHI). Furthermore, the results can be used as a foundation for future research and to identify under- and postgraduate training needs in SA.

2.5 Methodology

2.5.1 Research design

A quantitative, cross-sectional descriptive research study design was implemented. The self-constructed questionnaire was based on literature and clinical expertise and was thereafter distributed to an expert panel consisting of pulmonologists, neurologists, a paediatrician and respiratory physiotherapists from Red Cross War Memorial Children's Hospital (RCWMCH) and Doctor George Mukhari Academic Hospital (DGMAH) and/or Sefako Makgatho Health Sciences University (SMU) for input (Appendix Ai).

2.5.2 Sample and participants

A non-probability purposive sampling frame was used to collect information from physiotherapists with experience working with children with NMD. The target population consisted of all physiotherapists registered with the SA Society of Physiotherapy (SASP), with a self-identified special interest in Cardiopulmonary rehabilitation (CPRG) and/or Paediatrics who were members of either one or both of these special interest groups.

Based on publications, presentations and known expertise in the field of respiratory paediatrics, local experts who were not members of the abovementioned special interest groups were identified and also invited to take part in the survey as their input could provide valuable information. The participants were from various vocational contexts, including the public health sector, specialised hospitals, special schools and private practice.

2.5.2.1 Eligibility criteria

If a participant indicated at the start of the survey that they had not previously worked with children and/or adolescents with NMD, or did not have expertise in this field, they were excluded from completing the questionnaire.

2.5.2.2 Population and sample size

The questionnaire was distributed to the entire population (N=519) of the two special interest groups of SASP, with a self-identified interest in Cardiopulmonary (n=256) and Paediatric (n=263) practice. However, 50 of these were dual memberships, leaving a total of 469 physiotherapists. Six additional physiotherapists with experience in NMD and respiratory management, who were not members of the included special interest groups, were purposively invited to participate (Appendix Aii). This brought the total of physiotherapists who received the questionnaire to 475.

2.5.3 Development of questionnaire and input from an expert panel

The self-constructed questionnaire used in this survey was based on literature, clinical practice guidelines and clinical expertise (Chatwin et al., 2003; Finder et al., 2004; HO, 2005; Nici et al., 2006; Chatwin & Simonds, 2009; Bushby et al., 2010; Hull et al., 2012; Morrow et al., 2013; Farrero et al., 2013) (Table 2.1).

After developing the questionnaire, it was distributed to the supervisor, research assistant (LC) and an expert panel from both institutions (RCWMCH and DGMAH/SMU) during 2015/2016, to provide input on content and face validity. During the first round of assessment, the selected experts critiqued the questionnaire and their corrections and recommendations were discussed and implemented. Members included in the expert panel and their detailed responses (first and second round of feedback) are reflected in Appendix Aiii. During the second round, the experts confirmed they were satisfied with the changes, whereafter the questionnaire was piloted (n=5) (Appendix Aiv).

The final questionnaire consisted of four sections (Appendix Av):

Section A described the demographic data, vocational background and years of experience in the field of NMD.

Section B outlined what participants viewed as standard respiratory management strategies for patients with NMD in an acute (hospital) setting, based on a case scenario:

“Patient X has been diagnosed with an NMD and is older than five years of age and has recently become wheelchair-bound⁴. He has been admitted to the hospital due to a respiratory infection and is presenting with a weak cough. He is haemodynamically stable, but oxygen saturation is 91%, and he is retaining secretions due to an ineffective cough”.

⁴ To note: although “wheelchair-bound” was the original term used in the questionnaire, the researcher was made aware of the preferred terminology as “non-ambulant”, and has since rather used this throughout the thesis document and manuscripts.

The four subdivisions of Section B asked questions relating to general respiratory care (including ventilator support), peripheral ACT (secretion mobilisation), proximal ACT (cough augmentation) as well as other physiotherapy and general management strategies related to children with NMD during acute care. The specific components of these sections are outlined below:

General respiratory management strategies

- Mechanical ventilatory support
- Supplementary oxygen
- Nebulisation
- 24-hour postural management

Peripheral airway clearance techniques (secretion mobilisation)

- Percussions
- Vibrations
- Oscillatory positive expiratory pressure
- Postural drainage (Trendelenburg vs no Trendelenburg)
- Positioning
- Autogenic drainage (including assisted autogenic drainage)
- Breathing exercises

Proximal airway clearance techniques (cough augmentation)

- Manually assisted cough
- Mechanical insufflation-exsufflation
- Suctioning

Physiotherapy specific and other general management strategies that might be applicable or recommended in this case scenario (open-text questions).

Section C asked questions regarding standard respiratory management strategies for patients with NMD in a chronic (out-patient) setting, based on a case scenario:

“Patient Y has been diagnosed with an NMD and is older than five years of age. He recently became wheelchair-bound⁵ and attends follow-up visits to the Neuro clinic every 3-6 months, depending on the need. Currently, his Vital Capacity is <80% predicted value for his age and he presents with a weak cough”.

⁵ To note: although “wheelchair-bound” was the original term used in the questionnaire, the researcher was made aware of the preferred terminology of “non-ambulant”, and has since rather used this throughout the thesis document and manuscripts.

The four subdivisions of this section about the patient's home programme included questions about muscle training and lung compliance, secretion mobilisation, airway clearance techniques/cough augmentation, ventilatory support as well as other physiotherapy and general management strategies related to children with NMD during chronic management. The specific components of these sections related to the patient's home programme are outlined below:

Muscle training and lung compliance

- Breath-stacking
- Inspiratory muscle training
- Expiratory muscle training
- Breathing exercises

Peripheral airway clearance techniques (secretion mobilisation)

- Nebulisation
- Oscillatory positive expiratory pressure
- Percussions
- Vibrations
- Postural drainage (Trendelenburg vs no Trendelenburg)
- Positioning
- Autogenic drainage (including assisted autogenic drainage)

Proximal airway clearance techniques (cough augmentation)

- Manually assisted cough
- Mechanical insufflation-exsufflation
- Suctioning

Ventilatory support

- Non-invasive ventilation (e.g. Continuous positive airway pressure and Bi-level positive airway pressure)
- Supplementary oxygen
- 24-hour postural management

Physiotherapy specific and other management strategies that might be applicable or recommended in this case scenario (open-text questions).

Section D requested those participants working in the field of NMD to describe the respiratory management strategies they had used/applied in their own setting, over the last six months.

The subdivisions of this section enquired about respiratory management strategies recently used in the hospital (acute setting) as well as what was used as part of the patients' home programme (chronic setting).

For **acute management**, participants were asked which peripheral ACT (secretion mobilisation), proximal ACT (cough augmentation) and other respiratory management strategies they had used in the past six months:

- Percussions
- Vibrations
- Postural drainage (including adapted postural drainage)
- Positioning
- Autogenic drainage (including assisted autogenic drainage)
- Breathing exercises
- Suctioning
- Nebulisation
- Breath-stacking

Proximal ACT (cough augmentation) techniques implemented:

- Manually assisted cough
- Mechanical insufflation-exsufflation

Other related physiotherapy management strategies:

- 24-hour postural management
- Supplemental oxygen

For **chronic management**, participants were asked which lung volume recruitment (LVR) and respiratory muscle training techniques, peripheral ACT, proximal ACT and other management strategies they had used in the six months before the survey:

Lung volume recruitment and respiratory muscle training:

- Breath-stacking
- Inspiratory muscle training
- Expiratory muscle training
- 24-hour postural management

Peripheral ACT (secretion mobilisation):

- Nebulisation
- Oscillatory device
- Percussions
- Vibrations
- Postural drainage (including adapted postural drainage)
- Positioning
- Autogenic drainage (including assisted autogenic drainage)
- Suctioning

Proximal ACT (cough augmentation):

- Manually assisted cough
- Mechanical insufflation-exsufflation

Other techniques/respiratory management strategies used.

2.5.4 Procedure

The procedure followed in the development, piloting and distribution of the questionnaire is outlined in Figure 2.1.

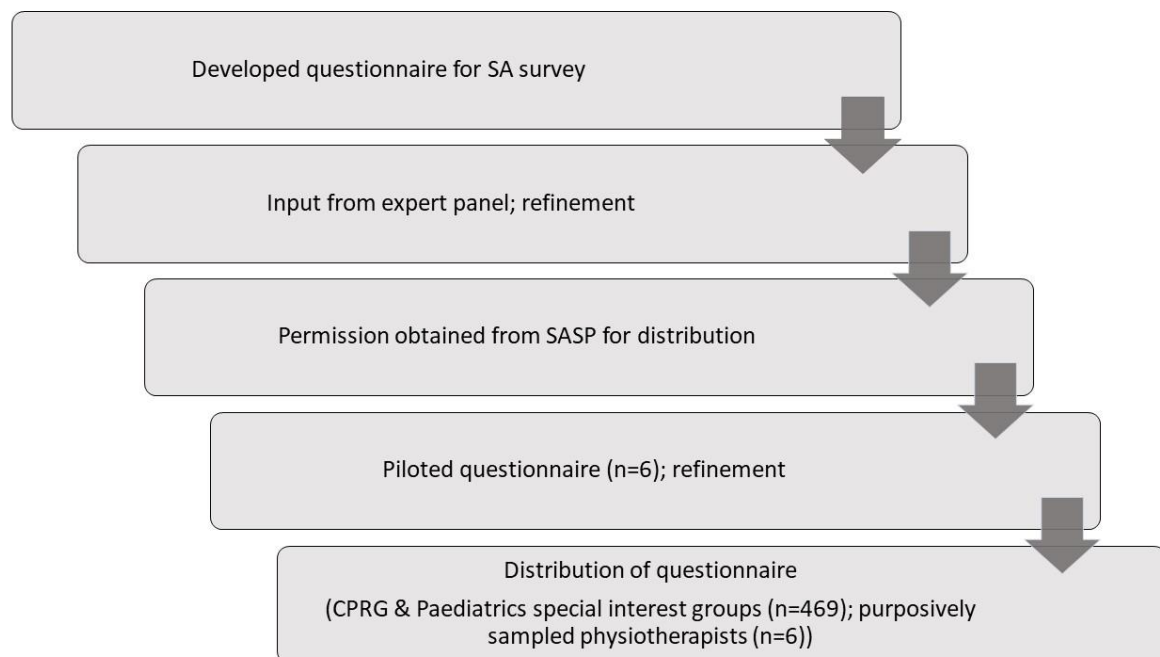


Figure 2.1: Procedure for a standard of care survey conducted among South African physiotherapists.

2.5.5 Pilot study

After consensus and confirmation from the expert panel were received (content validity), the questionnaire was piloted (Figure 2.1). The pilot study aimed to determine the approximate time for completion and if questions were clear and unambiguous (face validity). Six physiotherapists with known expertise in NMD (n=6), who were either not members of the SASP at the time, or were SASP members, but did not belong to one of the two special interest groups (CPRG or Paediatrics), were invited to participate in the pilot study. By implication, these physiotherapists would not receive the survey once distributed, as they did not form part of the specified population (Appendix Aii).

Five of the selected physiotherapists responded and one physiotherapist did not respond, despite numerous attempts. The five pilot study participants were provided with an information letter questionnaire (either hand delivered/provided electronically) as well as a feedback sheet requesting input about the completion time, face validity and clarity of questions (Appendix Avi; Appendix Avii).

The data from the pilot study were planned to be used in the final data analysis if there were no subsequent substantial changes to the questionnaire or research process. The time to completion ranged from 12 to 60 minutes and four participants (80%) stated that the questions were clear and unambiguous.

Regarding face validity, participants noted that there was a logical flow of questions, the lay-out was clear and regarding content, all aspects of ACT (previously referred to as chest physiotherapy) had been covered. General suggestions made after the pilot study included minor rephrasing (differentiation between the standard of care and current management), technical formatting and additions to options available (“unsure” and “patient dependent”), as well as adding open-ended spaces at the end of each section of the questionnaire for additional comments/elaboration.

A detailed outline of the feedback from pilot study participants can be found in Appendix Avii. Data provided by the pilot study participants (n=5) were captured in an Excel spreadsheet for analysis. A summary of the development and adaptations made to the questionnaire is provided (Table 2.1).

Table 2.1: Development and revision of the questionnaire.

Section (Questions)	Reference (literature)	Amendments post expert panel review and pilot study
General Resp Management		
Mechanical ventilatory support -NIV (general) -BiPAP -CPAP	(Finder et al., 2004; Anderson et al., 2005; McCool & Rosen, 2006; Nici et al., 2006; Rosiere et al., 2009; Ishikawa, Miura, Ishikawa, Aoyagi, Ogata, Hamada & Minami, 2011)	Bagging/hyperinflation/air stacking added in combination with cough augmentation. Ventilation/support: frequency per treatment; frequency per day; hours per day (range), short term or long-term ventilation were added. CPAP and BiPAP were moved to the non-invasive ventilation section.
Supplemental O ₂	(McCool & Rosen, 2006; Nici et al., 2006; Rosiere et al., 2009)	No amendments.
Nebulisation -saline -bronchodilators	(McCool & Rosen, 2006; Bott, Blumenthal, Buxton, Ellum, Falconer, Garrod, et al. 2009; Straub, 2013)	Used the term mucolytics instead of specific products, for example hypertonic saline, Mistabron etc.
24h postural management	(Bushby et al., 2005; Wang et al., 2007)	24-hour postural management was added for optimisation of respiratory function, for example seating.

Peripheral ACT (Secretion mobilisation)		
Percussion, vibrations	(Tzeng & Bach, 2000; McCool & Rosen, 2006; Hough, Flenady, Johnston & Woodgate, 2010; Hough et al., 2010; Hull et al., 2012)	“Flutter” was changed to oscillatory devices and examples were provided, e.g. Flutter, Acapella.
Section (Questions)	Reference (literature)	Amendments post expert panel review and pilot study
Oscillatory device	HFCWO and IPV (McCool & Rosen, 2006; Panitch, 2006; Hull et al., 2012) Flutter (Anderson et al., 2005; McCool & Rosen, 2006)	HFCWO was removed, as not used in SA and limited evidence of efficacy.
PD, adapted PD, positioning	(Anderson et al., 2005; Bott et al., 2009; Rous et al., 2014)	Postural drainage and adapted postural drainage was explained (as Trendelenburg and non-Trendelenburg positions).
AD; assisted autogenic drainage (AAD)	(McCool & Rosen, 2006; Bott et al., 2009; Rous et al., 2014)	Assisted autogenic drainage was added (this “passive” technique can be successfully used in infants and young children).
Breathing exercises	Glossopharyngeal breathing (Hull et al., 2012; Wang et al., 2010; Benditt & Boitano, 2013) Various breathing exercises including ACBT (Anderson et al., 2005)	“Please specify” was added as an answer option, if participants stated that they would use breathing exercises.
Proximal ACT (cough assistance)		
Cough assist: MAC	(Finder et al., 2004; McCool & Rosen, 2006)	Write out in full first time when used.

	Patients with expiratory mm weakness (McCool & Rosen, 2006; Anderson et al., 2005; Haas, Loik, & Gay, 2007; Volsko, 2013)	
Cough assist: MI-E	(Finder et al., 2004; Anderson et al., 2005; McCool & Rosen, 2006; Haas et al., 2007; Rosiere et al., 2009; Ishikawa et al., 2011)	Write out in full first time when used.
Suctioning	(Sancho, Servera, Vergara & Marin, 2003 ;Haas et al., 2007; Rosiere et al., 2009)	The suggestion was made to specify suctioning through the nose/mouth, but it was left as suctioning in general.
Muscle training & lung compliance: Breath-stacking/ hyperinflation	(Kang & Bach, 2000; Finder et al., 2004; Nici et al., 2006; Bach et al., 2007; Hull et al., 2012) Air stacking /hyperinflation (improve MIC)(Finder et al., 2004; Anderson et al., 2005; Toussaint et al., 2009; Wang et al., 2010; Benditt & Boitano, 2013)	Added the option of “both”, besides the independent or assisted breath-stacking Also, if “yes” specify the method of breath-stacking.
Inspiratory muscle training (IMT)	(Finder et al., 2004; Nici et al., 2006; Eidenberger & Nowotny, 2014) Respiratory muscle training (Hull et al., 2012)	No amendments.
Expiratory muscle training (EMT)	(Finder et al., 2004; McCool & Rosen, 2006; Haas et al., 2007; Farrero et al., 2013) Respiratory muscle training (Hull et al., 2012)	No amendments.
General		
“University”, “research centre” or “other” (please specify) were added as options for place of work, as a participant could be an expert in the NMD, but might not currently be working in clinical practice. The study aimed to determine what is best practice (based on literature and clinical expertise), therefore physiotherapists (with a special interest in the field) were asked for their input. To gain knowledge on what was currently being done in SA, Section D was added. Participants were asked which techniques they used over the past six months. Change of the case scenarios: specific age was removed; only stated that they were older than five years. Added an option of “unsure” as well as “Patient dependent” (i.e.as per patient need) besides the “Yes” and” No” answers, especially when it came to management strategies (time and frequencies). Added a precautionary measure: namely what needs to be done in the case of cardiomyopathy when applying MI-E. A question was added regarding the prevention and management of complications, or other techniques/modalities that might be applicable in the acute and chronic setting.		

AAD=Assisted autogenic drainage; ACBT=Active cycle of breathing technique; AD=Autogenic drainage; BiPAP=Bi-level positive airway pressure; CPAP= Continuous positive airway pressure; EMT=Expiratory muscle training; IMT=Inspiratory muscle training; MAC= Manually assisted cough; MI-E=Mechanical insufflation-exsufflation; NIV=Non-invasive ventilation; PD=postural drainage; HFCWO=High frequency chest wall oscillation.

Survey Monkey, an online cloud-based software programme, was used to distribute the questionnaires and summarise responses (Survey Monkey: <https://www.surveymonkey.com>). After implementing the corrections (Table 2.1), the online questionnaire was finalised and refined in preparation for distribution.

Thereafter, the final survey link was created (<https://www.surveymonkey.com/r/8RF3F5J>) and distributed by the SASP to physiotherapists with a special interest in the field of cardiopulmonary rehabilitation (respiratory care) and/or paediatrics (Figure 2.1). In addition, the Survey Monkey link was sent via email to the six non-member experts (Appendix Aii).

2.5.6 Ethical considerations and permissions obtained

This survey formed part of this PhD study, which received ethical clearance from the Human Research Ethics Committee of the University of Cape Town (513/2015).

Permission was granted from the SASP President, as well as the chairpersons of CPRG and Paediatric Special Interest Groups to distribute the questionnaire to their members (Figure 2.1), as the Protection of Personal Information (PoPI) Act did not allow the SASP to provide the researcher with the members' email addresses.

2.5.6.1 Informed consent and anonymity

Experts in the field of respiratory management and or/neurology were asked to provide input on the face and content validity of the questionnaire. These experts received a cover letter explaining the aims and objectives of the survey as well as an informed consent form (Appendix Ai) and all provided written informed consent before assessing the questionnaire. After corrections/recommendations were implemented, the panel received a follow-up letter (Appendix Aiv) , before piloting. A cover letter explaining the purpose of the study, together with a feedback sheet, was distributed to the pilot study participants (Appendix Avi).

After the pilot study, the questionnaire was finalised and electronically distributed to the population as previously described. Informed consent was obtained from SASP participants by including study information and a confirming consent statement on the opening page of the Survey Monkey questionnaire. Participants could not continue with the online survey if they did not accept the terms of the study⁶ and provided consent (Appendix Aviii). In the opening statement, participants were reminded that participation was voluntary and completing the survey posed no risk to them. Academics, researchers and/or experts in the field of NMD were eligible to complete the survey although they might not have consulted/treated patients at the time of participating in the survey.

⁶I hereby agree that I have read and understand the abovementioned terms and conditions, and grant my permission that data supplied by myself may be used for research and publishing purposes.

Participants were also provided with the contact details of the researcher if they had any questions or required additional information. One email enquiry was received which was followed up within 24 hours.

The anonymity of participants was ensured as Survey Monkey allocates a unique ID code to each participant, which is not traceable. Anonymity could potentially increase response rates as participants might feel safer disclosing information and their opinions (Anseel, Lievens, Schollaert & Choragwicka, 2010).

2.5.7 Data collection

Six physiotherapists with a special interest in respiratory management, who were not members of CPRG or Paediatrics at the time, were identified (purposive sampling) and requested to participate in the survey (May 2016). A formal invitation letter including the link to the questionnaire was sent to these physiotherapists (Appendix Aii).

The survey system on Survey Monkey was opened for SASP member participation in June 2016. To increase the response rate and emphasise the importance of participation (Nulty, 2008; Anseel et al., 2010), reminder emails were sent from the marketing representative and chairperson to CPRG and Paediatric members respectively. Reminder emails were sent approximately every two weeks for a period of eight weeks. Responses were captured by the Survey Monkey software programme and sent to the researcher via email. These results were already coded, ensuring the anonymity of participants, and the researcher exported the data from Survey Monkey into Excel spreadsheets for data analysis.

2.5.8 Data analysis

The researcher downloaded the completed survey data and manually added the results from the pilot study, whereafter the Excel spreadsheet was exported to statistical software programmes for analysis (STATA (StataCorp, www.stata.com), Statistical Package for the Social Sciences (version 23) and STATISTICA (Data Analysis Software System, Version 12, www.statsoft.com).

Depending on the normality of continuous data (tested using the Shapiro Wilks W and Kolmogorov-Smirnov tests), the relevant parametric or non-parametric statistical tests were applied. Statistical significance was accepted as $p < 0.05$.

Due to the distribution of responses and the variety of answers from participants for “repetitions” and “frequency” of treatment techniques, parametric tests could not be applied. Descriptive statistics were described using frequency tables, proportions and histograms/bar graphs. Chi-square tests and/or Yates χ^2 (depending on the frequencies/responses per cell) were applied to determine the association between vocational background, physiotherapists’ years of experience and respiratory management techniques recommended. Open-ended responses were summarised in tabular form.

2.6 Results

The survey was open to SASP members for a duration of eight weeks (June to July 2016).

2.6.1 Survey response rate

A flow chart of survey responses is presented in Figure 2.2. Considering that only minimal changes were made to the survey following the pilot study, the pilot study data (n=5) were included in the final analysis as planned *a priori*. The link to the survey was distributed online to 469 SASP members and, through purposive sampling, to six experts and the six eligible pilot study participants (N=481). Five (83.3%) pilot study participants completed the questionnaire and 74 physiotherapists (15.6%) initially responded to the general survey distribution (16.4%; 79/481) (Appendix Aix). This response constitutes a margin of error of 10.09%, with a 95% confidence interval (CI) (Check Market: <https://www.checkmarket.com/sample-size-calculator/>). The number of responses however diminished with every section of the questionnaire (Figure 2.2) and the recalculated margin of error was indicated for each.

Three of the initial respondents did not provide consent; two provided incomplete vocational information (Section A) and ten reported that they had not previously worked with children with NMD or had no experience in the field. These 15 participants were therefore excluded and the final sample of 64 responses was included in the final analysis (margin of error: 11.42%) which constitutes a response rate of 13.3% (64/481).

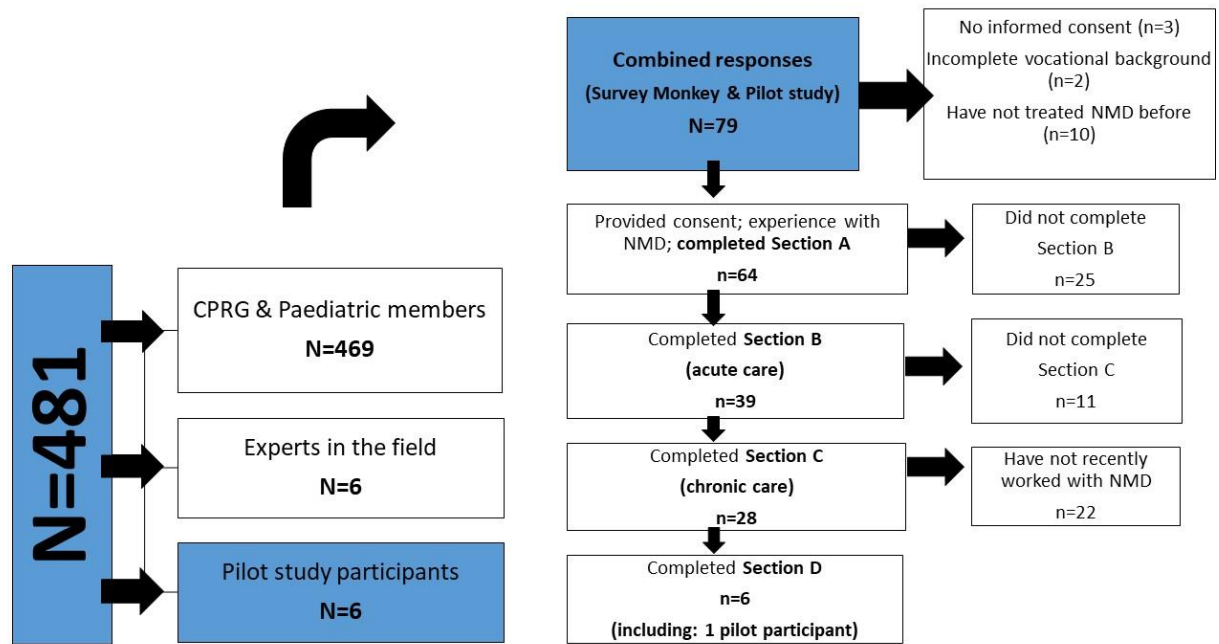


Figure 2.2: Flow chart of combined responses for the pilot study and Survey Monkey.

2.6.2 Section A: Vocational background of participants

Questions on the vocational background (area of work) allowed for more than one option to be chosen by a participant as some physiotherapists worked in more than one area (e.g. in a rehabilitation centre and the hospital wards).

Table 2.2: Vocational background of eligible participants indicated as frequencies and percentages (n=64).

	Hospital wards (general and specialised) n (%)	Special school n (%)	Rehabilitation centre n (%)	University (academic, lecture, researcher) n (%)	Total (n)
Public sector (n=27)	19 (70.37)	5 (18.52)	2 (7.41)	4 (14.8)	30
Private sector (n=32)	19 (51.35)	3 (9.38)	4 (10.81)	1 (2.70)	27
Both public and private sector (n=5)	2 (40)	5 (100)	0	0	7
Total (n=64)	40	13	6	5	64

The majority of the 64 participants worked in the private sector, which included out-patient departments and hospital wards (58%; n=37) as compared to approximately 42% (n=27) working in the public healthcare sector including hospitals (general and specialised), special schools, rehabilitation centres/clinics and universities. Five participants worked in both the private and public healthcare sectors (Table 2.2).

2.6.3 Section A: Years of experience of participants

There were 65 eligible responses to this question (Figure 2.3). Most participants (42%; n=27) reported one to five years of experience working with NMD, and the majority (66%; n=43) of respondents indicated between one to 10 years of experience in this field.

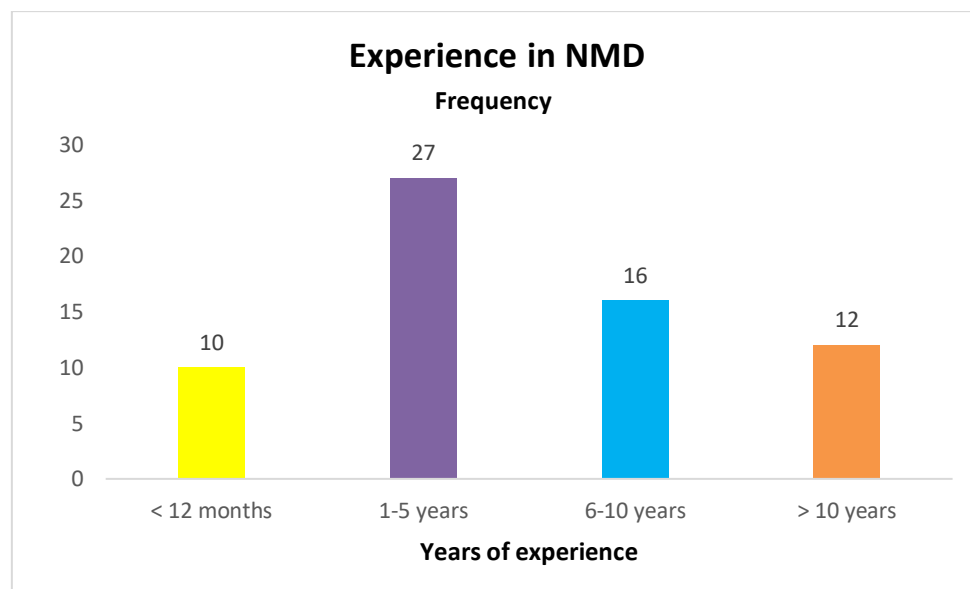


Figure 2.3: Years of experience in patients with neuromuscular disease (n=65).

2.6.4 Section B: Acute care of patients with neuromuscular disease

In Section B of the questionnaire, participants were asked to indicate which respiratory management techniques they thought would be suitable for a child with NMD within an acute or hospital setting.

2.6.4.1 Introduction

This section included questions regarding relevant general respiratory care, secretion mobilisation (peripheral airway clearance techniques), cough augmentation (proximal airway clearance techniques) as well as other physiotherapy and general management techniques relevant to a specific case scenario (Appendix Av).

Some participants did not answer all the questions on acute management; therefore this section presented with a varying number of responses (range n=34 to 44), inclusive of pilot study participants (Figure 2.4), resulting in a margin of error ranging from 16.22%-14.10%. Oscillatory devices were initially not included in this section during the pilot study therefore the maximum possible number of responses for this question was lower.

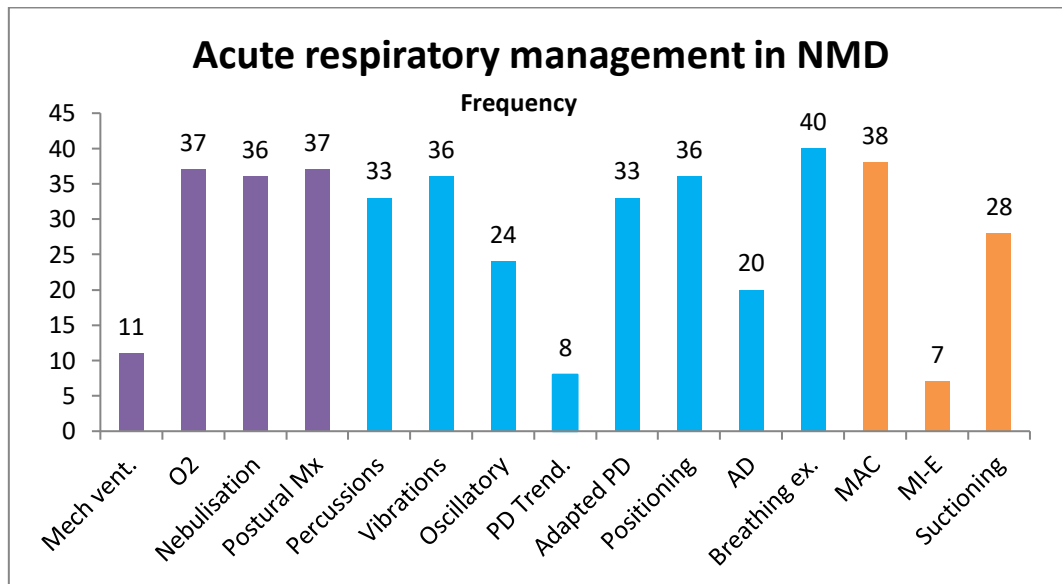


Figure 2.4: Acute respiratory management in patients with neuromuscular disease (n=34-44).

General respiratory care (purple); peripheral ACT (secretion mobilisation) ((blue); proximal ACT (including cough augmentation) (orange).

Under general respiratory care, the most frequent techniques chosen were supplemental oxygen, nebulisation and 24-hour postural management (Figure 2.4). For secretion mobilisation (peripheral ACT), most participants favoured breathing exercises, vibrations and positioning and for cough augmentation (proximal ACT), manually assisted cough (MAC) was strongly supported.

Support for the use of alternative cough augmentation techniques such as mechanical cough assist devices was limited. Twenty-two participants indicated that they were unsure of the usage of MI-E and seven responses were in favour of MI-E, but only two participants provided details regarding the settings such as pressure and time. For a detailed description of the responses for acute management, including frequencies and treatment time, refer to Table 2.3 and Appendix Ax.

2.6.4.2 General respiratory management

Under **general respiratory management** (indicated in purple; Figure 2.4) oxygen supplementation was strongly supported, with the majority (10/37) indicating they would advocate for a level of 40% oxygen, with a flow of either two litres or a range of 2-5 litres per minute (9/37). Most participants also recommended nebulisation using isotonic or normal (0.9%) saline only (16/31), while a few suggested the use of saline in combination with bronchodilators or mucolytics such as Duolin, Combivent, Atrovent/Berotec (4/31). Four participants suggested using hypertonic saline based on the acute management case scenario. Slightly more than half of the participants (16/28) indicated that nebulisation should be used once per treatment and a third recommended a frequency of twice per day (11/34).

To improve ventilation in an acute context, 24-hour postural management was highly supported (37/44); specifically supported sitting, (alternate) side-lying, Semi-Fowler's position/Fowler's/elevation of the head. For mechanical ventilation, most indicated that they would use non-invasive ventilation (NIV) (14/44) as a mechanical ventilation option.

2.6.4.3 Secretion mobilisation (peripheral airway clearance techniques)

For **secretion mobilisation** (indicated in blue; Figure 2.4) the majority of participants agreed they would use manual techniques such as percussions, vibrations, adapted postural drainage (no Trendelenburg positioning), as well as the use of oscillatory devices and breathing exercises (e.g. active cycle of breathing (ACBT) and/or deep breathing exercises). The treatment duration and frequency per day recommended by the majority of participants are outlined in Table 2.3.

Almost a third (9/31) of respondents suggested percussions should be performed for either 10 or 15 minutes, with a recommended frequency of twice per day (23/31). Vibrations were suggested to be performed for a shorter duration per treatment, either five or 10 minutes (12/33) and similar to percussions, almost three quarters supported a frequency of twice per day (24/33).

Postural drainage (Trendelenburg/head-down position) was poorly supported (8/41) and the treatment time varied, however, most suggested PD should be performed twice a day (6/7). Conversely, modified PD without head down position was supported by the majority (33/41). Suggested treatment time varied, mostly 10 or 20 minutes (7/30), for a frequency of twice per day (18/28). Positioning was recommended by most respondents (36/41) with varied responses for the treatment duration, but slightly stronger support was seen for 10 and 30 minutes respectively (6/32).

Performing positioning twice a day was suggested by just over half the participants (15/29). Almost half of the respondents (20/41) recommended using autogenic drainage (AD), including assisted autogenic drainage (AAD), for acute management, while 15 participants were unsure. The frequency of application was mostly recommended as twice per day (13/18).

The use of oscillatory devices during the acute stage of management was well supported by participants (24/36), with two-thirds opting for the Flutter device (16/24).

The specification of application (duration and frequency of oscillatory device use) were not included as part of the questions on acute care. Breathing exercises such as ACBT (18/36) and deep breathing exercises (DBE) (9/36) were recommended by most, either alone or in combination or as an adjunct to other exercises such as forced expiratory technique (FET) or “huffing” and thoracic mobility exercises.

Recommended time for breathing exercises per treatment was mostly five (7/35) and 10 minutes (5/35) respectively, with a frequency of twice per day (18/32).

Table 2.3: Summary of suggested treatment duration and frequencies for peripheral and proximal airway clearance techniques (acute care).

Treatment	Duration per treatment (minutes)	Proportion advocating duration (%)	Frequency (per day)	Proportion advocating frequency (%)
Percussions	10 or 15	9/31 (29)	2	23/31 (74)
Vibrations	5 or 10	12/33 (36)	2	24/33 (73)
Postural drainage (Trendelenburg)	1-20	N/A	2	6/8 (75)
Adapted postural drainage (No Trendelenburg positioning)	10 or 20	7/30 (23)	2	18/28 (64)
Positioning	10 or 20 or 30	8/32 (25)	2	15/29 (52)
Autogenic drainage (including AAD)	5 or 10	6/19 (32)	2	13/18 (72)
Breathing exercises: Active cycle of breathing (including modified ACBT) (18/36); Deep breathing exercises (alone or in combination) (9/36)	5-10	15/35 (43)	2	18/32 (56)
Manually assisted cough	Frequency per treatment: 3-5 or 5 or 5-10 coughs per treatment	6/32 (19)	Patient dependent	27/38 (71)
Mechanical insufflation-exsufflation	Only two participants answered the questions regarding the pressures, sets and repetitions	-	-	-
Suctioning	Frequency per treatment: 1 (once)	8/22 (36)	2	10/22 (46)

AAD: Assisted autogenic drainage, ACBT: Active cycle of breathing

2.6.4.4 Cough augmentation (proximal airway clearance techniques)

For **cough augmentation** (indicated in orange; Figure 2.4), MAC was the most popular choice, with a combination of thoracic and abdominal compression as the favoured technique (19/38). The frequency for MAC was strongly recommended as patient dependent (27/38) or twice a day (10/38). Regarding the number of coughs to be performed, there was no consensus among the 32 responses (ranging from 2-10 times), however, the majority indicated a minimum of two coughs per treatment and most favoured three to five, five or five to 10 coughs (Table 2.3). As a safety precaution, when asked if MAC should be continued when the patient gets tired, the majority indicated that the technique should be changed (22/38), and some (15/38) indicated that they would rather stop.

Participants were mostly unsure about the use of mechanical cough assistance (22/39) and a very small number of participants commented on the application of MI-E (7/39). Those that recommended MI-E (7/39) preferred the auto mode, specifically the basic auto function. Only two participants provided suggested settings for MI-E, indicating inspiratory pressures ranging from +10 to +20; or +30cmH₂O, and expiratory pressures ranging from 0 to -10; or -30cmH₂O. Insufflation-exsufflation repetitions were recommended as three to five, with five sets or patient dependent, inspiratory time as 2 or 3 seconds or patient dependent, while expiratory time was recommended as one or three seconds. The pause (rest-interval) between sets of insufflation exsufflation was recommended to be 30-60 seconds or two minutes. Both respondents agreed that all settings would be dependent on patient presentation (or as needed). The last question regarding precautions with the use of MI-E showed that 26 participants were “unsure” if they would continue with MI-E if the patient presented with cardiomyopathy, while nine stated that they would rather stop MI-E.

Suctioning as an ACT was strongly supported by most (28/38) for acute management, and the majority recommended suctioning once to twice per treatment (12/26) or patient dependent (6/26) at a frequency of twice (10/22) or as needed by the patient (8/22), per day (Table 2.3).

2.6.4.5 Open-ended responses (acute management)

Five open-ended questions in Section B provided relevant additional information. A detailed description can be found in (Appendix Ax).

The first open-ended question asked participants to describe other general respiratory management techniques that might be relevant during the acute management phase.

Twelve participants provided an answer under this section, but one response was “No” indicating that in this person’s view no other techniques would be relevant. In addition to what was already mentioned in the survey, the remaining 11 responses suggested the use of breathing exercises and breathing control, respiratory muscle training, blow bottle (Positive expiratory pressure (PEP)), facilitating mobility (activities of daily living) and providing advice and/or a home programme. Secondly, 12 respondents commented on additional techniques related to secretion mobilisation. The main emphasis from responses was on mobilisation (change of position, thoracic/upper limb mobility) as well as breathing exercises including huffing, breath-stacking, ACBT and PEP such as blow bottle/windmill blowing.

Regarding airway clearance techniques, including cough augmentation, the emphasis from 12 respondents was mainly on suctioning, education and precautionary measures (Detailed responses in Appendix Ax). None of the participants recommended alternative cough augmentation techniques such as LVR or GPB. In addition, participants recommended that suctioning be used as an assessment and/or treatment method and should only be used if the patient cannot clear their secretions, even with assistance, for example in young children unable to cough and intubated patients. Training of both the child and caregivers was highlighted as an important part of ACT and that treatment should be tailored to the child’s level of consciousness, cooperation and preferences.

The fourth open-ended question enquired about other physiotherapy techniques that can be implemented to prevent and manage respiratory complications associated with NMD. Most responses referred to mobilisation (including thoracic), active and passive movements, exercises (including respiratory muscle training and DBE) and education (Appendix Ax).

The last open-ended question asked for feedback regarding general recommendations in patients with NMD during the acute stage. The comments included descriptions on nocturnal ventilation, mobilisation, caregiver education and support, as well as carry-over to the home environment.

2.6.5 Section C: Chronic care of patients with neuromuscular disease

In Section C of the questionnaire, participants indicated which respiratory management techniques they felt would be applicable for a child with NMD, within a chronic context (home/school setting).

2.6.5.1 Introduction

This section included questions on ventilation/respiratory support, secretion mobilisation (peripheral ACT), cough augmentation (proximal ACT), respiratory muscle training, breathing exercises and lung compliance as well as other physiotherapy and general management techniques relevant to the specific case scenario. This section was completed by 28 participants, including the pilot study responses (margin of error: 17.99%) and are depicted in Figure 2.5.

Twenty-four-hour postural management techniques, NIV and nebulisation were recommended for ventilation or respiratory support (indicated in **purple**, Figure 2.5). For secretion mobilisation (peripheral ACT) indicated in **blue**, positioning and using oscillatory devices were well supported. Similar to the response for acute management, MAC was very well supported as a cough augmentation technique (**orange**), but four responses were in support of mechanical cough augmentation (MI-E). Under respiratory muscle training and lung compliance, the majority of participants were in favour of inspiratory muscle training (IMT) and breathing exercises (**yellow**).

2.6.5.2 Ventilation/respiratory support

Ventilatory support included NIV (Bi-level positive airway pressure (BiPAP), Continuous positive airway pressure (CPAP)), supplemental oxygen and 24-hour postural management (Figure 2.5). Most participants recommended NIV during chronic management (16/27), in particular nocturnal (7/17) or intermittent ventilation, as required by the patient (9/17). Approximately a third of respondents specifically recommended BiPAP for ventilatory support (10/28), but most were unsure (11/28) regarding the average hours per day, or if nocturnal BiPAP should be prescribed. On the other hand, CPAP was not supported by a similar number of respondents (10/27). Supplemental oxygen usage was supported by just over half of the participants (15/27), but there was no consensus about the dosage to be delivered. Nebulisation was well supported (24/28), especially 0.9% saline or in combination with mucolytics such as mesna/bisolven (10/19). Similar to acute care, respondents recommended nebulisation once per treatment or as needed (9/19), to be performed twice daily or depending on the patient's need (13/20). Most agreed that 24-hour postural management should be used during chronic care, with high or supported sitting particularly recommended (10/15), but no additional recommendations for ventilatory/respiratory support were made.

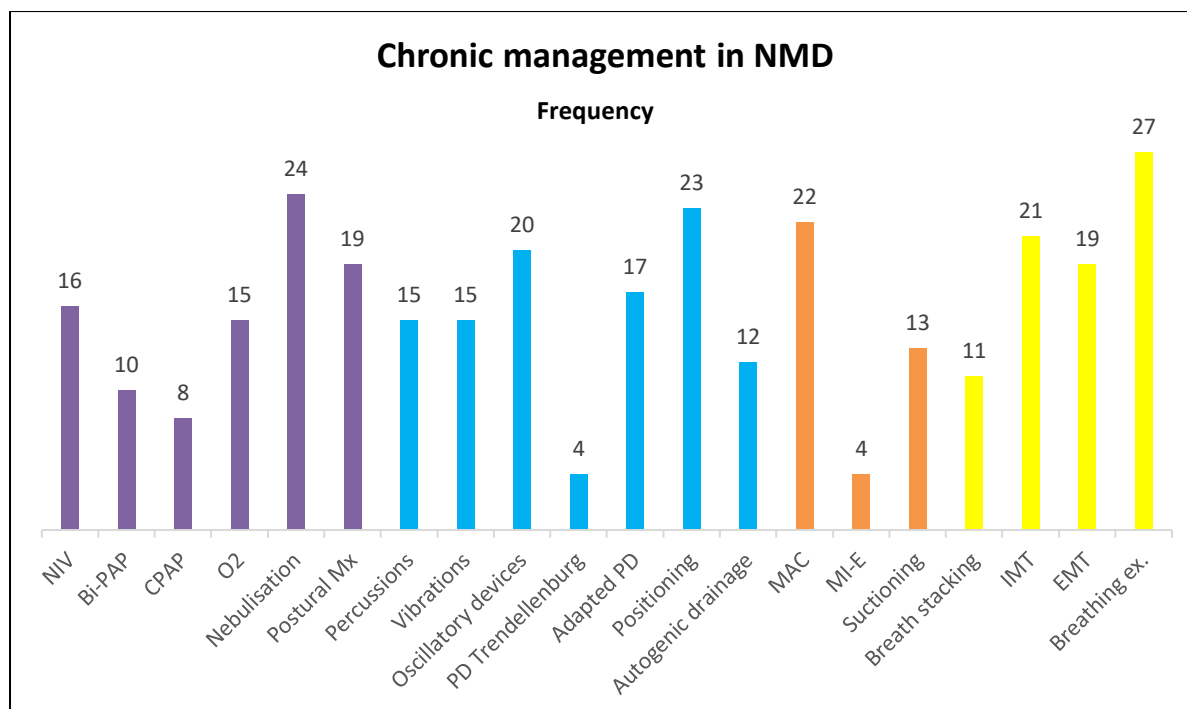


Figure 2.5: Chronic respiratory management in patients with neuromuscular disease (N=28).

Ventilation/respiratory support (purple); peripheral ACT (secretion mobilisation in blue); proximal ACT (including cough augmentation) (orange) and respiratory muscle training and lung compliance (yellow)

2.6.5.3 Secretion mobilisation (peripheral airway clearance techniques)

The use of oscillatory devices, such as Flutter and Acapella was recommended by most (13/18), but there was no consensus about dosage during chronic management with recommendations ranging from once a day (3/18) to ten times daily (4/18); or as needed (3/18). The majority however agreed that oscillatory devices should be used two or three times per day (11/18). Use of percussions was better supported for chronic (15/27) than for acute management; with most suggesting 10 minutes; twice a day (8/12). Similarly, vibrations were recommended by just over 50% of participants (15/28), for five or 10 minutes per treatment (6/12); twice a day (5/12).

Postural drainage (PD) with Trendelenburg/head down tilt was not recommended by most (18/28), but the use of adapted PD (17/28), for either 10 or 20 minutes (4/14), twice a day (6/14) was preferred. As part of chronic management, positioning was strongly supported by participants (23/28), suggesting a duration of either 30 minutes (2/19), every two to four hours (2/19), or patient dependent (4/19). As with previous answers, respondents suggested positioning to be performed based on the patient's need (4/17) or twice a day (5/17).

Autogenic drainage, including assisted autogenic drainage (AAD) for younger children and infants, was supported by less than half of the participants (12/28), for five minutes per treatment or determined by the patient's reaction, mostly twice per day (5/10). A more detailed description of the management strategies suggested for chronic care, including frequencies of treatment can be found in Table 2.4 and Appendix Ax.

2.6.5.4 Cough augmentation (proximal airway clearance techniques)

Similar to acute management, manually assisted coughing was supported by the majority (22/28), favouring a combination technique of abdominal and thoracic compressions/thrusts (13/23). The majority of participants who recommended MAC indicated that the frequency of cough assistance should be patient dependent (19/22). If the patient should get tired during cough augmentation, the majority opted to stop (16/24) and the remaining respondents stated they would change the technique or procedure (8/24). Regarding MI-E most participants were unsure of its use (16/26), as was the case with acute management.

The four participants who recommended the use of MI-E preferred automatic settings (basic auto/timed programmed). Two participants provided recommendations regarding the settings namely inspiratory pressure of 30cmH₂O, and expiratory pressure of 20 or 30cmH₂O. Three or five repetitions of the cycle were suggested, with a suggested inspiratory time of 1.5 or two seconds, and expiratory time of 1.5 or three seconds, with a pause of one to two/two seconds between breaths. Both participants agreed that all settings were dependent on the patient's needs.

Almost 50% of responses supported suctioning as part of chronic care (13/27) while 11 participants did not support this intervention. For those in favour of suctioning the frequency per treatment was suggested as once or twice (4/12), or as required (6/12); and frequency per day as twice (3/9) or as required by the patient (6/9).

2.6.5.5 Lung volume recruitment, breathing exercises and respiratory muscle training.

Under respiratory muscle training and lung compliance as part of chronic management and home programme (indicated in yellow, Figure 2.5), half of the participants were unsure of the use of LVR (breath-stacking/insufflation) (14/28).

Those in support (n=11) recommended the use of independent/assisted/combination of insufflation techniques, depending on what worked best for the individual patient. Eight participants provided examples of applicable breath-stacking/insufflation exercises (Appendix Ax). Breathing exercises were very well supported by participants (27/28); specifically active cycle of breathing (ACBT) (13/22), either independently or in combination with other breathing exercises such as bubble blowing and DBE (6/22), recommended as five minutes per treatment, twice daily.

Many participants supported respiratory muscle training, both IMT (21/28) and expiratory muscle training (EMT) (19/28), for the chronic management of children with NMD. In both IMT and EMT, resistant devices were preferred, followed by threshold training devices five to ten repetitions, twice a day or individualised for the patient.

A summary of recommended repetitions per treatment and frequency per day for the ACT, breathing exercises and respiratory muscle training is outlined in Table 2.4, with the exclusion of MI-E, as this was only specified by two participants.

Table 2.4: Summary of suggested repetitions and frequencies per day for respiratory muscle training, lung compliance and airway clearance techniques (chronic care).

Treatment	Repetitions per day	Proportion advocating repetitions (%)	Frequency per day	Proportion advocating frequency (%)
Inspiratory muscle training (one participant was unsure)	5 10 Patient dependent	2/19 (11) 3/19 (16) 3/19 (16)	2 Patient dependent	6/19 (32) 4/19 (21)
Expiratory muscle training (5 participants were unsure)	5 10 Patient dependent	2/16 (13) 4/16 (25) 3/16 (19)	2 Patient dependent	5/16 (31) 3/16 (19)
Breathing exercises	<u>Repetitions per Rx:</u> 5 min	5/22 (23)	2	11/22 (50)
Oscillatory devices	<u>Frequency per Rx:</u> 10 times	4/18 (22)	2	7/18 (39)
Percussions	<u>Time per Rx:</u> 10 minutes	5/12 (42)	2	8/12 (67)
Vibrations	<u>Time per Rx:</u> Five minutes	4/12 (33)	2	5/12 (42)
Adapted postural drainage (No Trendelenburg)	<u>Time per Rx:</u> 10 min or 20 min	4/14 (29)	2	6/14 (43)
Positioning	<u>Time per Rx:</u> Patient dependent	4/19 (21)	2	5/17 (29)
Autogenic drainage	<u>Time per Rx:</u> Patient dependent	3/10 (30)	2	5/10 (50)
Manually assisted cough	<u>Coughs per Rx:</u> Patient dependent/as needed	9/17 (53)	Patient dependent	19/26 (73)
Suctioning	<u>Frequency per Rx:</u> As required/needed	6/12 (50)	As required/needed/ patient dependent	6/9 (67)

2.6.5.6 Open-ended responses (chronic management)

Similar to section B, this section also included open-ended questions asking participants to elaborate on their answers (Appendix Ax). No additional comments were provided under ventilation/respiratory support or breath-stacking/insufflation. Additional comments under secretion mobilisation (peripheral ACT) in chronic management referred to the use of nebulised normal saline for secretion mobilisation, percussions and the role of hydrotherapy to improve deep breathing and strengthen the respiratory muscles. Regarding cough augmentation (proximal ACT), some participants indicated that they would suction if necessary and that for MI-E they would use both manual and automatic settings.

For breathing exercises in chronic management of children with NMD, the majority of the 17 responses suggested using ACBT. Additional comments for respiratory muscle training included the use of cardiovascular exercises, LUFT and maintenance breathing activities as part of play therapy. To prevent and manage respiratory complications associated with NMD, participants (n=6) recommended the use of active and passive mobilisation, maintaining range of motion as well as muscle strength for the trunk and upper limbs, and general cardiovascular endurance/exercise. Under general recommendations, three participants recommended including the use of play therapy and exercise to improve mobility and respiratory function; prevention of respiratory tract infections with pharmacological interventions, nutrition and home hygiene were also highlighted.

Table 2.5 provides a summary of preferred respiratory management techniques for both acute and chronic management, as reported by the survey respondents.

Table 2.5: Summary of preferred techniques in acute and chronic management of children with neuromuscular disease.

Management	Acute (n=39-44)	Chronic (n=28)
General respiratory care/respiratory support	<i>Non-invasive ventilation</i> <i>Nebulisation (normal saline)</i> <i>Supplemental O₂</i> <i>24-hour postural management</i>	<i>Non-invasive ventilation</i> <i>Supplemental O₂</i> <i>24-hour postural management</i>
Secretion mobilisation	<i>Percussions</i> <i>Vibrations</i> <i>Adapted postural drainage</i> (No Trendelenburg) <i>Positioning</i> <i>Oscillatory devices (e.g. Flutter)</i> <i>Breathing exercises</i>	<i>Nebulisation</i> <i>Adapted postural drainage</i> (No Trendelenburg) <i>Positioning</i> <i>Oscillatory devices</i>
Airway clearance and cough augmentation/assistance	<i>Manually assisted cough*</i> (Thoracic and abdominal compressions) <i>Suctioning</i>	<i>Manually assisted cough*</i> (Thoracic and abdominal compressions)
Lung compliance exercises and respiratory muscle training	Not included as part of acute management	<i>Breathing exercises</i> # <i>Inspiratory and expiratory muscle training</i>

* The majority were either not aware of mechanical insufflation-exsufflation (MI-E) as an alternative cough augmentation option or were aware of the device, but had never used it before; # 50% of participants were unsure about the use of lung volume recruitment such as breath-stacking or glossopharyngeal breathing (GPB). The frequency of techniques was mostly recommended twice a day.

2.6.6 Section D: South African management of patients with neuromuscular disease

In this last section of the questionnaire (Section D) respondents were asked to indicate which respiratory management physiotherapy techniques they had used in the previous six months for acute as well as chronic care in children with NMD.

If participants indicated that they had not recently worked with patients with NMD, they were redirected to the end of the survey.

Of the 28 participants that completed Section C (chronic management), only six indicated that they had recently worked with patients with NMD and continued to complete Section D (margin of error: 39.80%). The techniques that had been clinically used for acute and chronic management are outlined in Figures 2.6 and 2.7 respectively (Appendix Ax).

2.6.6.1 Acute respiratory management

For the acute management context, participants were asked to report their use of respiratory management techniques as part of acute management in children with NMD, including general respiratory management (in purple), secretion mobilisation (peripheral ACT) indicated in blue; cough augmentation (proximal ACT) (in orange) as well as breath-stacking (LVR) and breathing exercises (in yellow) (Figure 2.6).

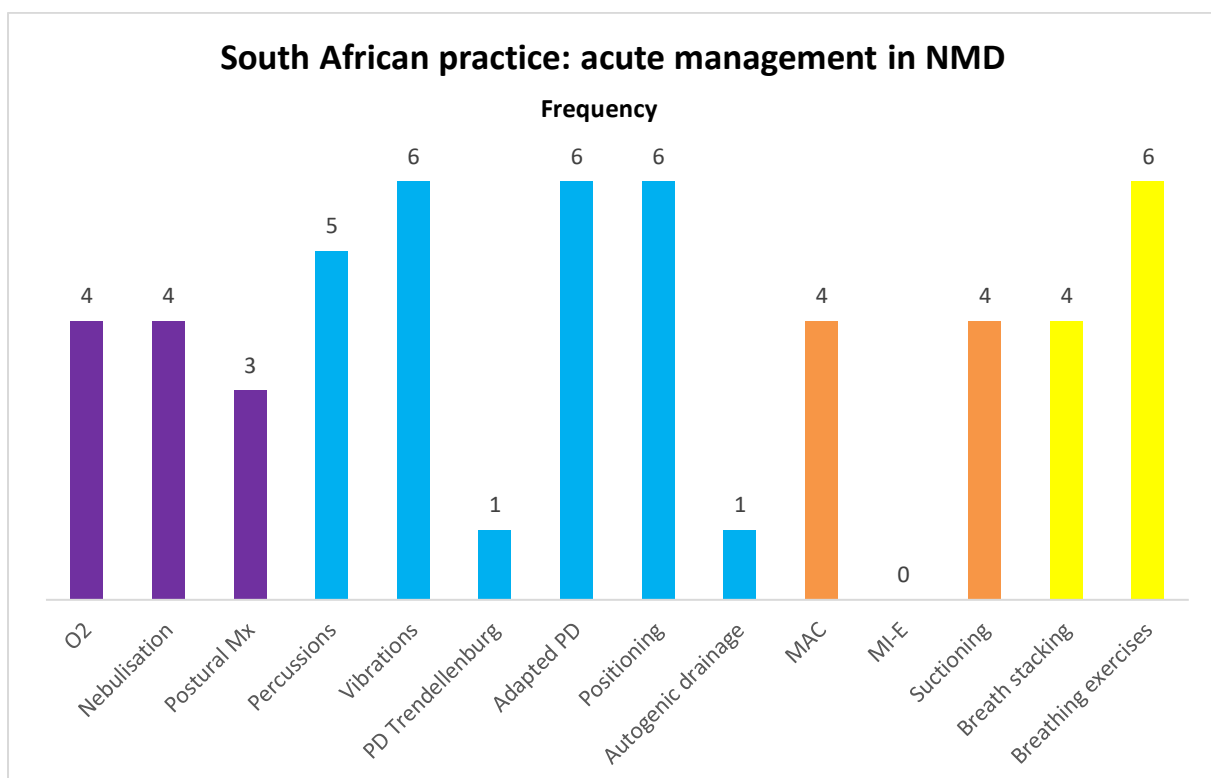


Figure 2.6: South African acute respiratory management in children with neuromuscular disease (n=6).

As can be seen from Figure 2.6 all participants reported the use of vibrations, adapted PD, positioning and breathing exercises during acute management. None of the respondents had used MI-E for cough augmentation.

2.6.6.2 Chronic respiratory management

Participants were asked about their recent use of respiratory management techniques in chronic management of children with NMD including general respiratory management such as 24-hour postural management (purple), secretion mobilisation techniques (peripheral ACT) (blue); cough augmentation (proximal ACT) (orange) as well as respiratory muscle training and breathing exercises (yellow) (Figure 2.7).

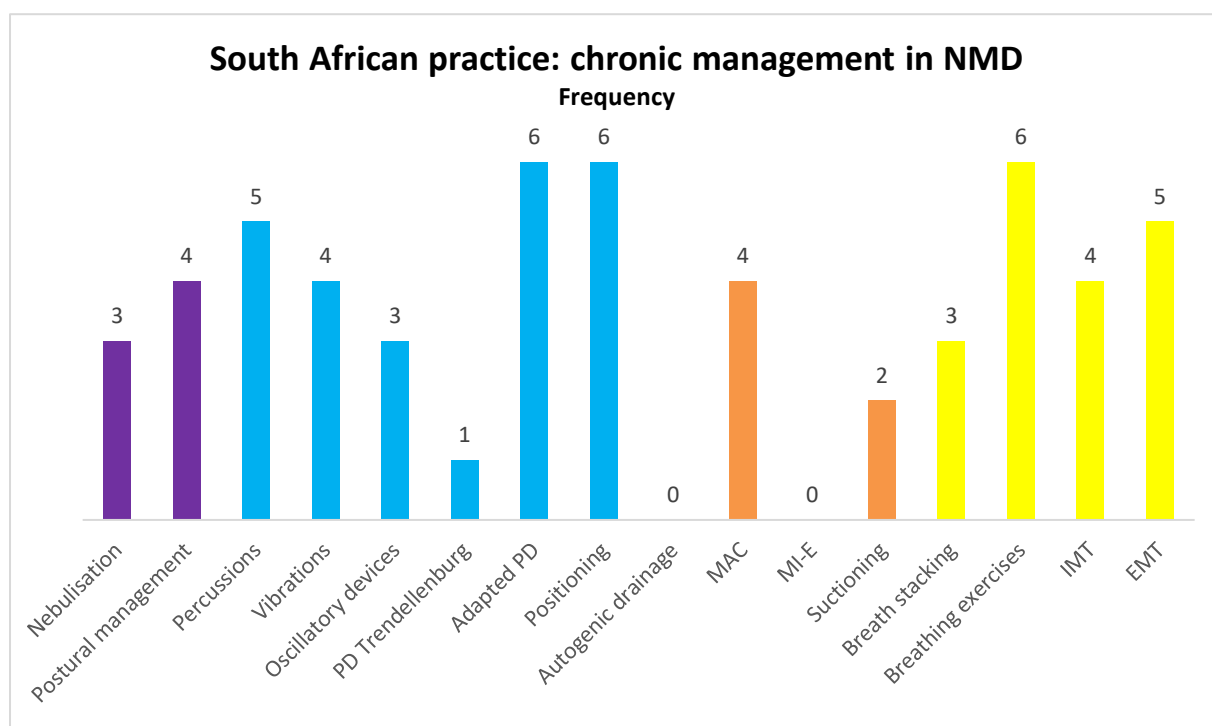


Figure 2.7: South African chronic respiratory management in children with neuromuscular disease (n=6).

From Figure 2.7 it is evident that adapted PD, positioning and breathing exercises were used by all participants as part of chronic care whilst percussions and respiratory muscle training (IMT and EMT) were also well supported. Similar to acute management trends, MI-E was not used by any of the participants (Appendix Ax).

At the end of Section D, participants were also asked if they utilised any other respiratory management techniques in the past six months for patients with NMD that was not mentioned in the questionnaire. Two participants responded that they had used thoracic mobility exercises and one mentioned that they implemented general active/active assisted exercises as well.

2.6.7 Associations between variables

The relationship between selected respiratory management techniques used and place of work (private healthcare vs public healthcare) as well as years of experience was analysed and are summarised (Tables 2.6 to 2.9).

Due to the small number of responses, most cells contained frequencies of <10 and therefore the association between yes and no/unsure answers were analysed using Yates χ^2 .

2.6.7.1 Work-setting and treatment techniques (acute and chronic management)

Table 2.6: Overview of respiratory management techniques used per work-setting for acute management of children with neuromuscular disease.

Technique (acute management)	Work setting (Private practice) n/N (%)	Work setting (Public sector) n/N (%)	Statistical value (Yates χ^2)	p-value
Ventilatory support (mechanical ventilation)	4/27 (14.81)	7/17 (41.18)	2.59	0.11
Supplemental oxygen	21/27 (77.78)	16/17 (94.12)	1.04	0.31
Oscillatory devices	17/24 (70.83)	7/12 (58.33)	0.14	0.71
Manually assisted cough	24/25 (96.00)	14/14 (100.00)	0.09	0.77
Mechanical insufflation-exsufflation	4/25 (16.00)	3/14 (21.43)	0.0001	0.99

No statistically significant association was found between vocational background (public vs private healthcare sector) and clinical practice trends such as ventilatory support, oxygen supplementation, ACT and respiratory muscle training, except for the use of breath-stacking (LVR) ($p=0.03$) (Table 2.6).

Table 2.7: Overview of respiratory management techniques used per work-setting for chronic management of children with neuromuscular disease.

Technique (chronic management)	Work setting (Private practice) n/N (%)	Work setting (Public sector) n/N (%)	Statistical value (Yates χ^2)	p-value
Non-invasive ventilation (ventilatory support)	9/15 (60.00)	7/12 (58.33)	0.09	0.76
Supplemental oxygen	9/15(60.00)	6/12 (50.00)	0.02	0.90
Oscillatory devices	10/16 (62.5)	10/12 (83.33)	0.62	0.43
Manually assisted cough	12/16 (75.00)	10/12 (83.33)	0.004	0.95
Mechanical insufflation-exsufflation	1/16 (6.25)	3/11 (27.27)	0.92	0.34
Breath-stacking	3/16 (18.75)	8/12 (66.67)	4.74	0.03
Inspiratory muscle training	12/16 (75.00)	9/12 (75.00)	0.19	0.66
Expiratory muscle training	11/16 (68.75)	8/12 (66.67)	0.09	0.77

As can be seen from Table 2.7 the use of breath-stacking during chronic management of children with NMD was the only moderate and significant association (Yates χ^2 (1; N=28) =4.74, p=0.03). Those working in public healthcare seemed more inclined to use breath-stacking as part of chronic management in children with NMD.

2.6.7.2 Years of experience and treatment techniques (acute and chronic management)

Years of experience were not significantly associated with a preference for the use of specific respiratory management strategies during either acute or chronic care, based on the Pearson's χ^2 test (Tables 2.8 and 2.9).

Table 2.8: Overview of respiratory management techniques used in the acute management of children with neuromuscular disease and years of experience.

Technique (acute management)	Years of experience (<12 months) n/N (%)	Years of experience (1-5 years) n/N (%)	Years of experience (6-10 years) n/N (%)	Years of experience (> 10 years) n/N (%)	Statistical value (Pearson's χ^2)	p- value
Ventilatory support (mechanical ventilation)	3/7 (42.86)	5/20 (25.00)	1/10 (10.00)	1/6 (16.67)	5.61	0.23
Supplemental oxygen	6/7 (85.71)	16/20 (80.00)	9/10 (90.00)	5/6 (83.33)	0.72	0.95
Oscillatory devices	3/5 (60)	14/17 (82.35)	3/8 (37.5)	4/6 (66.67)	5.04	0.28
Manually assisted cough	6/6 (100.00)	16/17 (94.11)	9/9 (100.00)	6/6 (100.00)	1.33	0.86
Mechanical insufflation- exsufflation	1/6 (16.67)	4/17 (23.53)	1/9 (11.11)	0/6 (0.00)	6.54	0.16

Table 2.9: Overview of respiratory management techniques used in the chronic management of children with neuromuscular disease and years of experience.

Technique (chronic management)	Years of experience (<12 months) n/N (%)	Years of experience (1-5 years) n/N (%)	Years of experience (6-10 years) n/N (%)	Years of experience (> 10 years) n/N (%)	Statistical value (Pearson's χ^2)	p- value
Non-invasive ventilation (ventilatory support)	3/5 (60.00)	5/10 (50.00)	5/8 (62.5)	2/3 (66.67)	1.15	0.89
Supplemental oxygen	3/5 (60.00)	5/10 (50.00)	4/8 (50.00)	2/3 (66.67)	1.22	0.88
Oscillatory devices	4/5 (80.00)	7/11 (63.64)	6/8 (75.00)	2/3 (66.67)	0.99	0.91
Manually assisted cough	3/5 (60.00)	8/11 (72.73)	7/8 (87.50)	3/3 (100.00)	2.72	0.61
Mechanical insufflation- exsufflation	1/4 (25.00)	2/11 (18.18)	0/8 (0.00)	0/3 (0.00)	8.09	0.88
Breath-stacking	1/5 (20.00)	6/11 (54.55)	2/8 (25.00)	1/3 (33.33)	4.13	0.39
Inspiratory muscle training	4/5 (80.00)	8/11 (72.73)	5/8 (62.5)	3/3 (100.00)	2.10	0.72
Expiratory muscle training	3/5 (60.00)	8/11 (72.73)	4/8 (50.00)	3/3 (100.00)	3.33	0.50

2.7 Discussion

2.7.1 Respondent background: A South African context

Many respiratory complications in patients with NMD can be either treated or prevented through proactive treatment strategies and clinical practice guideline implementation (Farrero et al., 2013; Landfeldt et al., 2015; Finkel et al., 2018; McDonald & Mercuri, 2018; Rose et al., 2018). The use of treatment strategies such as gluco-corticosteroid therapy, ventilatory support and pro-active cardiac and respiratory management has improved clinical outcomes and life expectancy of patients with NMD, but treatment variation across institutions and countries remains a concern (Sejerson & Bushby, 2009; van Ruiten et al., 2014; Landfeldt et al., 2015; Janssen, Hendriks, Geurts & de Groot, 2016; Vry Gramsch, Rodger, Thompson, Steffensen, Rahbek et al. 2016; Jalloh et al., 2018; Toussaint et al., 2018).

Applying clinical practice guidelines can assist in decision making, implementation of appropriate treatment strategies and improved consistency of healthcare across various settings (Woolf et al., 1999; Stander et al., 2020). However, there may be considerable barriers to implementation, resulting in variable management approaches; these barriers may include resource constraints, for example, lack of expertise or availability of cough augmentation devices and insufficient patient access to chronic health services (PoPONICK et al., 1997; Eagle, 2002).

Optimal, cost-effective and preventative cardiopulmonary management of patients with NMD requires coordinated input from all members of the multi-disciplinary team and physiotherapists with experience in the field of NMD can play an important role as part of such an evidence-based management team (Rosiere et al., 2009; Bushby et al., 2010; Landfeldt et al., 2015; Birnkrant et al., 2018; Finkel et al., 2018; Chatwin et al., 2018; Stander et al., 2020). Similar to other countries, despite the availability of clinical practice guidelines for children with NMD, standardisation of such care in SA is lacking (Bushby et al., 2010; Hull et al., 2012; Farrero et al., 2013; Vry et al., 2016; Panitch, 2017; Jalloh et al., 2018; Toussaint et al., 2018) (Appendix Axi).

2.7.2 Response rate

The overall initial response rate for this survey was poor at 16.4%, which is lower than the general reported 33% response rate average for electronic surveys (Nulty, 2008), but higher than previous online surveys among physiotherapists (Struyf, De Hertogh, Gulinck & Nijs, 2012; Clenzos, Naidoo & Parker, 2013; Silva, Costa & Costa, 2015).

Online survey response rates tend to be lower than paper-based surveys (Nulty, 2008) and can be influenced by various factors such as the length of the survey, face validity/user-friendliness, compensation and affiliation of the researcher (Sheehan, 2001). Online surveys, however, have the advantage of being cost-effective, convenient and anonymous, but lack direct interaction between the researcher and participants and may create concerns about internet security, which could result in a lower response rate (Bott et al., 2009; Anseel et al., 2010). Attempts to improve survey responses included reminders being sent, as recommended previously (Sheehan, 2001; Nulty, 2008).

Of the projected total number of practising/registered physiotherapists in SA (n=7708), an estimated 4140 members (53.7%), of which the majority are females (77-86%), belong to the SASP (Personal communication, SASP (2019); Stander et al., 2019; World Physio: <https://world.physio/membership/south-africa>).

Only a small proportion of these are members of SASP special interest groups such as CPRG and/or Paediatrics which might limit the external validity of the study.

Although NMD is rare and considered a niche area of practice (Ballo et al., 1994; Theadom et al., 2014), it was concerning that the attrition rate in this survey increased from section B (acute care) to Section D (SA management strategies) leading to a varying number of responses per section. Possible reasons could include the nature and/or length of the questionnaire or limited expertise regarding acute and/or chronic management of children with NMD (Toussaint et al., 2018; Stander et al., 2019). The margin of error for this survey was higher than 5% for all sections but increased from Section A to D. An acceptable margin of error of 10% for exploratory studies was only met for section A and then increased for section B and C, up to 18%. The low number of responses provided for Section D (n=6), with a margin of error of 40%, might not be a true reflection of the physiotherapy management strategies used in SA, but could also allude to the fact that very few physiotherapists are involved in the management of children with NMD. Empowering more physiotherapists and advocating for the involvement of physiotherapists as part of the multi-disciplinary team managing children with NMD in SA should be recognised as a healthcare priority. It is also recommended that future questionnaires focus on single case scenarios and are reduced in length.

2.7.3 Vocational background and years of experience

Considering that 76.5% of SASP members work in the private healthcare sector (SASP email communication; Nov 2019), it was not surprising that most respondents in this survey (58%, n=37) were also private practitioners. The fact that the majority of responses were from physiotherapists in the private healthcare sector, which only services approximately 17% of the SA population (WHO: https://www.who.int/workforcealliance/031616south_africa_case_studiesweb.pdf?ua=1), highlights the inequality of the SA healthcare system and may reflect an imbalance in the distribution of knowledge and expertise between these healthcare sectors. The experience of public health sector physiotherapists in the management of children with NMD (42%, n=27) may however not be adequately reflected in this study, and constitutes a potential limitation. Certainly, most children in SA with NMD are likely to attend specialised clinics at tertiary public hospitals and attend public schools for children with special needs, hence they should be seen by government employed physiotherapists. Nonetheless, a recent SA study indicated that the barriers and facilitators to the implementation of clinical practice guidelines among physiotherapists seem to be similar regardless of geographical location or work context (private, public healthcare and education) (Stander et al., 2019).

Most respondents (66%; n=43) indicated one to ten years of NMD experience, but we were unable to show an association between years of experience and clinical practice trends. This is similar to the findings of Clenzos et al. (2013) regarding knowledge of pain among SA physiotherapists (n=207) and a recent SA qualitative study (n=31), which reported that years of experience was not an indicator of whether a physiotherapist was more or less likely to implement clinical practice guidelines (Stander et al., 2020). Conversely, a study by Iles and Davidson (2006) reported that physiotherapists with higher qualifications and years of experience had greater knowledge and understanding of clinical practice guideline concepts. Our study also suggested that there may be differences in respiratory management strategies between private and public healthcare sectors, as seen by the discrepancy in the use of breath-stacking (LVR) techniques ($p=0.03$). Participants working in public seemed more inclined to use breath-stacking as part of chronic management than those in the private healthcare sector. The reasons for this difference between the healthcare sectors are unknown and should be interpreted with caution due to the small sample, but warrants further research. A recent SA based study reported that the barriers and facilitators to the implementation of clinical practice guidelines among physiotherapists seem to be similar, regardless of geographical location or work context (private or public healthcare) (Stander et al., 2019).

2.7.4 General respiratory management, mechanical ventilation and support during acute and chronic management

The acute management case scenario described a child with NMD who had recently lost ambulation and was admitted to hospital due to a respiratory infection, presenting with desaturation, secretion retention and a poor cough. Similarly, the chronic management case scenario described an older non-ambulant child with signs of pulmonary function decline and poor cough.

Required ventilation and respiratory management techniques can be determined through regular clinical and pulmonary function assessment (Finder et al., 2004). Participants recommended the use of nebulisation, 24-hour postural management and oxygen supplementation during acute and chronic management. Oxygen supplementation was strongly supported for acute management, whilst for chronic management, non-invasive ventilation (NIV) was preferred, as recommended by clinical practice guidelines (Birnkranz et al., 2018; Finkel et al., 2018).

2.7.4.1 Oxygen supplementation

The acute case scenario indicated desaturation ($\text{SpO}_2 < 95\%$), which could warrant the use of supplemental oxygen. Furthermore, nocturnal hypoventilation and desaturation are commonly observed in children with neuromuscular weakness (Finder et al., 2004; Panitch, 2017; Finkel et al., 2018; Mary, Servais & Vialle, 2018; Chatwin et al., 2020). Hence, ventilatory support (with or without oxygen supplementation) may form part of respiratory management in patients with NMD (McCool & Rosen, 2006; Sejerson & Bushby, 2009; Hull et al., 2012; Rous et al., 2014). Although most participants indicated that supplemental oxygen (40%; 2-5 L/min) might be required during acute management in NMD and 50% of participants supported its use during chronic care; hypoxaemia in patients with NMD is usually caused by hypoventilation, mucus plugging, atelectasis and/or pneumonia. Supplemental oxygen as a stand-alone treatment is therefore not routinely advised, but if indicated, should rather be combined with ventilatory support such as NIV and cough augmentation (proximal ACT) (Nici et al., 2006; Bushby et al., 2010; Hull et al., 2012; Birnkrant et al., 2018; Finkel et al., 2018). Administering supplemental oxygen, especially in children with NMD, should be done with caution. Possible impairment of the central respiratory drive can cause exacerbation of hypercapnia if the underlying reason for respiratory distress or sleep-disordered breathing is not addressed and therefore monitoring of O_2 and CO_2 levels are advised (Bushby et al., 2010; Bourke, 2014; Boentert et al., 2017; Toussaint et al., 2018; Birnkrant et al., 2018; Chiang et al., 2018).

Most participants correctly indicated the use of NIV and ACT (peripheral and proximal) once a patient becomes non-ambulant and presents with an acute infection, saturation $< 95\%$ on room air and secretion retention due to a poor cough, as outlined in both case scenarios (Goemans & Buyse, 2014; Finkel et al., 2018; Birnkrant et al., 2018; Chatwin et al., 2018). Once a patient with NMD presents with desaturation, hospital admission could be considered to provide the necessary ventilatory, antibiotic and cough augmentation support (Guglieri & Bushby, 2011; Finkel et al., 2018), if this cannot be provided at home.

2.7.4.2 Nebulisation and 24-hour postural management

Clinical practice guidelines on the use of nebulisation and postural management strategies in children with NMD are limited and management is therefore usually based on clinical reasoning and patient presentation, as indicated by many participants.

In this survey, many respondents recommended the use of nebulisation similar to the BTS guidelines (Hull et al., 2012), particularly of 0.9% (normal) saline, usually once during the treatment and twice a day or depending on the patient's needs, during acute and chronic care. It is important to note that the use of normal saline is not supported by objective evidence. Isotonic saline is not an effective secretion dilutant and the potential benefit of improving airway hydration has not been demonstrated. Hypertonic saline may be useful as an osmolytic agent, to normalise secretion osmolality and facilitate clearance, but although this is effective in specific, disparate populations such as those with cystic fibrosis (Wark & McDonald, 2018), this intervention has not been well studied in the NMD population. A recent, small pre-experimental study (n=20) reported that nebulised hypertonic saline was well-tolerated, eased airway clearance and decreased respiratory morbidity in children and young people with NMD, but the authors acknowledged that larger randomised controlled trials (RCT) were needed (Souza, Bush & Tan, 2019). A minority of respondents advocated for the use of bronchodilators and mucolytics. Bronchodilator therapy would only be appropriate if children presented with asthma or bronchial hyperresponsiveness (bronchospasm), but the chronic use of bronchodilators, mucolytics and hypertonic saline in NMD is not advised (Balachandran et al., 2005; Piper & Moran, 2006; Wang et al., 2007; Panitch, 2017; Finkel et al., 2018). Furthermore, devices such as nebulisers might not be accessible or feasible, especially in rural areas of SA where electricity is not always available.

Postural management strategies during acute and chronic management of children with NMD was strongly supported by survey participants, likely owing to clinical benefits such as prevention of postural abnormalities/deformities as well as enhanced general and respiratory function (Farley et al., 2003; Mercuri, Finkel, Muntoni, Wirth, Montes, Main, et al. 2018). Various positions such as supported sitting/Semi-Fowler's, side-lying and adapted side-lying were recommended for acute management while supported sitting/high sitting was advocated during chronic care. This aligns with the physiological principle that functional residual capacity (FRC) can be affected by postural positioning and improves progressively from supine to standing (Katz, Arish, Rokach, Zaltzman & Marcus, 2018; Lumb & Thomas, 2020). In addition, and associated with FRC, lung compliance can be improved and airway resistance decreased by changing a patient's position from supine (Wahba, 1991).

Children with NMD tend to have lower FRC due to decreased thoracic muscle support and normal lung recoil which puts them at risk for respiratory complications (Schechter, 2007) and therefore postural management strategies to improve FRC might be of benefit. Currently, postural management techniques are widely implemented and accepted as a treatment modality in patients with NMD (Farley et al., 2003). Although positioning of patients such as side-lying and supported sitting could be beneficial for enhanced regional lung ventilation and/or secretion mobilisation (ACT) (Lupton-Smith, Argent, Rimensberger & Morrow, 2014; Katz et al., 2018; Mercuri et al., 2018; Toussaint et al., 2018), there is very little high-level supporting evidence available for patients with NMD. In addition, postural management might pose a challenge in patients with NMD due to secondary complications such as scoliosis, contractures and osteoporosis (Panitch, 2006; Goemans & Buyse, 2014; Mary et al., 2018; Toussaint et al., 2018).

2.7.4.3 Ventilatory support

Assisted ventilation, such as NIV and invasive positive pressure ventilation (NPPV), may be indicated for patients with NMD to ameliorate symptoms of hypoventilation and/or hypercapnia; decrease hospitalisations for chest infections; minimise the occurrence and severity of chest deformities; improve patient comfort and HRQoL, and prolong life in patients with NMD (Perrin et al., 2004; Rosiere et al., 2009; Guglieri & Bushby, 2011; Birnkrant et al., 2018; Finkel et al., 2018; Mary et al., 2018). It is recommended that NIV should form part of the first line of treatment during acute hypercapnic respiratory failure in children with NMD (Hull et al., 2012; Boentert et al., 2017). In palliative care, NIV can decrease work of breathing, normalise ventilation patterns and enable the patient to be discharged from the hospital (Wang et al., 2007; Farrero et al., 2013; Finkel et al., 2018). Nonetheless, when a patient needs more than 16 hours of NIV per day; presents with feeding problems; does not tolerate NIV or is otherwise contra-indicated, cannot use mouthpiece ventilation or presents with poor oral control, then invasive ventilation may be indicated (Finder et al., 2004; Hull et al., 2012; Goemans & Buyse, 2014; Finkel et al., 2018; Chatwin et al., 2020). Tracheostomy for chronic ventilation is an option that needs to be discussed with the child and family, considering the child's HRQoL and family's preferences (Wang et al., 2007; Finkel et al., 2018).

Similar to clinical recommendations for non-ambulant children with NMD presenting with associated restrictive lung disease and pulmonary function regression, survey participants supported the use of NIV during acute and especially chronic management (Finder et al., 2004; Hull et al., 2012; Finkel et al., 2018; Birnkrant et al., 2018).

Responses related to the indications for and application of NIV were variable, but BiPAP was mostly recommended as CPAP alone does not decrease the ventilatory load, may fatigue the patient and could interfere with weaning, while BiPAP is likely to be more comfortable for the patient (Wang et al., 2007; Finkel et al., 2018). Hypoxaemia in patients with NMD is mostly caused by partial or complete hypoventilation, for which BiPAP will be more effective than CPAP unless an obstructive component is present (Finder et al., 2004; Ho et al., 2015; Boentert et al., 2017). Although the use of CPAP is not indicated for chronic respiratory failure, it might prove of value temporarily to maintain resting lung volume and in younger patients who are unable to synchronise with a ventilator (Finkel et al., 2018).

The NIV interface does not seem to affect outcomes, but should be fitted by an experienced clinician and settings should be individualised for each patient (Wang et al., 2007; Finkel et al., 2018). Implementation of BiPAP is indicated when there is significant daytime hypercapnia or nocturnal hypoventilation, which can be determined by capnometric and oxymetric measures (Finder et al., 2004; Sejerson & Bushby, 2009; Birnkrant et al., 2018; Finkel et al., 2018). Nocturnal hypoventilation can be defined as <90% SpO₂ over 30 minutes of recording time and carbon dioxide tension (pCO₂/tcCO₂) of >50mmHg (Boentert et al., 2017). With disease progression, swallowing problems and sleep-disordered breathing might occur, hence at first nocturnal and later continuous NIV might be necessary (Perrin et al., 2004; Goemans & Buyse, 2014; Bourke, 2014; Birnkrant et al., 2018; Mary et al., 2018).

This survey inquired about the trends of ventilator usage in the management of patients with NMD and how it compares to international clinical practice guidelines, but the primary focus of the survey was respiratory physiotherapy management techniques. It has to be noted that in the SA healthcare system, physiotherapists form part of the multi-disciplinary team responsible for respiratory management in patients with NMD, but do not prescribe or initiate mechanical ventilation, including NIV, unlike respiratory therapists in other countries (Bushby et al., 2010). Combining ACT, including cough augmentation with NIV, particularly during acute illness and post-operatively, can prevent respiratory complications, improve hypoventilation, secretion retention, may prevent the need for hospitalisation and/or intubation and may improve survival (Sejerson & Bushby, 2009; Farrero et al., 2013; Ho et al., 2015; Mayer et al., 2017; Panitch, 2017; Finkel et al., 2018).

2.7.5 Secretion mobilisation techniques (peripheral ACT) for acute and chronic management

Assisted ventilation as well as peripheral and proximal ACT (Figure 2.8) can improve pulmonary function and prevent respiratory complications, especially once ambulation is lost (Panitch, 2006; Schechter, 2007; Bianchi & Baiardi, 2008; Aboussouan, 2009; Benditt & Boitano, 2013; Farrero et al., 2013; Birnkrant et al., 2018). While some respiratory management strategies such as NIV are supported by high level evidence with subsequently improved prognosis as well as HRQoL in patients with NMD (Wang et al., 2007; Verhaart et al., 2017; Jalloh et al., 2018), research on ACT in children and in particular children with NMD is limited (Hess, 2001; Rosiere et al., 2009; Volsko, 2013).

The absence of evidence to indicate efficacy of ACT in NMD does not, however, constitute evidence of absence of benefit and the implementation of manual techniques and external devices in conjunction with NIV, especially in younger patients and those unable to cooperate, are of clinical relevance (Perrin et al., 2004; De Boeck et al., 2008; Toussaint et al., 2018; Morrow, 2019).

Secretion management with ACT is advocated in order to maintain health, improve HRQoL and minimise respiratory complications, even more so post-operatively and with rapid disease progression, which may explain why these techniques were well supported by respondents

(Finder et al., 2004; Balachandran et al., 2005; Gauld, 2009; Finder, 2010; Volsko, 2013;

Birnkrant et al., 2018; Finkel et al., 2018).

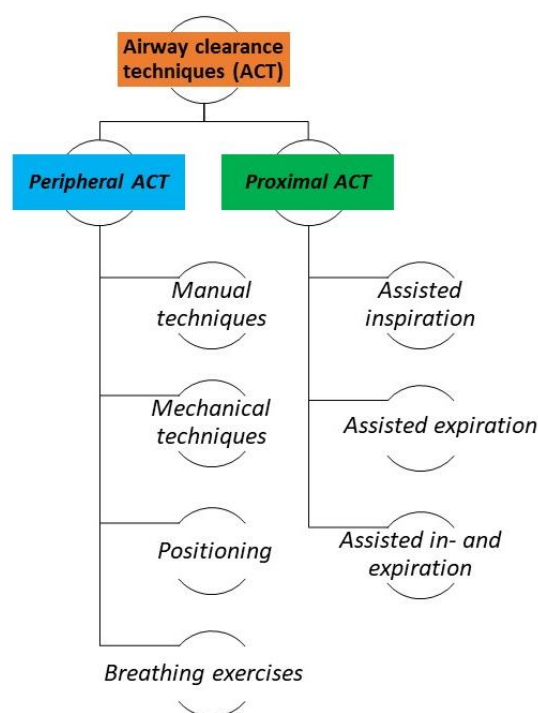


Figure 2.8: Airway clearance techniques (peripheral and proximal) [Adapted from Chatwin et al., 2018].

In the survey, the case scenario for acute management indicated secretion retention and for both acute and chronic management the patients presented with a poor cough ability, which could lead to secretion retention. Peripheral ACT may therefore be indicated for both scenarios. The aim of all peripheral ACT is to improve expiratory flow and facilitate secretion movement from the peripheral to the central airways in order to improve ventilation and prevention of atelectasis and pneumonia (Dohna-Schwake et al., 2006; Guglieri & Bushby, 2011; Rous et al., 2014; Birnkrant et al., 2018). There is however a lack of empirical evidence to determine the superiority of any airway-clearance device or treatment modality, especially in NMD (McCool & Rosen, 2006; Volsko, 2013; Finkel et al., 2018; Toussaint et al., 2018). Prescription of ACT should be individualised, based on various factors such as age, type of NMD, patient preference, advantages and the possibility of adverse events (risk/harm), in order to determine which modality will be optimal for the patient (Panitch, 2006; Volsko, 2013; Auger et al., 2017; Castrillo et al., 2019; Morrow, 2019).

Peripheral ACT encompasses positioning, breathing techniques (e.g. AD, ACBT), manual techniques (e.g. PD, percussions, vibrations) and mechanical techniques (e.g. PEP, oscillatory devices, high frequency chest wall compression/oscillation, and intrapulmonary percussive ventilation (IPV)) (Finder et al., 2004; Wang et al., 2007; Bhowmik et al., 2009; Finder, 2010; Toussaint et al., 2018). Although the use of ACT in children with NMD has been advocated and may be of clinical benefit, particularly for patients with difficulty clearing secretions (Hull et al., 2012; Farrero et al., 2013; Birnkrant et al., 2018; Chatwin et al., 2018; Finkel et al., 2018) evidence for efficacy, long-term outcome and safety in this population is limited (Schechter, 2007; De Boeck et al., 2008; Auger et al., 2017; Toussaint et al., 2018). In addition, mechanical ACT modalities such as high frequency chest wall oscillation (HFCWO) and IPV (Boentert et al., 2017) are costly, not always available and their clinical benefit, safety and settings in children with NMD have not been established (Finder et al., 2004; Bhowmik et al., 2009; Finder, 2010; Birnkrant et al., 2018). Choosing the most appropriate ACT device or technique for a specific patient with NMD, therefore, requires knowledge of the various device functions and limitations, evidence-based techniques as well as an assessment of the patient's cognitive ability and the severity of their pulmonary impairment (Guglieri & Bushby, 2011; Farrero et al., 2013; Volsko, 2013; Ho et al., 2015).

Most survey participants supported the use of conventional, manual ACT including percussions, vibrations and adapted PD (excluding the Trendelenburg position) (De Boeck et al., 2008; Sejerson & Bushby, 2009; Hough et al., 2010). The majority of participants correctly indicated avoiding the use of head down PD (Trendelenburg) as it has been suggested that this technique could cause harm in the paediatric population (Morrow, 2019); therefore adapted PD is rather encouraged during acute and chronic management. Peripheral ACT such as percussions, vibrations and PD aims to enhance secretion mobilisation, but may be associated with adverse effects such as desaturation, bronchospasm, increase in gastro-esophageal reflux, blood pressure and rib injuries (Balachandran et al., 2005; Panitch, 2006; Hough et al., 2010; Rous et al., 2014). Furthermore, the efficacy of techniques such as percussion and vibrations, combined with PD, may be limited in children with NMD due to the presence of scoliosis, contractures and/or osteoporotic ribs (Panitch, 2006; Goemans & Buyse, 2014; Ho et al., 2015; Toussaint et al., 2018).

Positions such as side-lying, upright sitting and prone could be used to enhance lung volumes (FRC) and secretion clearance, but the optimal position should be chosen according to individual patient response (Wahba, 1991; Morrow, 2019; Lumb & Thomas, 2020). Positioning to improve ventilation and perfusion during acute and chronic management was strongly supported by participants, with a suggested duration of 30 minutes or every two to four hours or based on patient preference/presentation. Appropriate positioning and management of secretions are recommended in patients with neuromuscular weakness (Hull et al., 2012; Katz et al., 2018; Mercuri et al., 2018). Changing the patient's position might assist with the redistribution of regional lung ventilation, resolving unilateral and/isolated lung infiltration and improve secretion mobilisation (Lupton-Smith et al., 2014; Katz et al., 2018; Toussaint et al., 2018). The benefit of positioning and active expiratory breathing combined could include improved length-tension relationship (Servera et al., 2003) or geometry of the diaphragm, which can decrease dyspnoea (Nici et al., 2006). On the other hand, the 228th ENMC meeting suggested that IPV, positioning and chest wall strapping may be the most effective peripheral ACT to use in patients with NMD, even infants and young children as they require little cooperation. It was however noted that IPV is expensive and not always readily available (Toussaint et al., 2018), especially in resource-constrained countries such as SA.

Breathing exercises such as pursed-lip breathing or diaphragmatic breathing could improve gas exchange, ventilation, respiratory muscle function, dyspnoea, exercise tolerance and HRQoL (Avendaño & Güell, 2003; Nici et al., 2006; Yeldan et al., 2008). Possibly due to these reported benefits, breathing exercises alone or in combination with manual peripheral ACT were strongly supported by survey participants for use in acute and chronic NMD management to facilitate airway clearance. All the SA physiotherapists (n=6) who worked with children with NMD and completed Section D reported that they used breathing exercises during acute as well as chronic management. Most respondents recommended ACBT, bubble blowing and oscillatory devices.

Oscillatory devices, such as the “Flutter VRP1” or locally manufactured Bronch-U-Vibe, create an oscillatory vibration in the airways together with PEP, which loosens and mobilises secretions from the peripheral to the proximal airways to be cleared with a subsequent cough (McCool & Rosen, 2006; Bhowmik et al., 2009; Toussaint et al., 2018). Flutter devices are likely to be well known to SA physiotherapists as they are readily available and commonly used for secretion mobilisation in patients with cystic fibrosis (CF) in this country (McCool & Rosen, 2006). Although there was no agreement among respondents regarding the dosage of oscillatory devices, the majority supported a frequency of two to three times a day during chronic management. Numerous studies among patients with CF indicated a PEP dosage of 20 minutes at a time (McCool & Rosen, 2006), which might not be plausible in children with NMD as they tire easily.

The disadvantage of breathing exercises such as ACBT, PEP and incentive spirometry, is that they are effort and flow-dependent and require a coordinated effort. This may diminish the efficacy of these techniques to enhance airway clearance especially in young children with NMD, those who are already non-ambulant and/or present with progressed and severe respiratory muscle weakness, as was the case in both case scenarios (Finder, 2010; Auger et al., 2017; Birnkrant et al., 2018; Chatwin et al., 2018). Similarly, deep breathing exercises without ventilatory support may be ineffective in patients with NMD, particularly in the case of severe restrictive lung disease. Peripheral ACT and breathing techniques such as ACBT might, however, be successfully adapted for children with NMD, if combined with NIV (Toussaint et al., 2018).

In general, survey participants recommended a frequency of twice per day or patient dependent for the peripheral ACT, which is similar to indications from other studies for patients with retained secretions. Literature suggests one to four times of ACT with a total duration that should not exceed 30 minutes, three to six minutes per position, 30 minutes before meals or a minimum of 60 minutes after meals (Balachandran et al., 2005; Piper & Moran, 2006). Participants provided varied responses regarding treatment duration and repetitions (Tables 2.3 and 2.4). The majority recommended treatment sessions ranging between five to 20 minutes, but no longer than 30 minutes or based on the patient's need, which is aligned with guidelines from other studies for patients with secretion retention (Balachandran et al., 2005; Piper & Moran, 2006).

2.7.6 Cough augmentation techniques (proximal ACT) for acute and chronic management

Secretions are cleared from the airways through alveolar and muco-ciliary clearance, two-phase gas-liquid flow, peristalsis and an effective cough which may be influenced by physiological factors such as age, sex, posture, sleep and exercise (Houtmeyers et al., 1999; Panitch, 2006; Bhowmik et al., 2009; Finder, 2010). The cough mechanism, as a method of proximal airway clearance, frequently becomes ineffective in children with NMD due to their underlying respiratory muscle weakness (Finder et al., 2004; McCool & Rosen, 2006; Boentert et al., 2017; Chatwin et al., 2018). To complement peripheral ACT and minimise respiratory morbidity, proximal ACT, which includes cough augmentation techniques, forms an important part of acute and chronic physiotherapy management in children with NMD (Wang et al., 2007; Finder, 2010; Farrero et al., 2013; Finkel et al., 2018; Toussaint et al., 2018).

Assessment and monitoring of cough ability (FVC, VC, PEF, Pimax and Pemax) is important to determine when and how to intervene with cough augmentation, but these practices differ among institutions, which makes early identification of cough weakness and early intervention challenging (Gauld, 2009; Sejerson & Bushby, 2009; Landfeldt et al., 2015; Birnkrant et al., 2018; Chiang et al., 2018; Stephan, Kristina, Corinna, Krisztina, Simone, Walter & Benedikt, 2020). Early identification and regular implementation of ACT, especially during acute infections, may assist in decreasing respiratory morbidity, hospitalisations, and prevent respiratory failure and the need for ventilatory support (Guglieri & Bushby, 2011; Hull et al., 2012; Rose et al., 2018; Toussaint et al., 2018; Morrow et al., 2019).

Survey participants correctly indicated the need for cough assistance based on the case study patient presentations (decreased lung volumes and flow (VC, FVC) oxygen desaturation and poor cough (PECF)), which aligns with clinical practice guidelines (Finder et al., 2004; Wang et al., 2007; Hull et al., 2012; Birnkrant et al., 2018; Finkel et al., 2018). Once a patient presents with an acute infection and oxygen saturation <95%, in room air, proximal ACT and NIV are recommended and peripheral ACT may also be indicated (Finder, 2010; Hull et al., 2012; Farrero et al., 2013; Birnkrant et al., 2018). Furthermore, it is recommended that if a patient with NMD presents with a weak cough (PECF of <270L/min), cough augmentation should be implemented, especially during times of respiratory infection (i.e. acute management) when cough ability will likely decrease even further (Bach et al., 1997; Gauld & Boynton, 2005; Dohna-Schwake et al., 2006; Farrero et al., 2013; Boentert et al., 2017; Chiang et al., 2018). A patient's cough effort can be enhanced with manual and/or mechanical techniques through assisting inspiration/insufflation (e.g. breath-stacking), expiration/exsufflation (e.g. MAC or both for example with MI-E) (Gómez-Merino et al., 2002; Finder et al., 2004; Sejerson & Bushby, 2009; Gauld, 2009; Finder, 2010; Chatwin et al., 2018; Katz et al., 2019).

2.7.6.1 Supporting inspiration (insufflation)

Lung volume recruitment or breath-stacking can be performed manually or mechanically and is recommended in patients with NMD. The benefits of LVR include secretion mobilisation, enhance and maintain compliance of the lungs and chest wall, improved ventilation and alveolar recruitment as well as cough ability; all to decrease pulmonary function regression and prevent respiratory morbidity (Avendaño & Güell, 2003; Hull et al., 2012; Farrero et al., 2013; Toussaint et al., 2018; Castrillo et al., 2019).

Improved inspiratory capacity increases the volume of air that can be expelled during a cough, hence improving the patient's cough effort (McCool & Rosen, 2006; Bach et al., 2007; Toussaint et al., 2009; Torres-Castro et al., 2016; Katz et al., 2019). Management strategies such as LVR techniques are recommended in patients with NMD and aim to decrease pulmonary function regression, respiratory morbidity and enhance HRQoL (Farrero et al., 2013; Chiang et al., 2018; Toussaint et al., 2018; Castrillo et al., 2019). The use of breath-stacking may delay the onset of daytime ventilation usage and decrease the frequency needed for patients who use daytime ventilation (Bach et al., 2007). A study by Marques et al. (2014) in children and adults with SMA and congenital muscular dystrophy, reported that LVR with an ambubag improved assisted and unassisted PECF, especially in patients without scoliosis.

In this survey questionnaire, insufflation techniques were only included as a treatment option under chronic management and SA management strategies (Section C and D). Despite supporting literature, only a minority of participants supported the use of cough augmentation techniques such as breath-stacking/hyperinflation/glossopharyngeal breathing and MI-E (Bach et al., 2007; Benditt & Boitano, 2013; Chiang et al., 2018; Toussaint et al., 2018). Half of the survey participants were unsure if insufflation techniques such as breath-stacking should be used during chronic management of children with NMD, but those that recommended its use supported independent/assisted or a combined technique, depending on the needs of the patient. On the contrary and aligned with clinical practice guidelines, breath-stacking was used by the physiotherapists that treated children with NMD six months prior to the survey (4/6 for acute and 3/6 for chronic). Availability of ambubags, ventilators and cough augmentation devices, variation in implementation and experience or training might affect the use of LVR techniques (Chatwin et al., 2018; Castrillo et al., 2019).

Although the inclusion of LVR in NMD standard care practice is recommended (Finder et al., 2004; Panitch, 2006; Bach et al., 2007; Sejerson & Bushby, 2009; Chiang et al., 2018; Toussaint et al., 2018), this technique has not been widely implemented among patients with DMD, partially due to limited clinical trial data supporting its efficacy and the additional burden of care (Katz et al., 2019). Lung volume recruitment can be performed manually or mechanically, either with a resuscitation bag, a positive pressure ventilator, or devices such as MI-E with a recommended frequency of once to twice, or even three times a day (Finder et al., 2004; Panitch, 2006; Farrero et al., 2013; Torres-Castro et al., 2016; Birnkrant et al., 2018). The advantage of manual LVR techniques such as breath-stacking and GPB is their low cost and relatively easy application (Finder, 2010; Bianchi et al., 2014; Castrillo et al., 2019; Katz et al., 2019).

Breath-stacking may be easier to learn and perform than GPB, but not all patients can master either technique, even with intact glottis function (Perrin et al., 2004; Bach et al., 2007; Toussaint et al., 2018). In children, particularly during respiratory exacerbations, application of single large breaths might be safer and more efficient than multiple, stacked breaths owing to children's smaller lung capacity (Toussaint et al., 2018). Furthermore, LVR techniques require coordinated effort and good oral control, which might be difficult to achieve, especially in younger children.

The chronic case scenario in this survey depicted a non-ambulant patient with progressed disease and a poor cough effort. Survey participants may have assumed that the patient would have severe respiratory muscle weakness and decreased oral control, impacting their treatment choices. Both GPB and spontaneous breath-stacking require good oral control and coordination while the safety and efficacy of using MI-E in patients with severe bulbar dysfunction is also of concern (Perrin et al., 2004; Farrero et al., 2013; Toussaint et al., 2018). Modalities such as IPPB (flow-driven pressure-limited device) might be considered more efficient, easier to use and they also do not always require caregiver assistance (Farrero et al., 2013; Mary et al., 2018; Toussaint et al., 2018). However not all children are likely to benefit from IPPB and these devices are costly (Finder et al., 2004; Dohna-Schwake et al., 2006).

Cough augmentation techniques should be selected according to individual patient comfort, tolerability and clinical effect, as was recommended by some of the participants (Finkel et al., 2018; Castrillo et al., 2019).

2.7.6.2 Supporting expiration (exsufflation)

Assisted expiration can be achieved through manually or mechanically assisted cough techniques in order to improve peak expiratory flow for enhanced airway clearance (Gómez-Merino et al., 2002; Boitano, 2006; Toussaint et al., 2009; Chatwin et al., 2018). Manual cough assistance (MAC) was very well supported by survey participants, and most recommended a combination of thoraco-abdominal thrusts/compressions, for both acute and chronic management of children with NMD, as recommended by clinical practice guidelines (McCool & Rosen, 2006; Finder, 2010; Farrero et al., 2013; Bianchi et al., 2014; Toussaint, Pernet, Steens, Haan & Sheers, 2016). This is well aligned with literature that indicates that the most commonly used and reported exsufflation techniques are MAC and the exsufflation component of MI-E (Gómez-Merino et al., 2002; Anderson et al., 2005; Toussaint et al., 2018). In weaker patients, an additional MAC can be provided during the exsufflation phase of MI-E (Chatwin et al., 2018). Manually assisted cough techniques are cost effective, recommended for use in patients with NMD from an early age and can easily be used within the SA context, as was evident from the survey responses (Finder et al., 2004; Chatwin et al., 2018).

Most survey participants suggested that the frequency of MAC should be either patient dependent or twice per day. Responses regarding the number of assisted coughs advocated per session varied, but the majority supported at least two coughs per session and the remainder ranged from three to 10. Participants were aware of safety precautions and most indicated that if the patient tires, the cough augmentation technique should either be adapted or stopped altogether. Unfortunately, MAC can be labour intensive, at times difficult to perform, requires coordinated effort by the patient and caregiver and is not always effective (McCool & Rosen, 2006; Panitch, 2006; Finder, 2010). Once MAC techniques become less effective, due to factors such as scoliosis or obesity, mechanical cough assistance (MI-E) might be needed, especially when PEF nears the 160L/min threshold (Bach et al., 1997; Gozal, 2000; McCool & Rosen, 2006; Finder, 2010).

2.7.6.3 Supporting both inspiration and expiration (mechanical insufflation-exsufflation)

Mechanical cough assists devices such as MI-E are recommended and used in many high income countries as a cough augmentation method to curb respiratory deterioration leading to intubation and mechanical ventilation (Miske et al., 2004; Finder, 2010; Farrero et al., 2013; Finkel et al., 2018). The combination of both inspiratory and expiratory cough augmentation is well tolerated and could improve cough ability (PECF), more than an unassisted cough effort or assisted insufflation or exsufflation alone (Boitano, 2006; Ishikawa et al., 2008; Auger et al., 2017; Chatwin et al., 2018; Toussaint et al., 2018). Mechanical insufflation-exsufflation may be indicated in cases where patients present with severe respiratory muscle weakness, decreased oral/bulbar control and/or an inability to cooperate with manual insufflation and MAC, or if these techniques have been proven unsuccessful (Finder, 2010; Hull et al., 2012; Auger et al., 2017; Boentert et al., 2017; Toussaint et al., 2018).

Mechanical cough assistance seems to have a positive effect on various outcome measures in NMD, including improved cough ability through enhanced expiratory flow rate, but the majority of studies have focused on adult patients. Studies that included children with NMD suggested short term benefits, improved clinical outcomes, and decreased treatment failure if MI-E is used in adjunct with ACT. Studies further reported that MI-E was generally well-tolerated by patients, without any serious adverse events or complications related to MI-E (Gómez-Merino et al., 2002; Miske et al., 2004; Vianello et al., 2005; Chatwin & Simonds, 2009; Chatwin et al., 2018).

There are potential risk factors associated with the application of positive pressure to the lungs, including aerophagia, gastric distention, pneumothorax, acute cardiovascular effects reflux and aspiration (Bach, 1993; Vianello et al., 2005; Homnick, 2007; Toussaint et al., 2018) some of which may be minimised with the use of gastrostomy tube venting (Finkel et al., 2018). Pneumothorax has been reported in an adult patient with DMD who used daily MI-E and positive pressure ventilation (Suri, Burns & Bach, 2008). Respiratory management guidelines in SMA (Finkel et al., 2018) suggest that in the absence of obstructive airway disease, air trapping and lung parenchymal pathology, there is no significant risk of pneumothorax when using MI-E.

The efficacy of MI-E in children with severe bulbar involvement might be limited and because the optimum pressures, sets and frequency of use for MI-E in the paediatric and adolescent NMD population are unclear, safety remains a concern and more RCT are needed to guide clinical practice (Chatwin et al., 2003; Anderson et al., 2005; Wang et al., 2007; Bhowmik et al., 2009; Auger et al., 2017; Birnkrant et al., 2018). None of the studies included in a systematic review on MI-E in children with NMD reported on morbidity, mortality, quality of life, serious adverse events and other important clinical outcomes; although they suggested short-term benefit with moderate to high levels of potential bias (Morrow, Zampoli, van Aswegen & Argent, 2013). Despite limited high level evidence supporting the use of MI-E in children with NMD, this technique is supported and recommended by international clinical practice guidelines (Finder et al., 2004; Wang et al., 2007; Finder, 2010; Farrero et al., 2013; Finkel et al., 2018). Mechanical cough assistance might not always be available or implemented in all institutions and/or sectors due to cost implications and a lack of coverage by medical insurance (Woolf et al., 1999; Finder, 2010).

Although MI-E is recommended and commonly used in many high income countries, challenges with its use include heterogeneity in application, limited or low level evidence and lack of availability in resource-constrained settings, such as SA, because of high cost and lack of training (McCool & Rosen, 2006; Auger et al., 2017; Toussaint et al., 2018). A study by LoMauro et al. (2014) reported that 59% (22/37) of children and adults with DMD used cough assist devices, which is a much higher usage than reported in SA. Only seven and four survey respondents recommended the use of MI-E for the acute and chronic scenario respectively, despite recommendations in NMD clinical practice guidelines and the progressed respiratory disease of the patients in the case scenarios.

The limited number of survey responses related to MI-E also suggests that a very small proportion of physiotherapists with experience in NMD are knowledgeable regarding mechanical cough augmentation, but all were aware of precautionary measures and indicated that they would not continue with MI-E in the presence of cardiomyopathy. Only two participants responded to questions related to MI-E settings for acute and chronic management, and therefore results may not be a true reflection of the knowledge or opinion of most physiotherapists in SA. However, recommended settings of those that did respond were aligned with international guidelines and recommendations (Finder et al., 2004; Miske et al., 2004; Wang et al., 2007; Chatwin & Simonds, 2009; Finder, 2010; Farrero et al., 2013; Lacombe, Castrillo, Boré, Chapeau, Horvat, Vaugier & Lofaso, 2014; Chatwin et al., 2018; Toussaint et al., 2018).

Various factors could be responsible for these findings, including resource constraints, as these devices have to be imported and are therefore very costly, limited exposure and/or knowledge of physiotherapists in using MI-E in SA and environmental factors such as lack of electricity, especially in the rural areas of SA. This survey highlighted the limited use and possible lack of knowledge regarding mechanical cough assist devices, as none of the physiotherapists used MI-E in the six months prior to the survey. The limited use of MI-E as part of respiratory management in SA was well described by one of the members of the expert panel that provided input on the questionnaire:

“I don’t think in SA any of the mechanical devices are standard treatment. In fact, in our rural settings, not even standard treatment are used.” [sic]

2.7.6.4 Suctioning

Conventional ACT (previously known as chest physiotherapy) and endotracheal suctioning in the paediatric population can cause numerous complications such as raised intracranial pressure, increased metabolic and oxygen demand, pneumothorax and atelectasis (Hough et al., 2010; Morrow, 2019).

Oral suctioning in patients with NMD might assist with secretion management after coughing (Finder et al., 2004; Boitano, 2006; Wang et al., 2007; Finkel et al., 2018). If suctioning is indicated to clear the airways, a clean suction technique should be used, with the necessary precautions, but deep suctioning as well as routine saline instillation through a tracheostomy should be avoided (Farrero et al., 2013; Morrow, 2019).

Suctioning as an airway clearance technique during acute management in children with NMD was strongly supported by the majority of participants and most recommended suctioning once to twice per treatment, at a frequency of twice per day.

As part of chronic care in NMD management, suctioning was supported by nearly 50% of participants, unlike acute management. Those in support of suctioning mostly suggested that the frequency per treatment and per day should be based on the patient's requirements. This aligns with clinical practice recommendations that proximal airway clearance with suctioning may be indicated after secretions have been mobilised in those with an ineffective cough or artificial airway, particularly in infants and young children (Hull et al., 2012; Panitch, 2017; Finkel et al., 2018; Morrow, 2019). However, routine suctioning is not recommended (Chatwin et al., 2018).

2.7.7 Respiratory muscle training in chronic management

Exercise regimes in NMD usually include aerobic exercises, muscle strengthening and respiratory muscle training which aim to reduce respiratory morbidity and improve HRQoL (Gozal & Thiriet, 1999; Avendaño & Güell, 2003; HO, 2005; Aboussouan, 2009). Respiratory muscle training includes strength and endurance training through repetitions of resisted forced inspiration or expiration using pressure threshold devices (Boentert et al., 2017; Woszezenki et al., 2017; Wenninger et al., 2019). Restrictive lung disease in NMD caused by decreased chest and lung compliance leads to a mechanical disadvantage for respiratory muscles, increasing the risk of respiratory morbidity and failure (Gauld, 2009).

The rationale for respiratory muscle training is that improved respiratory muscle strength and endurance may assist with lung function preservation and improved cough ability; potentially delay the onset of respiratory complications and improve the lifespan of patients with NMD (Finder et al., 2004; McCool & Rosen, 2006; Woszezenki et al., 2017). Because NMD usually affects both inspiratory and expiratory muscles (especially in DMD), strengthening these muscles may improve cough efficacy, but studies related to the safety and efficacy of respiratory muscle training in NMD are limited (McCool & Rosen, 2006; Wenninger et al., 2019). Hence respiratory muscle training (IMT and EMT) is not currently recommended as standard therapy in children with NMD and larger, randomised controlled trials have been recommended (Finder et al., 2004; Boentert et al., 2017) (Chapters 1 and 3).

The majority of survey participants supported both IMT and EMT in the chronic management of children with NMD, despite the controversy of this intervention and the limited evidence base (Chapter 1). For both IMT and EMT, participants suggested using resistant and threshold training devices, performed five to ten repetitions, twice a day or depending on the patient. Airway clearance might be improved by inspiration against a fixed inspiratory resistance (Bhowmik et al., 2009), but there is no evidence for the superiority of resistive, threshold or normocapnic IMT (Nici et al., 2006). There is no clear evidence for or against the use of IMT in children and adolescents with NMD (Woszezenki et al., 2017), and the safety of this intervention remains a concern, especially in patients with dystrophinopathies (Chapters 1 and 3). Similarly, EMT for patients with neuromuscular weakness has only been supported by low level evidence and expert opinion, with the suggested mechanism of enhancing peak expiratory pressure, thereby improving cough ability (McCool & Rosen, 2006; Volsko, 2013). Regardless, the majority of survey participants supported using both IMT (75%) and EMT (67.9%), while 67% and 83% of respondents respectively reported having used these techniques clinically for chronic management of children with NMD. Respiratory muscle training devices are available in SA and used in practice, and further investigation is therefore warranted to determine their safety, practicality, acceptability and efficacy within a SA context.

2.7.8 Limitations of the South African standard of care survey

Limited experience in the field of NMD and the length of the questionnaire (approximate completion time of 20 to 40 minutes) likely contributed to the high attrition rate, which increased from Section B to D. Another explanation is that participants may have been more knowledgeable about acute management strategies for NMD as compared to chronic, or that fewer responses were provided for the latter due to other barriers such as resource limitations and time constraints (Iles & Davidson, 2006; Silva et al., 2015; Mu, Bahle-Lampe & Qi, 2018; Stander et al., 2019). Shorter surveys on specific areas regarding treatment in NMD, with focused short answer questions, might produce higher response rates and lower attrition. A recent study indicated that lack of time as a barrier for the uptake of clinical practice guidelines among SA physiotherapists describes a wider phenomenon of challenges that hinder readiness for behavioural change and implementation of EBP (Stander et al., 2020).

Although the response rate was expected, the small number of responses limits the generalisability of the results (external validity) and the sample was not representative of all physiotherapists in SA, but only those that are members of the SASP. The increase of the margin of error from Section A to C and especially Section D relates to the small sample size and constitutes a limitation of this study.

Respondent bias is also a limitation of this survey because those who are knowledgeable about NMD might have been more likely to complete the survey as compared to other physiotherapists. Lung volume recruitment techniques such as insufflation were not part of the treatment options available for acute care (Section B), however, respondents were able to provide open-text responses and the fact that none recommended the use of LVR under acute management, implies that this most likely did not affect the results.

A theoretical framework could however not be applied, neither was an integration/synthesis of results possible for the open-ended responses of survey participants, due to the limited number of responses provided.

As only six participants in total responded to Section D, the results provided cannot be seen as a true reflection of the physiotherapy management strategies used for children with NMD in SA. To improve the sample selection for future studies, questionnaires should be distributed to all SA physiotherapists, via platforms such as theHPCSA. If this small number is a true reflection of the number of SA physiotherapists providing clinical care to patients with NMD, though, then this is greatly concerning, as it implies suboptimal management of vulnerable children with complex medical and health-related needs.

2.7.9 Recommendations for clinical practice

In SA, physiotherapists as first-line practitioners play a primary role in the multi-disciplinary team responsible for evidence-based respiratory management of children with NMD to prevent, delay and/or manage respiratory complications (Piper & Moran, 2006; Goemans & Buyse, 2014; Ho et al., 2015; Landfeldt et al., 2015; Birnkrant et al., 2018; Chatwin et al., 2018).

The heterogeneity of NMD; limited RCT available; limited clinical exposure to children with NMD; and the variety of ventilation devices, ACT and technological advances available might make it difficult for SA physiotherapists to know about clinical practice guidelines and/or be familiar with the different treatment strategies available (Straub, 2013; Vry et al., 2016; Chatwin et al., 2018; Rose et al., 2018). South African physiotherapists may have had little or no exposure to the range of cough augmentation techniques and devices at undergraduate and/or post-graduate levels. Likewise, a lack of financial and human resources might limit the availability and use of these techniques after qualification.

Although the use of mechanical cough augmentation devices such as MI-E in patients with NMD is recommended in various clinical practice guidelines, the devices and the clinical expertise are not readily available in many middle- and low-income countries such as SA (Birnkrant et al., 2018; Chatwin et al., 2018; Finkel et al., 2018; Toussaint et al., 2018). This survey confirmed the limited use and expertise of respondents regarding the use of mechanical cough assist devices, with none of the physiotherapists having used MI-E in the six months prior to the survey. Manual LVR and cough augmentation techniques such as the use of manual insufflation and MAC might be cost-effective alternatives to consider (Anderson et al., 2005; Finder, 2010; Bourke, 2014; Torres-Castro et al., 2016). Although MAC was well supported by most of the survey participants, there was limited support for LVR/breath-stacking. In SA, with limited resources and many patients living in rural areas, it is imperative to implement inexpensive treatment strategies such as GPB (requiring no equipment), or other low cost options such as LVR with an ambubag, rather than expensive insufflation/exsufflation devices requiring electricity (Toussaint et al., 2018). Limited evidence is available to indicate the superiority of any specific ACT in children with NMD, however, clinical practice guidelines support the use of NIV, LVR (with GPB; ambubag) and MAC to improve ventilation and airway clearance (Wang et al., 2007; Wang et al., 2010; Benditt & Boitano, 2013; Boentert et al., 2017; Birnkrant et al., 2018; Chatwin et al., 2018; Finkel et al., 2018).

South African physiotherapists should be empowered to implement these safe, cost-effective techniques to reduce morbidity and mortality in SA children living with NMD. Raising awareness and providing access to clinical guidelines, equipment and training in both public and private healthcare sectors might increase knowledge and facilitate the implementation of NMD clinical practice guidelines among SA physiotherapists (Straub, 2013; Bircher & Kuruvilla, 2014; Rose et al., 2018; Stander et al., 2019; Stander et al., 2020).

2.7.10 Recommendations for future research

Clinical practice guidelines for the most common types of NMD (DMD, congenital myopathies and SMA) have been published (Wang et al., 2007; Bushby et al., 2010; Wang et al., 2010; Finkel et al., 2018; Birnkrant et al., 2018). This survey provides novel data regarding the understanding and implementation of NMD clinical practice guidelines among physiotherapists in SA.

Identifying the barriers to implementation of guidelines in the public and private healthcare sectors was beyond the scope of this study, but should be considered in future research (Iles & Davidson, 2006; Silva et al., 2015; Mu et al., 2018; Stander et al., 2019; Stander et al., 2020).

Future surveys can also be conducted in SA to establish the adherence of other categories of healthcare professionals with NMD clinical practice guidelines, including the frequency of follow-up specialist clinic visits in both the public and private healthcare sectors (Landfeldt et al., 2015). Although this survey provided an indication of SA physiotherapists' knowledge and perception of respiratory management in children with NMD, due to the poor response rate, there is still uncertainty about which respiratory management techniques are implemented in SA in both acute and chronic settings. To obtain results that are more generalisable to the SA physiotherapy population, future studies should target all HPCSA registered physiotherapists and not only those registered with the SASP.

Context-specific research is recommended to identify the most efficient, feasible and safe respiratory care techniques to decrease respiratory morbidity and improve HRQoL in SA children with NMD (Dohna-Schwake et al., 2006; Panitch, 2017). The effect of respiratory management of patients with NMD should be assessed using longer-term, clinically relevant end-points such as frequency of hospitalisations, length of hospital stay, HRQoL and preventing long-term respiratory complications instead of short term effects such as improved cough, quality of sputum, respiratory score or acute change in lung function (Tzeng & Bach, 2000; Hess, 2001; McCool & Rosen, 2006; Auger et al., 2017). Since IMT was strongly recommended by SA physiotherapists responding to this survey, and because these training devices are readily available and relatively inexpensive in this country, this intervention was selected as the focus of further research in this dissertation, to determine the safety and efficacy of IMT in SA children with NMD.

Due to the relatively low prevalence and a broad spectrum of clinical presentations of NMD, the availability of systematic reviews and scientifically rigorous randomised controlled trials to guide clinical practice, especially in children, remain limited (Moseley et al., 2002; Finder et al., 2004; Hull et al., 2012; Woszezenki et al., 2017). Sufficiently powered, multi-centre randomised controlled trials and the development of context-specific clinical practice guidelines are therefore recommended to establish safe, effective and feasible respiratory management strategies, for children with NMD (Rosiere et al., 2009; Straub, 2013; Volsko, 2013; Birnkrant et al., 2018; Stander et al., 2019).

Although general evidence-based clinical recommendations are useful to guide practice, individualised patient-centred care should be prioritised, with respiratory management modalities chosen according to the individual patient presentation (severity, progression of the disease), level of development, risk factors, outcome and preferences (Woolf et al., 1999; Avendaño & Güell, 2003; Toussaint et al., 2018; Morrow, 2019).

To guide such patient-centred multi-disciplinary healthcare service delivery, research is recommended to determine the respiratory care needs and perspectives of SA patients, families and caregivers affected by NMD.

2.8 Conclusion

Decreased airway clearance and cough ability in patients with NMD requires respiratory physiotherapy intervention (Farrero et al., 2013). The results of this survey suggest that few SA physiotherapists may have clinical experience and expertise regarding the respiratory management of children with NMD, which requires skilled clinicians (Rose et al., 2018; Toussaint et al., 2018).

Although respondents were generally aware of international NMD clinical practice guidelines and recommendations they still favoured traditional, manual ACT (McCool & Rosen, 2006; Finkel et al., 2018). This survey confirmed that similar to other countries, healthcare in SA falls short regarding the uptake and implementation of the recommended clinical practice guidelines for standard care of children with NMD (Landfeldt et al., 2015; Boentert et al., 2017; Stander et al., 2019).

This survey provided novel insight into the knowledge, perspectives and implementation of NMD clinical practice guidelines among SA physiotherapists. Results from this survey can inform healthcare managers and policymakers, especially in light of the proposed changes to the SA healthcare system, as well as planning for future clinical trials.

Chapter 3: WHAT DOES THE LITERATURE SAY?

Inspiratory muscle training for paediatric and adolescent patients with neuromuscular disease: a systematic review.

3.1 Background and introduction

The diaphragm is the strongest inspiratory muscle and diaphragmatic weakness or dysfunction can cause severe respiratory complications. These complications include decreased lung volumes (such as vital capacity (VC)), altered and ineffective breathing, decreased thoracic and shoulder mobility, decreased chest expansion and alveolar ventilation, poor secretion clearance (cough ability), chronic respiratory insufficiency and ultimately may lead to respiratory failure and death (Wang et al., 2007; Ambrosino et al., 2009; Farrero et al., 2013; Boentert et al., 2017). As the child with neuromuscular disease (NMD) grows older and their condition progresses, respiratory complications may increase in frequency and severity (Nicot et al., 2006; Meier et al., 2017; Panitch, 2017; Kinane et al., 2018).

3.2 Description of how inspiratory muscle training might work

Inspiratory muscle weakness is the impaired capacity of the inspiratory muscles (mainly the diaphragm) to generate sufficient contractile force (Eagle, 2002; Wenninger et al., 2019). Inspiratory muscle strength is important, as it influences both the volume preceding a cough and the length-tension relationship of the abdominal muscles, which both affect the amount of force and airflow that can be produced during a cough (Finder, 2010; LoMauro et al., 2014; Chatwin et al., 2018). The rationale for inspiratory muscle training (IMT) in NMD is based on the assumption that improving or maintaining inspiratory muscle strength may preserve lung function over time, thereby potentially reducing the risk of recurrent respiratory infections (Wanke et al., 1994; Koessler et al., 2001; Finder et al., 2004) and improving activity levels and participation of patients in their schools and communities.

The diaphragm is responsive to training, with a change in muscle fibre size/volume (hypertrophy); an increase in the number of muscle fibres and improved circulation (Pinto & Carvalho, 2014; Wenninger et al., 2019). The effect of IMT may be influenced by the type of NMD (severity and nature) as well as the frequency, intensity and specificity of training (Aboussouan, 2009; Woszezenki, Paulo Heinzmann-Filho, & Donadio, 2017; Wenninger et al., 2019). Other studies confirm this notion, as the effect of IMT on inspiratory muscle strength and/or endurance in patients with NMD seems to be dose-dependent (Winkler et al., 2000; Topin et al., 2002; Yeldan et al., 2008).

Longer-term IMT might also be more effective than short-term training, as a study conducted among boys with Duchenne muscular dystrophy (DMD) (9-14 years old) by (Rodillo et al., 1989) could not convincingly show improvement in lung function due to short-term IMT (18 days). Despite the limited evidence for the use of IMT in NMD, especially among patients with dystrophinopathies, observational studies conducted in Chile and Brazil, mainly among patients with DMD, have suggested positive outcomes (Bezerra, Borges & Brunherotti, 2010; Núñez, Araos & Delgado, 2014; Nascimento, de Andrade, de Faria, de Souza, Jacó, Rocha & Borges, 2015). Further research, especially on the long-term outcomes of IMT is therefore recommended, to guide clinical practice.

As mentioned in Chapter 1, some authors have suggested that IMT might be more beneficial in some types of NMD than others (Boentert et al., 2017) and preferably implemented relatively early in the disease progression (Gozal & Thiriet, 1999; Winkler et al., 2000; Koessler et al., 2001; Huang et al., 2003). The patient's level of respiratory muscle weakness might affect their response to respiratory muscle training (HO, 2005; Aboussouan, 2009) and therefore training programmes should be individualised and reviewed regularly as the condition progresses (HO, 2005). Inspiratory muscle training might improve respiratory function and reduce pulmonary morbidity, but it could also accelerate fatigue of weakened muscles and cause muscle damage, especially in patients with dystrophinopathies (Sander et al., 2000; Finder et al., 2004; Woszezenki et al., 2017). Due to these safety concerns, IMT might be considered as an adjunct therapy in patients presenting with respiratory muscle weakness (Topin et al., 2002; Nici et al., 2006; Hull et al., 2012), but is not fully endorsed by the American Thoracic Society (ATS)(Finder et al., 2004). Consequently, when implementing muscle strengthening and IMT programmes, especially in children with dystrophinopathies such as DMD, caution should be taken to not overexert patients during training.

3.3 Rationale and significance of the study

Promising pulmonary function outcomes due to IMT in other conditions such as stroke, chronic airflow limitation, chronic obstructive pulmonary disease (COPD) and cystic fibrosis (CF) have been reported (Dekhuijzen, Folgering & Van Herwaarden, 1991; Lötters, Van Tol, Kwakkel & Gosselink, 2002; Geddes et al., 2008; Hill, Cecins, Eastwood & Jenkins, 2010; Sutbeyaz, Koseoglu, Inan & Coskun, 2010). Other suggested benefits of IMT, such as decreased dyspnoea, increased exercise capacity and health-related quality of life (HRQoL) is supported by weak evidence and warrants further research (Geddes et al., 2008; Reid, Geddes, O'Brien, Brooks & Crowe, 2008; Xiao et al., 2012; Rietberg, Veerbeek, Gosselink, Kwakkel & van Wegen, 2017).

In healthy subjects, IMT has been shown to improve maximal pressure generation ability with a corresponding decrease in inspiratory motor drive (Huang et al., 2003). There is a need for well-designed studies among different patient populations because “the ideal respiratory muscle training programme has as yet not been identified” (Haas et al., 2007).

Inspiratory muscle training may be useful in improving and/or preserving respiratory function; delaying the onset of serious respiratory complications; decreasing discomfort, prolonging patient’s lives and improving HRQoL in NMD (Servera et al., 2003; HO, 2005; McCool & Rosen, 2006; Finder, 2010; Aslan et al., 2013); but study findings in this population are limited and conflicting. The use of IMT in children and adolescents with NMD to improve inspiratory muscle strength and/or endurance is still controversial and warrants further research. The purpose of this systematic literature review was therefore to determine the safety and efficacy of IMT using an external device (threshold, resistance or flow) and its effect on pulmonary function, including lung volumes and flow, cough ability, inspiratory muscle strength and endurance, exercise capacity and dyspnoea scores as well as HRQoL in children (5-18 years) with NMD, presenting with respiratory muscle weakness.

3.4 Objectives

The specific objectives for this study were to determine the effect of IMT in children and adolescents (5-18 years) based on primary and secondary outcome measures as outlined in Chapter 1 (1.3.1).

The NMD conditions (OPERATIONAL DEFINITIONS) included in this review were congenital or acquired conditions that manifest in the paediatric and adolescent population, including (but not limited to):

- *Muscular dystrophies such as Duchenne (DMD), Becker (BMD), Emery-Dreifuss (EDMD), Limb-girdle (LGMD), Congenital myotonic muscular dystrophy (DM), distal muscular dystrophy (DD), congenital muscular dystrophy (CMD) and myopathies such as congenital myopathies, nemaline rod myopathy and central core disease (CCD).*
- *Motor neuron diseases including spinal muscular atrophy (SMA I, SMA II, SMA III).*

3.5 Methods

This review was based on the Cochrane methodology for systematic reviews (Higgins & Green, 2008) and was registered with Prospero (PROSPERO (NIHR): <https://www.crd.york.ac.uk/prospero>) in September 2014 (CRD42014013875).

3.5.1 Criteria for considering studies for this review

3.5.1.1 Types of studies

Randomised controlled trials, cross-over randomised controlled trials (RCT), and quasi-experimental/clinical controlled trials (CCT) of IMT making use of an external device (threshold, resistive or flow) in ventilated and non-ventilated patients, compared to no intervention/sham IMT intervention/an alternative intervention group were included.

3.5.1.2 Language, date and document format restrictions

The reviewers included studies in the following languages: Afrikaans, English, Dutch, French, German, Portuguese and Spanish to limit language bias. Other non-English studies were also considered for translation if English abstracts were available. The most recent publications and reports (including grey literature such as conference abstracts and proceedings) were included in this review in order to minimise publication bias. Language experts were consulted for articles written in languages other than Afrikaans or English.

3.5.1.3 Types of participants

All children between the ages of five to 18 with a confirmed diagnosis of NMD⁷, with resulting respiratory muscle weakness⁸, were eligible for inclusion. Descriptions of participant characteristics indicating respiratory muscle weakness that were considered included PEF <270L/min⁹, forced vital capacity (FVC) <50% predicted and inspiratory muscle strength (Pimax) or expiratory muscle strength (Pemax) of <80cmH₂O (Bach et al., 1997; ERS, 2002; Lötters et al., 2002; Finder et al., 2004; Guglieri & Bushby, 2011; Farrero et al., 2013).

Participants were defined according to age, namely paediatric/children (five to <13 years) and adolescents (13 to 18 years) (OPERATIONAL DEFINITIONS). Adults were excluded from this review because they differ anatomically, physiologically and pathologically from children and adolescents (Schechter, 2007). All children with NMD within a hospital/clinic setting, outpatient or chronic care institution/centre were included.

⁷ Confirmed with medical diagnostics such as family history, clinical assessment, muscle biopsy, genetic testing, electrodiagnostic testing (EMG, ECG, nerve conduction studies),

⁸ Participants included in studies with respiratory muscle weakness/insufficiency as indicated by objective outcome measures such as pulmonary function testing, cough ability (PECF), inspiratory muscle strength (Pimax/MIP, SNIP) and/or Ultrasound of the diaphragm.

⁹ Minimum normal PEF value in adults 400/Lmin which is reached by 12, 13 years of age (Bach & Saporito, 1996; Bianchi & Baiardi, 2008; Chiang et al., 2018). A cut-off value for children has not been determined as yet.

3.5.1.4 Types of interventions

For this systematic review, IMT was defined as training/intervention targeted at improving inspiratory muscle strength (diaphragm, intercostals) or delaying respiratory regression in NMD using any external device with flow, resistive and/or threshold load in ventilated and non-ventilated patients. Studies including different types and makes of IMT devices were included as well as a variety of IMT protocols (intensity, frequency, duration and administration). Studies were included whether treatment was delivered and/or supervised by health professionals or caregivers/parents.

- Inspiratory muscle training used as an intervention (modality), at hospital, home or an institution (centre) during acute, sub-acute and chronic stages, were included.
- Studies that assessed both IMT and expiratory muscle training (EMT) were included in order to analyse the IMT component.
- Specific IMT (experimental) was compared to no intervention/standard care (inactive control), sham IMT intervention or alternative respiratory training intervention(s) (active control).

3.5.1.5 Types of outcome measures

The following primary and secondary outcomes were considered:

Primary outcomes

Primary outcomes indicating the level of morbidity were included:

- Hospitalisations (frequency and duration);
- Rate of respiratory infections (based on the need for antibiotics);
- Any adverse events¹⁰ related to the IMT intervention.

Secondary outcomes

Secondary outcomes indicating the patient's pulmonary function including inspiratory muscle strength as well as health-related quality of life (HRQoL):

- Pulmonary function tests including measures of lung volumes and flow (VC, FVC, forced expiratory volume in one second (FEV₁) and total lung capacity (TLC)), plethysmography and multiple gas washout techniques;
- Measures of cough efficacy (PECF/PCF¹¹);

¹⁰ Including, but not limited to, mild to moderate adverse events such as chest pain/discomfort (hyperinflation/barotrauma), nausea/vomiting, fatigue and gastric distension; severe adverse events such as pneumothorax, desaturation, bradycardia, muscle damage, disease progression/muscle deterioration, cardiac arrest, respiratory failure, bleeding and death.

¹¹ Peak expiratory cough flow (PECF) or peak cough flow (PCF)

- Vital signs: Heart rate (HR), Respiratory Rate (RR) and measures of gaseous exchange (e.g. Partial oxygen pressure (PaO₂), Partial carbon dioxide pressure (PaCO₂));
- Diaphragm thickness through ultrasound imaging;
- Measures of inspiratory muscle strength, including Pimax/MIP, maximum insufflation capacity (MIC), sniff nasal inspiratory pressure (SNIP);
- Respiratory muscle endurance (e.g. 12sMVV);
- Transdiaphragmatic pressure (Pdi) and;
- Health-related quality of life measured by any valid measure (e.g. PedsQL).

Both primary and secondary outcomes measures were considered for all time frames (short, medium and long-term), and not only at selected time points.

3.5.2 Search methods for identification of studies

Searches were mostly electronic, but other sources such as abstracts and conference proceedings were also included.

3.5.2.1 Electronic searches

Fifteen online databases were searched from inception to October/November 2014 for randomised controlled trials, quasi-experimental/clinical controlled trials, cross-over trials, pre-experimental and on-going studies by making use of pre-specified search strategies (Appendix Bi):

- Africa-wide information databases
- The Cochrane Central Register of Controlled Trials (CENTRAL)
- Cumulative Index to Nursing and Allied Health Literature (CINAHL)
- The Cochrane Neuromuscular Disease Group Specialized Register
- Medline via Ebsco Host
- Pan African Clinical Trials Registry (PACTR)
- PEDro
- Pubmed
- Respiratory care (online journals)
- The South African National Clinical Trial Register (SANCTR)
- Sabinet (E-theses and dissertations) including WorldCat, SACat and SANB
- Science Direct
- Scopus
- Trial registers such as Clinicaltrials.gov (for on-going studies)
- WHO International Clinical Trials Registry Platform (ongoing trials)

The keywords used for searching the databases included conditions (NMD commonly seen among children and adolescents), intervention and study design/type (combined with the truncation “AND”):

- neuromuscular diseases OR neuromuscular dis* OR NMD OR muscular dystrophy OR Duchenne* OR spinal muscular atrophy OR central core disease OR congenital myopathy OR restrictive lung dis* OR respiratory muscle condition OR diaphragm* weakness OR diaphragm* strength*
- respirat* musc* training OR respirat* musc* strength* OR respirat* musc* endurance OR inspirat* musc* training OR inspirat* musc* strength* OR inspirat* musc* endurance OR IMT.
- random* OR trial* OR clinical trial OR placebo OR comparative stud* OR controlled trial OR CCT OR RCT OR double-blind* OR single-blind* OR cross-over.

Truncation (*) and “wild cards” were used to ensure that all relevant articles were included.

3.5.2.2 Searching other sources

To ensure the inclusion of all relevant information, the following sources were also searched:

- Conference abstracts, proceedings and internal reports from international and national NMD, cardiorespiratory/cardiopulmonary and physiotherapy congresses (2004-2014) were screened for relevant studies.
- Research funders, device (IMT) manufacturers, as well as experts in the field, were contacted to identify any additional publications or relevant information such as unpublished trial data.
- References from included articles were hand-searched to ensure that all additional, relevant studies were included. Where needed, formal letters of request were sent to authors of the included articles to identify any additional published and unpublished data.
- Ongoing trials were included by searching ClinicalTrials.gov as well as Pubmed (publicaccess.nih.gov/policy.htm).
- International and national experts in the field and physiotherapy colleagues were contacted via email to identify any additional, relevant published and unpublished data.

3.5.3 Data collection and analysis

3.5.3.1 Selection of studies

Fifteen electronic databases were searched by the primary researcher (AH¹²) using the pre-specified search strategies. The number of citations per database was documented and a list of potential articles was compiled (titles and abstracts).

¹² AH=Anri Human

After each database was searched, two reviewers (AH & LC¹³) independently reviewed the abstracts to determine eligibility for inclusion. Following the independent selection of eligible papers for full-text review, the reviewers compared their findings. Any disagreement was resolved through discussion in order to reach a consensus and no arbitration was needed. The final sample included seven eligible articles for data extraction.

3.5.3.2 Data extraction and management

Two reviewers (AH & BM¹⁴) independently extracted data from the seven included studies using a pre-structured data extraction form (Appendix Bii). Information was collected on participants (demographic data, diagnosis, clinical picture/presentation, inclusion/exclusion criteria, co-morbidities, trial setting, allocation procedure, blinding, number of patients/participants), interventions (type of IMT device, resistance settings, duration and frequency of training) and the results from the studies (outcomes measurements, precision, measure of variability, descriptive statistics).

Any disagreements between the two researchers pertaining to data extraction were resolved through discussion and consensus was reached. No arbitration was needed. The reviewers attempted to obtain additional information or data where needed by contacting the authors of the included studies. The primary researcher (AH) collated and entered data into the Revman software program version 5.2. The accuracy of data capturing was confirmed by a reviewer/research assistant (LC).

3.5.3.3 Assessment of risk of bias in included studies

The methodological quality of the included studies was independently assessed by two reviewers (AH; BM) using the Cochrane Collaboration “risk of bias” tool (Higgins & Green, 2008): Selection bias (sequence generation; allocation concealment), performance bias (blinding of participants; staff and other potential threats to validity), detection bias (blinding of outcome assessment and other potential threats to validity), attrition bias (incomplete outcome data), reporting bias (selective outcome reporting) and other types of bias were assessed. These various types of bias were described for each study as low risk (green), high risk (red) and unclear risk of bias (yellow). Differences in assessment between the reviewers were resolved through discussion and there was no need for arbitration.

¹³ LC=Lieselotte Corten

¹⁴ BM=Brenda Morrow

3.5.3.4 Measures of treatment effect

Results from only two studies could be pooled for the outcome inspiratory muscle strength (Pimax), as they used similar techniques of assessment and execution. Data analysis was performed using RevMan software version 5.2. None of the data extracted for any other outcome measures could be pooled for a meta-analysis, owing to the heterogeneity of outcome measures and methodology of assessment used in these studies, as well as insufficient data being supplied. The remaining data were therefore synthesised narratively, making use of tables to describe the included studies individually.

3.5.3.5 Unit of analysis issues

For cross-over studies, we intended to only include the first period data for analysis. However, the included studies that made use of more than one intervention group or performed a cross-over trial did not report separate period or individual group data and these data could not be obtained; therefore meta-analyses could not be performed (Ramsay, 2006; Higgins & Green, 2008).

3.5.3.6 Dealing with missing data

The reviewers attempted contacting the authors of included studies for missing data and additional information. No response was received from the authors after numerous attempts.

3.5.3.7 Assessment of heterogeneity

The heterogeneity level for the seven included studies could not be calculated as the studies used different outcome measures and were not comparable. Although five studies used inspiratory muscle strength (Pimax), the measurements differed to such an extent that this outcome could not be compared among all five studies. The heterogeneity between the only two comparable studies for Pimax was assessed by making use of the Chi-square test and I-square statistic. A Chi-square level of $p < 0.1$ was considered statistically significant.

3.5.3.8 Assessment of reporting biases

Due to an insufficient number of included studies in the final sample, a funnel plot could not be applied to determine reporting bias.

3.5.3.9 Data synthesis

Due to the heterogeneity of outcome measures used, a meta-analysis of the seven included studies could not be performed, hence a systematic approach was followed and a narrative synthesis was done.

3.5.3.10 Subgroup analysis and investigation of heterogeneity

The factors that could influence heterogeneity across studies included the following:

Age, sex, various types of NMD (diagnoses), disease stage/severity, co-morbidities, mobility/functional independence (Vignos and Brooke scale), presence or degree of scoliosis (Cobb angle), bulbar involvement, acute and chronic setting, IMT device used (resistance, threshold, flow), frequency and duration of the IMT, intensity/resistance and repetitions of IMT, rest-periods in-between sets, interfaces used with IMT and duration of follow-up.

3.5.3.11 Sensitivity analysis

Sensitivity analysis aims to determine whether conclusions are robust, based on methodological decisions made during the review process. These methodological aspects include eligibility criteria (inclusion/exclusion criteria), imputing missing data and analysis method (Higgins & Green, 2008).

A sensitivity analysis could not be conducted due to the small number of studies included in the final sample.

3.6 Results

3.6.1 Description of studies and search results

The search of fifteen databases yielded a total of 32 006 titles (Figure 3.1), subdivided by database: Africa-Wide (n=83), CENTRAL (n=5975), CINAHL (n=2249), Clinicaltrials.gov (n=39), Cochrane neuromuscular Disease Group (n=100), ICTRP (n=1674), Medline (n=2591), PACTR (n=0), PEDro (n=1251), Pubmed (n=1475), Respiratory Care Journal (n=5272), Sabinet (n=0), SANCTR (n=264), Scopus (n=5126) and Science Direct (n=5907).

After duplicates were removed, 119 abstracts remained, but based on eligibility criteria only 34 abstracts were included for full-text review. After full-text review, 25 were excluded for various reasons, including methodology, limited data, conditions, age range and interventions other than IMT (Appendix Biii).

Six databases (Africa-wide, CINAHL, Cochrane Neuromuscular Disease Group, PACTR, SANCTR and Sabinet) did not yield any articles that could be included in the final sample. Nine studies (seven articles and two on-going trials) met the inclusion criteria and were included in the final sample (Figure 3.1).

The on-going trial studies included were: "Respiratory Muscle Strength in Patients With NMD" and "Patterns of respiratory muscle involvement and the effects of respiratory muscle training in muscular dystrophy". The authors were contacted in June 2015 for the results from these studies, but no response was received. From the reference lists of the included studies, nine titles were identified for possible inclusion but were excluded based on abstract and full-text (Figure 3.1).

For additional information, funded articles (National Centre for Biotechnology information (NCBI): www.ncbi.nlm.nih.gov/pmc) and manufacturers' websites (Respironics: <http://www.respironics.com>; Powerbreathe: <https://www.powerbreathe.com>) were searched and experts/specialists in the field, colleagues and funders were consulted. No additional studies were identified for inclusion in the final sample.

The final sample, therefore, included seven studies for appraisal, data extraction, analysis and synthesis (Martin, Stern, Yeates, Lepp & Little, 1986; Rodillo et al., 1989; Stern, Martin, Jones, Garrett & Yeates, 1989; Wanke et al., 1994; Gozal & Thiriet, 1999; Topin et al., 2002; Yeldan et al., 2008) and two on-going trials (from clinicaltrials.gov and ICTRP respectively). The search results are depicted in Figure 3.1.

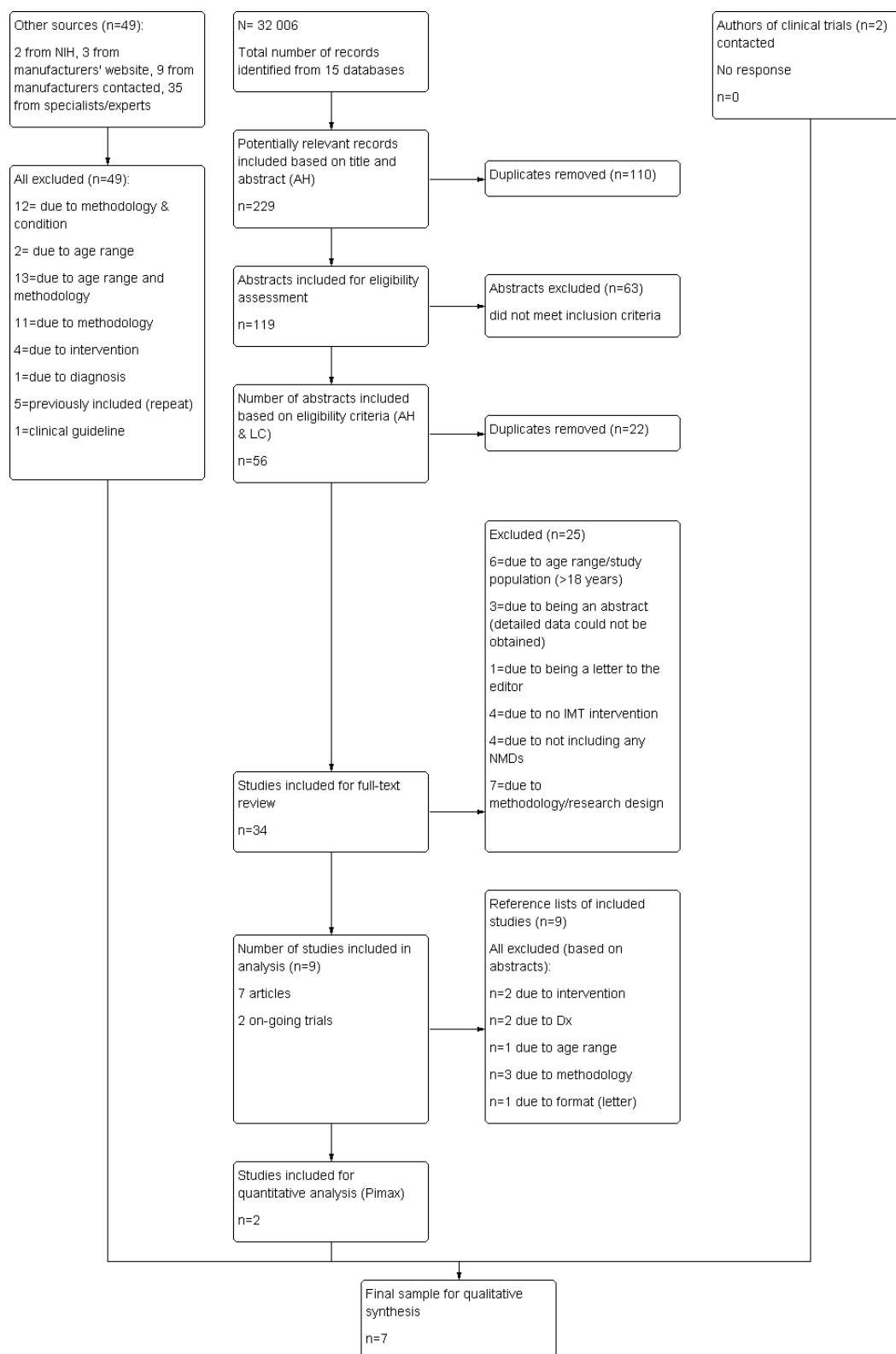


Figure 3.1: Flow diagram of study selection and results

3.6.2 Included studies

Four of the included studies were randomised controlled trials (Rodillo et al., 1989; Wanke et al., 1994; Gozal & Thiriet, 1999; Topin et al., 2002); two were randomised cross-over trials (Martin et al., 1986; Stern et al., 1989) and one study was a quasi-randomised trial that made use of alternate allocation (Yeldan et al., 2008)(Table 3.1). All the included articles were published in English, although language was not an exclusion criterion.

The seven studies were conducted in various, mostly high income countries, and none of the research was conducted in Africa. Two studies (Martin et al., 1986; Stern et al., 1989) were conducted in South Australia whilst the others were from the USA (Gozal & Thiriet, 1999), UK (Rodillo et al., 1989), France (Topin et al., 2002), Austria (Wanke et al., 1994) and Turkey (Yeldan et al., 2008). All the included studies conducted IMT in a chronic environment (home, school or medical centre) and not in an acute setting (hospital).

3.6.3 Participants

From a total of 168 participants in the seven included studies, only 148 (88%) completed the interventions/trials (range: 16-41). Participant age ranged between seven and 34 years and only three of the included studies recruited children within the specified age range of five to 18 years (Rodillo et al., 1989; Gozal & Thiriet, 1999; Topin et al., 2002). The remaining four studies included mixed data on paediatric and adult participants, making separation of data impossible (Martin et al., 1986; Stern et al., 1989; Wanke et al., 1994; Yeldan et al., 2008). Two studies did not specify age range and reported only means (M) and standard deviations ($\pm$ SD) of 22.5 $\pm$ 7.5 years (experimental/intervention); 24.27 $\pm$ 9.4 years (control) (Yeldan et al., 2008) and 14.7 $\pm$ 4.5 years (experimental/intervention); 12.6 $\pm$ 1.8 years (control) (Topin et al., 2002). The majority of participants (112/168) were male and 24 were female. In one study, Wanke et al. (1994) did not specify the sex of their 30 participants, while the study by Yeldan et al. (2008) did not report the sex of two participants who did not complete the study. The narrative description of the included studies can be seen in Table 3.1.

Table 3.1: Systematic literature review: Included studies (n=7).

Authors, date, country	Study design	Sample size, age, sex	Diagnosis	Clinical picture	Intervention	Control	Conclusion
Martin et al.1986 (Australia)	RCT (cross-over)	N=18 (allocated). Mean age 14.2 years, all male. <u>Group 1(n=9)</u> 7-12 years. <u>Group 2 (n=9; 1 died)</u> 11-20 years. Groups were pooled, no separate data available for the different periods of the cross-over trial.	DMD	n=17 (non-ambulant). n=1 (ambulant). Disease severity was expressed as VC (% predicted) and ranged from 9-82 (mean: 47.7).	Bore diameters in mouthpiece, resistance determined based on the resistance that caused exhaustion within three minutes. (flow limitation with resistance).	No treatment.	Specific respiratory training in DMD led to improved ventilatory muscle endurance, but muscle strength remained unaffected. Improvement most likely due to training of type I muscle fibres. Longer and more rigorous trials recommended.
Rodillo et al. 1989 (UK)	RCT	N=22 allocated, 20 analysed, all male. <u>Experimental</u> (n=9). <u>Control</u> (n=11). Separate group data not provided. Mean age: 11.6 years (range 9-14).	DMD	Not specifically described. Non-ventilated.	Triflow II Spirometer (Cheseborough Ponds) Resistance device. (Resistance increases with increased flow, no values provided). Arbitrary 6-point scale.	Mini peak flow meter. 10 expirations per day. Once a day for 18 days.	Short-term respiratory muscle training showed no benefit. Supine lying was associated with impaired lung function, possible clinical relevance post-operatively.
Stern et al. 1989 (Australia)	RCT (cross-over)	N=18 allocated, 12 analysed	DMD	<u>Group 1 (n=7)</u> Non-ambulant.	Inhale through a mask whilst playing a video	No training for 6 months	Some respiratory function changes could be attributed to respiratory muscle training

Authors, date, country	Study design	Sample size, age, sex	Diagnosis	Clinical picture	Intervention	Control	Conclusion
		<u>Group 1</u> (n=7) Mean age: 15 years (range: 12.8-17.1 years) All male <u>Group 2</u> (n=11) Mean age: 15 years (range: 10.4-23.4 years) All male		Non-ventilated. <u>Group 2</u> (n=9) Non-ambulant n=2 (ambulant) Non-ventilated.	game – work of inspiratory muscles had to exceed a pre-set level. Range of restriction holes fitted to an intake tube (6.35; 4.76; 3.18 and 2.38mm).		in the short term; this study could not prove the value of long-term training. Despite some individual improvements after 6 months of training (FVC, respiratory muscle endurance and strength), overall results were not statistically significant.
Wanke et al. 1994 (Austria)	RCT	N=30 allocated, 21 analysed, sex not specified <u>Experimental (n=15):</u> 10 analysed, 5 discontinued and analysed separately (VC <25%) Mean age $\pm$ SD: 13.6 $\pm$ 4.5 (Range 10-24) <u>Control (n=15)</u> 11 analysed, 1 excluded 3 analysed separately (VC <25%)	DMD	n=12 (experimental: non-ambulant) n=11 (control: non-ambulant) Functional capacity stage: Inkleby 9 No signs or symptoms of: Respiratory Tract Infection; Inspiratory Muscle Fatigue, or Sleep Disturbance. Non-ventilated.	IMT using specially constructed training apparatus.	No treatment	A specific IMT programme, if implemented during the early stages of DMD, can be effective.

Authors, date, country	Study design	Sample size, age, sex	Diagnosis	Clinical picture	Intervention	Control	Conclusion
		Mean age $\pm$ SD: 14.5 $\pm$ 3.8 (Range 9-20)					
Gozal & Thiriet 1999 (USA)	RCT	N=41, 32 ♂, 9 ♀ <u>Group 1: (NMD)</u> n =11, Mean age $\pm$ SD: 12.7 $\pm$ 2.2 years <u>Group 2: (NMD)</u> n= 10, Mean age $\pm$ SD: 13.2 $\pm$ 2.6 <u>Group 3:</u> Matched control for Group 1 n= 10, Mean age $\pm$ SD: 12.9 $\pm$ 2.4 <u>Group 4:</u> Matched control for Group 2 n= 10, Mean age $\pm$ SD: 13.0 $\pm$ 2.9	DMD SMA III	Group 1 & 2 (NMD): Functional capacity stage Inkleby 9, non-ambulant.	Group 1: Threshold IMT and Threshold PEP.	Group 2: NMD (no training) Group 3: Control RMT Group 4: Control (no training)	Respiratory muscle training in NMD causes long-lasting improvement in resp. load perception and may be associated with decreased respiratory symptoms. Improvement in expiratory muscle strength was rapidly reversible once training stopped. Further studies recommended assessing the long-term effect of respiratory muscle training on morbidity and quality of life in NMD.
Topin et al.2002 (France)	RCT	N=16 (allocated and analysed), all males	DMD	N=16 (non-ambulant).	Threshold: Healthscan Products Inc, Cedar Grove, NJ, USA	Placebo/ sham IMT 5% of Pimax	IMT improves respiratory muscle endurance in DMD, but the efficacy of training appears to be dose-dependent.

Authors, date, country	Study design	Sample size, age, sex	Diagnosis	Clinical picture	Intervention	Control	Conclusion
		<u>Experimental (n=8):</u> Mean age $\pm$ SD: 14.7 $\pm$ 4.5 years <u>Control (n=8):</u> Mean age $\pm$ SD: 12.6 $\pm$ 1.8 years		No major spinal deformities, and clinically stable at evaluation, no symptoms of inspiratory muscle fatigue such as orthopnoea or paradoxical breathing. Non-ventilated		(Ventilatory pattern was controlled)	Even with very weak muscles, training manoeuvres could be easily performed. Recommendation: home training may be used as an effective adjunct to other therapies.
Yeldan et al. 2008 (Turkey)	Quasi-RCT Alternate allocation	N=23 (allocated): <u>Experimental</u> (n=11) Age reported in 10 (22.5 $\pm$ 7.5) 7 ♂, 3 ♀ <u>Control</u> (n=12) Age reported in 11 (24.27 $\pm$ 9.4) 6 ♂, 5 ♀	LGMD, (n=17) BMD, (n=6) Disease duration (11.5 $\pm$ 4.97 years)	All ambulatory at the start of the study, non-ventilated, no visible signs or symptoms of: Spinal deformities; Inspiratory muscle fatigue; Respiratory tract infections, or Cardiomyopathy. Patients who smoked: N=5 (n= 2 experimental group, n=3 control group)	Threshold inspiratory muscle trainer	Breathing exercises (diaphragm and segmental) 10 repetitions with 30s rest 8-10 sets per session	Respiratory muscle strength of muscular dystrophy patients is enhanced by training. Inspiratory and/or expiratory training effect is specific to the muscles trained Recommends the inclusion of respiratory muscle strength training in physiotherapy management.

BMD=Becker muscular dystrophy; DMD=Duchenne muscular dystrophy; IMT=Inspiratory muscle training; LGMD=Limb-girdle muscular dystrophy;

RCT=Randomised controlled trial; SD=Standard deviation; SMA=Spinal muscular atrophy

Most participants presented with DMD and only two studies included participants with other NMD diagnoses such as SMA III, LGMD and BMD (Gozal & Thiriet, 1999; Yeldan et al., 2008). Conditions were confirmed through clinical presentation/standard clinical measures (Martin et al., 1986; Stern et al., 1989; Wanke et al., 1994; Gozal & Thiriet, 1999; Topin et al., 2002; Yeldan et al., 2008), muscle biopsy (Martin et al., 1986; Stern et al., 1989; Wanke et al., 1994; Topin et al., 2002), laboratory criteria (Gozal & Thiriet, 1999), enzymatic testing/raised creatine kinase (CK) levels (Martin et al., 1986; Wanke et al., 1994; Topin et al., 2002) and electromyogram (Martin et al., 1986; Wanke et al., 1994). Only one study (Rodillo et al., 1989) did not specify which diagnostic tests were used.

Regarding ventilation, four studies (Rodillo et al., 1989; Stern et al., 1989; Topin et al., 2002; Yeldan et al., 2008) specified that their participants were non-ventilated, while Gozal and Thiriet (1999) and Martin et al. (1986) did not specify ventilatory status. One study reported that none of their participants was using invasive ventilation, and when one of the participants required ventilation he was excluded from the study (Wanke et al., 1994). Limited information was provided regarding the general clinical picture and functional mobility level of participants. The majority of patients were non-ambulant, and two studies indicated disease severity/ambulation by using the Inkley scale (Wanke et al., 1994; Gozal & Thiriet, 1999). No co-morbid conditions were mentioned in any of the seven included studies.

3.6.4 Inspiratory muscle training interventions (training programmes)

Included studies differed regarding the type of IMT device used (make, model and flow/resistance/threshold) as well as the intensity, frequency, duration and administration of IMT, including whether the intervention was delivered by healthcare professionals or parents/caregivers. Two of the seven studies (Martin et al., 1986; Gozal & Thiriet, 1999) used both inspiratory and expiratory muscle training, whilst the remaining studies focused on IMT. The IMT programme and interfaces of the studies differed; the majority (n=5) used mouthpieces as their IMT interface. Table 3.2 provides a detailed description of the respiratory muscle training programmes including inspiratory and/or expiratory muscle training as indicated by the included studies.

The majority of the devices used were threshold devices, where a certain pressure can be reached, independent of the flow created.

Inspiratory muscle training devices included: the Triflow II inspirometer (primary resistive, secondary flow-not threshold) (Rodillo et al., 1989), Threshold IMT and Threshold PEP (Healthdyne) (Gozal & Thiriet, 1999), Threshold inspiratory muscle trainer: RESPI FITT 1000 (Respironics) (Yeldan et al., 2008) and Threshold device (Healthscan Products Inc) (Topin et al., 2002). Three studies did not specify the device used, but participants inhaled through a mask whilst playing a video game (Stern et al., 1989); used a device with bore diameters in the mouthpiece (flow limitation with resistance) (Martin et al., 1986) and one study used a specially constructed training apparatus (no specific name mentioned) with variable inspiratory resistance (Wanke et al., 1994). Durations of interventions ranged from 18 days to six months. Three studies investigated short-term IMT intervention (Martin et al., 1986; Rodillo et al., 1989; Topin et al., 2002), one study implemented a medium- to long-term intervention of three months (Yeldan et al., 2008) and the remaining three studies applied long-term IMT of six months duration (Stern et al., 1989; Wanke et al., 1994; Gozal & Thiriet, 1999).

Table 3.2: Respiratory muscle training (RMT) programmes and devices used (n=7).

Authors, date	RMT device interface	RMT device	Training intensity (Resistance)	Repetitions/ Duration	Frequency	Rest period	Duration of RMT
Martin et al. 1986	Mouthpiece	No specific name/brand	Maximal static inspiratory manoeuvres (strength).	Each manoeuvre sustained for 3-5s. Sequence repeated once; 30 min per day	Once-daily	Not mentioned	2 months (5 days a week)
		Flow and resistance (flow limitation, with resistance).	Endurance: ventilated to exhaustion.	Ventilated to exhaustion	Three times daily	Only mentioned recovery intervals between 3 times of endurance training	
		Bore diameters in mouthpiece. Initial resistance (led to exhaustion within 3 minutes). (Inspiratory and expiratory muscle training)	20% intervals over VC range, resistance: 3.2, 11, 58.6 and 190.7cmH ₂ O/L/sec [flow rate of 20 L/min]. When a participant could ventilate without exhaustion for three minutes or longer, resistance was increased.				
Rodillo et al. 1989	Not mentioned	Triflow II Inspirometer (primary resistive, secondary flow)	Arbitrary 6-point scale attached to Triflow, no specific values provided. Resistance increased with increased flow.	20 inspirations daily	Once-daily	Not mentioned	18 days

Authors, date	RMT device interface	RMT device	Training intensity (Resistance)	Repetitions/ Duration	Frequency	Rest period	Duration of RMT
Stern et al. 1989	Mask (covering nose and mouth)	No specific name/brand Inhale through a mask whilst playing a video game (flow and resistance). (resistance and airflow)	Muscle work (flow) had to exceed a pre-set level. [Threshold not provided] Restriction apertures were: 6.35mm, 4.76mm; 3.18mm & 2.38mm Resistance was increased (based on heart rate)	20 minutes daily	Once daily (5 days a week).	Not mentioned	6 months
Wanke et al. 1994	Mouthpiece	No specific name/brand Specially constructed resistance-training apparatus. Resistance, threshold and flow	Resisted breathing manoeuvres against a variable inspiratory resistance (not specified). 1-minute duration for each cycle (endurance).	10 cycles (1 min per cycle) (endurance) 10 maximal static inspiratory efforts (strength) against an almost occluded resistance.	Twice daily	20s interval between cycles (endurance). 15 minutes of recovery after 10 resistive breathing exercises 20s interval between static inspiratory manoeuvres	6 months

Authors, date	RMT device interface	RMT device	Training intensity (Resistance)	Repetitions/ Duration	Frequency	Rest period	Duration of RMT
Gozal & Thiriet 1999	Mouthpiece	Threshold IMT and PEP; Healthdyne, Cedargrove, NJ (inspiratory and expiratory muscle training).	Started at low intensity (7cmH ₂ O) for 1 min, increased by 2cmH ₂ O with rest periods until targeted max training pressures were reached (equal/greater than 30% Pimax/Pemax).	Dependent on when minimum Pimax/Pemax was reached.	Twice daily	One minute, interspersed with one minute of rest	6 months
Topin et al. 2002	Mouthpiece	Inspiratory threshold device (Healthscan Products Inc)	30% of individual Pimax Ventilatory pattern was controlled	10 minutes (depending on compliance)	Twice daily	Not mentioned. Some stopped training for <10 minutes (lack of motivation/transitory fatigue).	Minimum 6 weeks
Yeldan et al. 2008	Mouthpiece	Threshold inspiratory muscle trainer (Respironics)	Initial load (15% of baseline Pimax for the first week), thereafter 30% of weekly Pimax.	15 minutes	Twice daily	Rest after 10 repetitions; (duration not specified).	3 months (5 days a week)

IMT=Inspiratory muscle training; PEP=Positive expiratory pressure; Pemax= Maximum expiratory mouth pressure

As can be seen in Table 3.2, many of the included studies did not specify the IMT intensity, but three studies used Pimax as a guideline (Gozal & Thiriet, 1999; Topin et al., 2002; Yeldan et al., 2008). The lowest intensities noted were 3.2cmH₂O/L/sec; 7cmH₂O and 15% of the patient's baseline Pimax. Repetitions and duration of training varied from ten repetitions to twenty, for a duration of ten to thirty minutes. Two studies did not indicate a specific training duration (Rodillo et al., 1989; Gozal & Thiriet, 1999).

Four included studies implemented bi-daily IMT sessions, for a minimum duration of six weeks (Topin et al., 2002), three months (Yeldan et al., 2008) or six months (Wanke et al., 1994; Gozal & Thiriet, 1999). Three studies performed IMT once a day for 18 days (Rodillo et al., 1989), two and six months respectively (Martin et al., 1986; Stern et al., 1989). Only Martin et al. (1986) trained the patients to exhaustion three times a day to improve respiratory muscle endurance. Most studies did not mention rest intervals (Martin et al., 1986; Rodillo et al., 1989; Stern et al., 1989). One study indicated that provision was made for recovery intervals in-between three sets of endurance training, where patients had to train until exhaustion, usually within three minutes (Martin et al., 1986). Gozal and Thiriet (1999) specified one minute of training interspersed with one minute of rest, whilst (Yeldan et al., 2008) allowed patients to rest after ten repetitions, but the duration was not specified. One study allowed a 20 second rest period between each maximum static inspiratory muscle manoeuvre (pressure dependent), and a fifteen minute recovery period after ten maximal resistive (flow and volume-dependent) breathing exercises (Wanke et al., 1994).

3.6.5 Risk of bias

All of the included studies presented a certain amount of potential bias. Selection (random sequence generation and allocation concealment), performance, detection, attrition, reporting and other types of bias were evaluated. (Figure 3.2). Red indicates a high risk of bias, yellow indicates unclear and green represents a low risk of bias.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Gozal 1999	?	?	?	?	+	-	?
Martin 1986	?	?	?	?	+	+	?
Rodillo 1989	?	?	-	+	-	+	?
Stern 1989	?	?	-	+	-	+	?
Topin 2002	?	?	+	+	+	-	?
Wanke 1994	?	?	?	?	+	+	?
Yeldan 2008	-	-	?	+	+	+	?

Figure 3.2: Summary of risk of bias of included studies (n=7).

3.6.5.1 Selection bias (Sequence generation and allocation)

Random sequence generation, as well as allocation concealment, was unclear in six of the included studies. The majority did not describe the randomisation process but only stated that participants were randomly allocated to their respective groups. The high level of bias in (Yeldan et al., 2008) was caused by participants being allocated to either the experimental or control group through alternate allocation.

3.6.5.2 Performance and detection bias (blinding)

Particularly in respiratory muscle training interventions, double blind studies are extremely difficult to implement. This is confirmed by the fact that only one study in this review (Topin et al., 2002) presented with low performance bias (described as a double blind randomised controlled trial).

In the study conducted by Stern et al. (1989), only the assessor was blinded to the participant's allocation. Although Rodillo et al. (1989) described their study as double blind, this could not truly be the case, because patients were either performing IMT (experimental group) or expiratory exercises. For this reason, participants would be aware of the differences between these interventions and only the assessor could truly be blind to the allocation of participants. Detection bias (blinding to the outcomes) was low in four studies (Stern et al., 1989; Rodillo et al., 1989; Topin et al., 2002; Yeldan et al., 2008), whilst the others were unclear. In three studies technicians/assessors were blinded (Rodillo et al., 1989; Stern et al., 1989; Yeldan et al., 2008), and in Topin et al. (2002) both the assessors and participants were blinded, but whether the clinicians were blinded to allocation remains unclear.

3.6.5.3 Attrition bias (Incomplete outcome data)

Five studies were assessed as having a low risk of attrition bias, but Rodillo et al. (1989) and Stern et al. (1989) were judged as high risk because no intention-to-treat analysis was performed to address the loss to follow-up. In Rodillo et al. (1989), two patients were lost to follow-up while in Stern et al. (1989) four participants died, two were lost to follow-up, and one patient could not complete the endurance testing due to cognitive impairment.

3.6.5.4 Reporting bias (selective reporting)

Most included studies presented with low reporting bias (selection of outcomes reported in published articles) and only two studies (Gozal & Thiriet, 1999; Topin et al., 2002) were classified as high risk. In the study by Gozal & Thiriet (1999), data were mostly depicted with figures and exact values were not provided; also in Topin et al. (2002) various outcome measures were not reported.

3.6.5.5 Other potential sources of bias

Three studies did not mention funding sources or any other conflict of interest (Martin et al., 1986; Stern et al., 1989; Wanke et al., 1994), whilst four studies declared their funding sources. None of these funding sources was IMT device manufactures, but rather a muscular dystrophy and myopathy associations (Rodillo et al., 1989; Gozal & Thiriet, 1999; Topin et al., 2002) as well as the Istanbul University Research Foundation (Yeldan et al., 2008). Other sources of bias were not mentioned by any of the included studies, therefore all seven studies were appraised as unclear alternative/other bias.

3.6.6 Effects of interventions

Due to the variety of IMT devices, intensities, frequencies and methodologies followed by the included studies, a meta-analysis of all included studies were not possible. Based on primary, secondary and other outcome measures as well as effect sizes of the two pooled studies, the clinical effect of IMT is described below.

3.6.6.1 Effect of IMT on patients with NMD

The majority of the included studies either did not distinguish between primary and secondary outcome measures or did not specifically describe any secondary outcome measures. All studies used a pulmonary function test variable and a measure of respiratory muscle strength and/or endurance.

Primary outcome measures

The primary outcome measure of this review was patient morbidity, which included frequency of hospital admissions, respiratory infections (need for antibiotics) as well as any adverse events related to IMT. None of the included studies specifically reported on morbidity rates/frequencies, complications or adverse events associated with IMT. Rodillo et al. (1989) reported that two children withdrew during the study, whilst in the study by Stern et al. (1989), four participants died during the trial because of acute illness. Martin et al. (1986) reported that one patient with poor pulmonary function at the commencement of the study died during his training period. As safety and precautionary measure, Wanke et al. (1994) measured participants' CK levels at baseline, as well as post-intervention to determine if there was any deterioration of the patient's condition. No trend towards higher CK levels was found among any of the participants during their observation time.

None of the illnesses or adverse events reported was considered to be a direct consequence of or directly associated with the intervention (respiratory muscle training).

Secondary outcomes measures

In all the included studies (n=7) pulmonary function tests, respiratory muscle strength (inspiratory and/or expiratory) and/or endurance were used as primary outcome measures. The majority described pulmonary function tests, as well as some measure of either inspiratory and/or expiratory muscle strength (Martin et al., 1986; Gozal & Thiriet, 1999) such as Pimax/MIP and Pemax as their primary outcome measures.

Pulmonary function tests

Pulmonary function tests included both relaxed and forced spirometry; with FVC (Rodillo et al., 1989; Stern et al., 1989; Yeldan et al., 2008), FEV₁ (Rodillo et al., 1989; Wanke et al., 1994; Gozal & Thiriet, 1999; Topin et al., 2002; Yeldan et al., 2008) and VC (Martin et al., 1986; Wanke et al., 1994; Topin et al., 2002; Yeldan et al., 2008) being the most common tests used by the majority of studies. Other tests used in the included studies were peak expiratory flow rate (PEFR) (Rodillo et al., 1989), forced expiratory flow (FEF₂₅₋₇₅), FRC, TLC (Topin et al., 2002), RV and RV/TLC (Gozal & Thiriet, 1999), but these were only reported as baseline parameters (pre-intervention). Two of the included studies used pulmonary function results at baseline in the description of participants' clinical profile of the participants and not for pre-and post-test measurement (Martin et al., 1986; Topin et al., 2002). The remaining studies reported no statistically significant changes in pulmonary function measures between patients in the experimental (respiratory muscle training) compared to the control groups. The control groups mostly received no intervention (Stern et al., 1989; Wanke et al., 1994; Gozal & Thiriet, 1999), but some used sham IMT (5% of Pimax) (Topin et al., 2002), diaphragmatic and segmental breathing exercises (Yeldan et al., 2008) or expirations through a mini peak flow meter (Rodillo et al., 1989).

Inspiratory muscle strength (Pimax/MIP) and endurance

Maximum inspiratory pressure (Pimax¹⁵) as an indicator of inspiratory muscle strength was measured in six of the included studies (Martin et al., 1986; Rodillo et al., 1989; Stern et al., 1989; Gozal & Thiriet, 1999; Topin et al., 2002; Yeldan et al., 2008). One study (Wanke et al., 1994) used an invasive technique (Pdi) to determine the strength of the diaphragm and some studies measured both inspiratory (Pimax/MIP) and expiratory muscle strength (Pemax/MEP¹⁶) (Martin et al., 1986; Stern et al., 1989; Gozal & Thiriet, 1999; Yeldan et al., 2008).

Two studies reported that the change in inspiratory muscle strength between the IMT (experimental) and control groups was not statistically significant (Stern et al., 1989; Topin et al., 2002). In the study by Martin et al. (1986) the absolute change (mmHg) for both inspiratory and expiratory muscle strength (absolute change in mmHg) was also not statistically significant; however, none of the three studies provided specific p-values or confidence intervals. Three studies reported a statistically significant improvement in inspiratory muscle strength measures (Pimax/Pdimax) before to after treatment.

¹⁵ Maximum inspiratory pressure (measured at the mouth)

¹⁶ Maximum expiratory pressure (measured at the mouth)

In Gozal and Thiriet (1999) the mean ($\pm$ SD) Pimax was presented graphically without providing specific values, however, the improvement in Pimax within the training group (pre vs. post-intervention) was reported as significant ($p<0.02$). Similarly, in Rodillo et al. (1989) the second group showed statistically significant improvement in Pimax after training ($p<0.02$). Yeldan et al. (2008) reported that both the IMT group and the breathing exercises group (active control) showed a statistically significant improvement in Pimax before to after treatment, and the difference between the groups trended towards significance ($p=0.05$). In Wanke et al. (1994), Pdimax was used as an expression of inspiratory muscle strength and changes within the group (pre- to post-test, after one year) as well as between the groups (experimental and control) were statistically significant ($p<0.001$).

A summary of significance levels reported for change in inspiratory muscle strength and endurance is provided in Table 3.3.

Table 3.3: Outcomes of muscle strength and endurance training (n=7)¹⁷.

Authors, date	Inspiratory muscle strength (Pimax/MIP/Pdimax/Pesmax) Between groups (p-values)	Inspiratory muscle strength (Pimax/MIP) within IMT groups (p-values)	Inspiratory muscle endurance (p-values)
Martin et al. 1986 (RCT cross-over)	None provided (mean change in Pimax) *	None provided	Pi time (<0.01) ** [both within group & between groups]
Rodillo et al. 1989 (RCT cross-over)	No statistically significant difference overall for complete study First period of study (p=0.02), favouring IMT. Second period of study (p<0.0001) favouring the placebo.	0.20 (Pimax) Group 1 0.02 ⁺⁺ (Pimax) Group 2	Not assessed
Stern et al. 1989 (RCT cross-over)	0.07 (mean change in Pimax % predicted)	None provided	0.12 [Measured in grams/converted to mmHg]
Wanke et al. 1994 (RCT)	<0.001 ⁺⁺ Pdimax; Pesmax Mean (±SD) change Pdimax Intervention group: 2.67 (±0.11) vs control: 0.16 (±0.09) Mean (±SD) change Pesmax Intervention group: 2.36 (±0.05) vs control: 0.05 (±0.04)	<0.001 ⁺⁺ (Pdimax; Pesmax)	12sMVV* [Specific p-values not provided] T _E cumulative time (in minutes) ⁺⁺ <0.001 Pressure/endurance time product Pdi x T _E (<0.001) ⁺⁺
Gozal & Thiriet 1999 (RCT)	<0.02 ⁺⁺ [specific values not provided]	p<0.02 ⁺⁺ [specific values not provided]	Not assessed
Topin et al. 2002 (RCT)	Specific p-values not provided [calculated as significant p <0.001]	Not statistically significant * No specific p-values provided [calculated as p=0.8]	Tlim measured in seconds' determined at 35% Pimax (<0.05) ⁺⁺ [Specific p-values not provided]

¹⁷ In cases where values were available, but specific p-values not reported, the p-values were calculated with Statistica based on data reported in the publications.

	Mean ($\pm$ SD) change Pimax Intervention group: 1.4 ($\pm$ 0.3) vs control: -1.5 ($\pm$ 0.2).	Calculated (Wilcoxon test): p=0.28 (pre-post IMT-values)	[calculated as significant between groups difference p<0.0001] Mean ($\pm$ SD) change Tlim intervention group: 140.8 ($\pm$ 50.1) vs control of 0.6 ($\pm$ 5.2). [calculated as non-significant within group improvement, p=0.08] Mean ($\pm$ SD) improvement 307.6 ($\pm$ 126.6) to 448.4 ($\pm$ 176.7)
Yeldan et al. 2008 (Quasi RCT)	<0.05 **	<0.01 **	Not assessed

*improvement (not statistically significant), ** improvement (statistically significant); 12sMVV=12 second maximum voluntary ventilation; Pdi=Transdiaphragmatic pressure/difference between gastric and esophageal pressures; Pesmax=Maximal sniffed esophageal pressure; Pimax/MIP=Maximum inspiratory mouth pressure; Pi time=Maximum static inspiratory time; T_E=endurance time. Additional calculations were performed on Statistica v13.

Respiratory muscle endurance was reported by four studies (Martin et al., 1986; Stern et al., 1989; Wanke et al., 1994; Topin et al., 2002) (Table 3.3). In the study conducted by Martin et al. (1986), inspiratory muscle endurance expressed as Pi time in seconds (maximum time for which each maximal static inspiratory pressure could be held) showed a statistically significant improvement ($p<0.01$) within and between groups (training and non-training) after training to exhaustion three times per session, five days a week for two months. On the contrary, ventilatory muscle endurance (highest pressure a patient could generate with each breath for 10 minutes measured with a Nickerson valve) in Stern et al. (1989) did not show statistical evidence of a change ($p=0.12$), although some individual patient improvement was observed. Similar results were reported by Wanke et al. (1994), with no significant difference between the experimental and control groups for 12sMVV, however, no p-values were reported. In the same study, no significance levels were provided for endurance time (TE), but it was stated that the patients in the training group who completed the trial ($n=10$) showed a significant improvement. In addition, these authors calculated a pressure/endurance-time product ($P_{di} \times TE$) for the ten participants to determine their inspiratory muscle working capacity and found a statistically significant difference between pre-and post-intervention measures ($p<0.001$) (Wanke et al., 1994). Topin et al. (2002) assessed inspiratory muscle endurance (time limit) and reported the mean and standard deviation values, but no p-values were provided. However, it was mentioned that there was a statistically significant ($p<0.05$) change in endurance before and after the six-week intervention, with a 30% Pimax load (Topin et al., 2002). Furthermore, a significant association ($p<0.001$) was found between the percentage of improved endurance and the total quantity of IMT during a six-week period (Topin et al., 2002) (Table 3.3).

3.6.7 Meta-analysis (effect size)

The only outcome measure that could be pooled across two similar studies was inspiratory muscle strength (P_{imax}/MIP) (Gozal & Thiriet, 1999; Yeldan et al., 2008). Other studies varied in their method of inspiratory muscle strength assessment, with measurements taken variably at residual volume (RV) or the end of tidal volume (FRC) (Martin et al., 1986; Rodillo et al., 1989; Stern et al., 1989; Gozal & Thiriet, 1999; Topin et al., 2002).

In both studies (Gozal & Thiriet, 1999; Yeldan et al., 2008), P_{imax} was measured from RV and the change in P_{imax} (cmH₂O) pre-and post-intervention was reported. In the study by Yeldan et al. (2008), 21 participants completed the trial ($n=10$ in the experimental group and $n=11$ in the control group).

The difference in Pimax between the experimental/intervention and control groups was expressed as mean ($\pm$ SD). In Gozal & Thiriet (1999) the maximum difference (M, SD) in inspiratory muscle strength pre-and post-intervention (cmH₂O) was reported and only the two NMD groups (with and without IMT) could be compared, as the other matched control group data was not available. The mean difference (MD) for Pimax, with a 95% confidence interval (CI) for the two studies was 15.69 (12.58-18.81)cmH₂O (Figure 3.3).

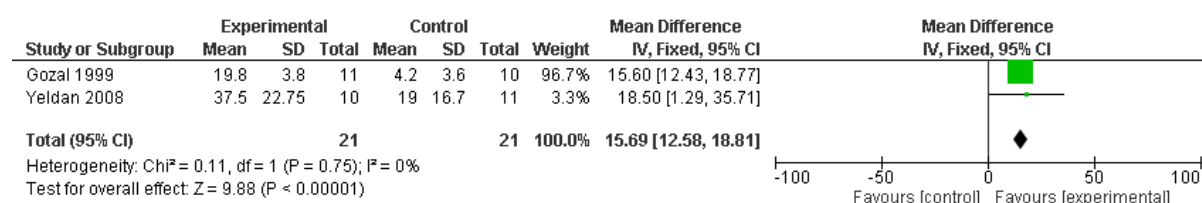


Figure 3.3: Effect size of the change in inspiratory muscle strength (Pimax).

As part of the meta-analysis, Cohen's d was also used to describe the effect size of these two studies, as a comparison between the two means (change in Pimax) (<https://www.statisticshowto.datasciencecentral.com/cohens-d/>). Cohen's d was 4.22 and 0.93 respectively (Gozal & Thiriet, 1999; Yeldan et al., 2008). The two studies presented minimal heterogeneity (Chi-square=0.11; I-square=0%) and favouring the experimental/intervention group (Figure 3.3).

Additional data for analysis were not available and attempts to contact the authors were unsuccessful. No data were available from any of the studies on pulmonary function tests such as multiple gas washout techniques, PEF, diaphragm thickness or HRQoL. Only two of the included studies evaluated vital signs: Wanke et al. (1994) measuring PaO₂ and PaCO₂ (mmHg) at baseline, after six months of training and six months after training; whilst Stern et al. (1989) mentioned that heart rate was measured at the beginning of each intervention session.

3.6.8 Other reported outcome measures

Other measures of respiratory function reported in the included studies were:

- Ventilatory muscle endurance (highest pressure a patient could generate with each breath for 10 minutes) (Stern et al., 1989);
- Pi time (maximum time that each maximum static inspiratory pressure could be maintained) and Pe time (maximum time that each maximum static expiratory pressure could be maintained) (Martin et al., 1986);

- Inspiratory muscle endurance (time limit), mouth pressure (Pm) (results were not reported) and endurance time (results were not reported) (Topin et al., 2002);
- Respiratory muscle endurance (12sMVV) as well as inspiratory muscle endurance (Te, cumulative time) (measured at baseline, after six months of training and six months after training) (Wanke et al., 1994).

Only one study (Gozal & Thiriet, 1999) measured respiratory load perception (RLP) as a secondary outcome measure, using the Borg scale (0-10). The study found a significant decrease in the RLP after three months of training which lasted for at least 12 months after training was ceased (Gozal & Thiriet, 1999).

3.7 Discussion

3.7.1 Summary of main results

Various neuromuscular diseases occur in the paediatric and adolescent population; however, the studies included in this review only included participants with DMD (majority), SMA, LGMD and BMD. A greater proportion of males were therefore included in the final sample, as DMD is the most common type of NMD among children and more prevalent among boys (Finder et al., 2004; Nicot et al., 2006; Yang & Finkel, 2010; Guglieri & Bushby, 2011). Only three studies recruited participants in the specified age range of 5-18 years. None of the participants was mechanically ventilated, most were non-ambulant and no co-morbidities were reported.

The studies included in this review were randomised, quasi-randomised and cross-over studies, which are appropriate study designs for assessing the efficacy of interventions. All studies investigated the effect of respiratory muscle training (inspiratory and expiratory muscle training) and five studies specifically investigated IMT. The training devices, intensity, duration and frequency varied but, most used mouthpiece interfaces, which might pose a problem for patients with bulbar involvement and decreased oral control. The majority of studies used a threshold device and implemented training over a medium to a long-term period (three; six months).

The variance in results among studies could be attributed to the heterogeneity in IMT protocols, including the devices used. With resistance and flow devices patients can minimise resistance by adapting their respiratory rate or mouth position whilst training (Houston et al., 2008; Hill et al., 2010; Bissett et al., 2012). Other IMT modalities such as normocapnic hyperpnoea and resistive training might have limited clinical usefulness.

As with normocapnic hyperpnoea, patients have to ventilate at a high proportion of their MVV and with resistance training, the training load/intensity can be decreased by the participant through reducing the inspiratory flow (Hill et al., 2010). With threshold devices, participants need to create a certain pressure for the threshold valve to open, thereafter pressure and flow are largely independent and the load cannot be decreased through changes in breathing pattern such as decreasing breathing frequency and flow (Wanke et al., 1994; Houston et al., 2008).

3.7.2 Applicability of evidence

The results from this review can be used to highlight the gaps in the literature, inform clinical practice, assist with the development of IMT protocols and serve as a baseline for the planning of clinical trials and future studies.

3.7.2.1 Guidelines for IMT programmes

In patients with NMD, the effect of IMT seems to be dose-dependent, provided the respiratory involvement of the condition is slowly progressive (VC decline is less than 10% during the year before training) (Winkler et al., 2000), as the number of exercises, duration and intensity of training performed correlated significantly with inspiratory muscle strength and endurance (Pimax and 12sMVV) (Wanke et al., 1994; Topin et al., 2002; Yeldan et al., 2008). Earlier intervention and prolonged use of IMT might therefore be more beneficial (Stern et al., 1989; McCool & Tzelepis, 1995; HO, 2005), but due to the paucity of available data, more clinical trials are recommended.

Three studies used Pimax as a guideline for training intensity (dosage), with repetitions ranging between 10-20, training duration from 10-30 minutes and a frequency of once to three times per day. Most studies did not mention the provision of rest intervals, but the studies that specifically stated they incorporated rest periods/intervals also showed significant improvements in inspiratory muscle strength and endurance parameters (Wanke et al., 1994; Gozal & Thiriet, 1999; Yeldan et al., 2008). The two pooled studies used similar IMT protocols for their participants: a threshold device (with a mouthpiece), training intensity of 30% or higher of the participant's Pimax, training twice a day, and providing for rest periods of either one minute after one minute of training (Gozal & Thiriet, 1999), or after 10 breaths (Yeldan et al., 2008) as well as keeping a training diary (DiMarco et al., 1985; Rodillo et al., 1989). The primary difference between these two studies was the training duration per day which was either not specified (Gozal & Thiriet, 1999) or reported as 15 minutes at a time (Yeldan et al., 2008), for three or six months.

These reports concur with manufacturer recommendations and literature (<https://www.powerbreathe.com/>; Lötters et al., 2002; Hill et al., 2010) for effective IMT training, viz. IMT intensity of at least 30% Pimax/MIP, for 30 breaths, twice a day.

3.7.2.2 Pulmonary function

Most of the included studies reported no statistically significant change in pulmonary function measures such as VC, FEV₁, FVC, FRC and TLC between the experimental (respiratory muscle training) and control groups. Respiratory muscle training might not be sufficient to counterbalance the natural decline of lung volumes and flow in these patients (Human, Honey & Morrow, 2019; Wenninger et al., 2019).

Vital capacity has been used as an indicator of disease severity and progression in NMD (Koessler et al., 2001), but if Pimax and VC are still within normal ranges, a statistically significant change in muscle strength might not cause a change in lung volumes such as TLC because of the sigmoid shape of the pressure-volume curve (Laghi & Tobin, 2003; Aboussouan, 2009). It is therefore clinically relevant that VC can be within normal ranges or slightly reduced if the respiratory muscle strength is more than 50% of the predicted value. When VC and respiratory muscle strength are 50% of the predicted value, the patient is also at risk of hypoventilation, even during a minor respiratory tract infection (Laghi & Tobin, 2003; Nicot et al., 2006). Once respiratory muscle strength falls below 50% predicted value, the decrease in VC can be even worse than expected (Laghi & Tobin, 2003), as a decrease in compliance of the chest wall and lungs adds to the worsening of pulmonary function (Avendaño & Güell, 2003; Laghi & Tobin, 2003; Servera et al., 2003). Once VC is reduced, muscle strength might already be severely affected, and respiratory muscle training might be less effective. Therefore, respiratory muscle training in the later stages of NMD may be less effective, as weakened muscles have to work relatively harder against the reduced chest and lung compliance, predisposing to fatigue (DiMarco et al., 1985; Kang & Bach, 2000; Koessler et al., 2001). This suggestion was supported by the observation that IMT in patients with VC <25% predicted value (or PaCO₂ >45 mmHg) did not show any benefit in patients with DMD and SMA (Wanke et al., 1994; Koessler et al., 2001).

3.7.2.3 Respiratory muscle weakness and IMT

Respiratory muscle weakness causes decreased VC and an inability to sustain normal quiet breathing (Rochester & Arora, 1983; Avendaño & Güell, 2003; Laghi & Tobin, 2003), which can lead to increased work of breathing, respiratory infections, respiratory failure and even death (Benditt & Boitano, 2013; Boentert et al., 2017; Chatwin et al., 2018).

In the presence of inspiratory muscle weakness, a ventilation/perfusion (V/Q) mismatch may occur due to micro and/or segmental atelectasis which can create relative hypoxaemia and predisposes the patient to lower respiratory tract infections (Eagle, 2002; Kirk, 2006; Yang & Finkel, 2010; Birnkrant et al., 2018). Respiratory failure in NMD is primarily caused by cough insufficiency during recurrent chest infections, because of underlying respiratory muscle weakness (Bach, 2003; Dohna-Schwake et al., 2006; Paschoal, Villalba & Pereira, 2007; Nascimento et al., 2015; Boentert et al., 2017). Improved respiratory muscle strength and endurance might assist with maintaining adequate lung inflation, expansion and ventilation; slow down the age-related regression of pulmonary function (VC) and improve gas exchange which can prevent atelectasis and reduce the risk of respiratory complications (DiMarco et al., 1985; Koessler et al., 2001; Aslan et al., 2013). In advanced stages of NMD, respiratory muscle failure could occur due to the inherent progressive muscle weakness and fatigue caused by increased work of breathing beyond the muscles' endurance capacity (Rochester & Arora, 1983; McCool & Tzelepis, 1995; Winkler et al., 2000; Laghi & Tobin, 2003).

An observational study implementing a six-week IMT programme in children, adolescents and adults with DMD, LGMD and one patient with facio-scapulo-humeral muscular dystrophy (FSHD) reported improved muscle endurance and suggested that IMT may delay the onset of respiratory complications (DiMarco et al., 1985). Another review suggested that the use of IMT to improve strength and endurance in NMD, including quadriplegia, is safe; however, the effect on morbidity was unclear (McCool & Tzelepis, 1995). On the other hand, studies conducted among patients with NMD might be underpowered to detect rare respiratory morbidity events such as respiratory tract infections and this should be considered when interpreting results.

3.7.2.4 Respiratory muscle endurance

Respiratory muscle training, like skeletal muscle training, seems to be dose-dependent and needs to be specific (inspiratory muscles, strength vs endurance) in order to condition the muscle fibres to respond to a certain task (Wanke et al., 1994; McCool & Tzelepis, 1995; Winkler et al., 2000; Topin et al., 2002; Yeldan et al., 2008; Pinto & Carvalho, 2014; Wenninger et al., 2019). For this reason, respiratory muscle *strength* training might not have a significant influence on respiratory muscle *endurance*. Most of the included studies (n=7) in this systematic review aimed at *improving inspiratory muscle strength*, which is also the focus of this thesis (Chapters 5 and 6).

Four studies specifically assessed respiratory muscle endurance, using various outcomes. Two studies observed no significant overall changes but reported that some patients showed individual respiratory endurance improvement. Two studies found a significant change in respiratory muscle endurance post-intervention and one of these studies also reported a statistically significant difference in the inspiratory muscles' working capacity (Martin et al., 1986; Wanke et al., 1994).

There seems to be a significant correlation between the total time of respiratory muscle training and the percentage of endurance improvement in patients with NMD (Wanke et al., 1994; Topin et al., 2002). To improve endurance, longer training times might be required, but all the included studies implemented training for six months or less.

3.7.2.5 Respiratory muscle strength and inspiratory muscle training

Inspiratory pressure at the mouth (Pimax/MIP) is commonly used as a global inspiratory muscle strength measure, because it is non-invasive and normative values have been established, although sample sizes are usually small (Fauroux, 2003; Ratnovsky, Elad & Halpern, 2008; Heinzmann-Filho, Vasconcellos Vidal, Jones & Donadio, 2012; Chiang et al., 2018). Recently, a few more studies have described normative, reference values for respiratory muscle strength in children and adolescents (Pimax, Pemax and Tension Time Index) (Da Rosa, Morcillo, de Assumpção & Schivinski, 2017; Hulzebos, Takken, Reijneveld, Mulder & Bongers, 2018). In this review, four studies (Rodillo et al., 1989; Wanke et al., 1994; Gozal & Thiriet, 1999; Yeldan et al., 2008) showed statistically significant changes between intervention and control groups (favouring IMT), for inspiratory muscle strength (Pimax/Pdimax). Possible reasons for the responsiveness of the inspiratory muscles to strength training could include the change in muscle fibre size/volume, number of fibres and improved circulation (Pinto & Carvalho, 2014; Wenninger et al., 2019).

A meta-analysis of two similar studies (Gozal & Thiriet, 1999; Yeldan et al., 2008)) showed a statistically significant overall effect of IMT, on change in Pimax. Of the two studies, one showed a very small confidence interval (12.43-18.77) for treatment effect after six months of IMT (threshold device, minimum intensity of 30% Pimax) in children and adolescents seven to 17 years of age (Gozal & Thiriet, 1999). These findings suggest that an IMT protocol of training twice a day with Pimax guiding resistance, over three to six months, can have a positive effect on inspiratory muscle strength in patients with NMD. However, the safety of IMT has not yet been determined, and this requires further investigation.

3.7.3 Respiratory morbidity and adverse events

None of the seven included studies in this review assessed the influence of IMT on morbidity of patients including frequency of hospitalisations and respiratory infections (confirmed by the use of antibiotics). Some patients did not complete the trial due to illnesses or adverse events, but none of these events was deemed to be the direct result of respiratory muscle training. One study monitored CK levels in patients with DMD whilst training and concluded that owing to no changes in CK levels, IMT did not seem to have a deleterious effect on the muscles (Wanke et al., 1994).

No adverse events or complications related to the intervention (respiratory muscle training) were mentioned, hence IMT might be considered as an adjunct in the treatment of NMD, but more clinical trials are warranted as respiratory morbidity events are rare and therefore safety and efficacy of IMT might be difficult to determine.

3.7.4 Methodological quality and bias of included studies

Caution has to be taken when interpreting the results from this review, as all studies presented with some level of bias and sample sizes were small (ranging from eight to eleven participants per group). The studies pooled for effect sizes presented with unclear (Gozal & Thiriet, 1999) and high levels of selection bias (Yeldan et al., 2008). When interpreting the positive effect size, favouring IMT, it has to be kept in mind that although one of the outcome measures used (Pimax) in both studies were similar, other elements of these studies were heterogeneous.

The inclusion of a variety of NMD may also influence findings from this review. Gozal and Thiriet (1999) included patients with DMD and SMA type III, whilst Yeldan et al. (2008) included patients with LGMD and BMD. For dystrophinopathies such as DMD, BMD and LGMD the pathology lies within the skeletal muscle fibre structure (in varying degrees of severity) (Eagle, 2002; Yeldan et al., 2008; Goemans & Buyse, 2014), whereas in SMA the atrophy and muscle weakness is caused by degeneration of spinal cord motor neurons. Furthermore, the distribution of respiratory muscle weakness might vary, as respiratory compromise in SMA is mainly caused by expiratory and intercostal muscle weakness, with relative diaphragmatic sparing (Wang et al., 2007). Respiratory muscle training may, therefore have different effects according to the underlying pathophysiology of the presenting conditions.

Duchenne muscular dystrophy is the most common NMD in the paediatric population (Emery, 1991; Nicot et al., 2006; Yang & Finkel, 2010; Boentert et al., 2017), and the majority of studies in this review included participants with DMD (Table 3.1). The data from the studies that only included participants with DMD could not be pooled. These studies did however share a few common conclusions:

- The effects of respiratory muscle training seem to be specific and dependent on the muscles being trained (inspiratory/expiratory); the intensity of training (dose-dependent); the aim of training (strength or endurance) and the duration of training.
- Short-term intervention (<three months) did not seem to show any benefit in patients with DMD (Martin et al., 1986; Rodillo et al., 1989; Stern et al., 1989; Wanke et al., 1994; Topin et al., 2002).
- Although results differed regarding the effect on respiratory muscle strength, endurance, respiratory symptoms and respiratory load perception, some studies concluded that IMT might be a beneficial adjunct to a physiotherapy home programme (Wanke et al., 1994; Topin et al., 2002; Yeldan et al., 2008).

The age and functional abilities of the participants in this review also varied. The study by Gozal and Thiriet (1999) included children and adolescents and those that performed respiratory muscle training were all non-ambulatory, whilst Yeldan et al. (2008) included mostly adolescents and adults, all of whom were ambulatory at the start of the study. Non-ambulatory participants would be at higher risk of scoliosis, poor respiratory function and respiratory infections. However, both studies reported that participants did not present with any co-morbidities such as cardiomyopathy, spinal deformities or signs of inspiratory muscle fatigue (Gozal & Thiriet, 1999; Yeldan et al., 2008). Notably, non-ambulatory patients showed a greater effect size based on inspiratory muscle strength (Pimax) following IMT, favouring the experimental group, which could imply that IMT might be beneficial in non-ambulatory children and adolescents.

3.7.5 Possible learning/training effect

Another factor to consider when interpreting the results from this review is the so-called learning/training effect. Some studies have indicated that an improvement in inspiratory muscle strength (measured by Pimax/MIP) and/or endurance could be accredited to an improved ability to perform breathing manoeuvres, rather than a true improvement in muscle strength/endurance (Houston et al., 2008), but it may be difficult to distinguish between the two (Smith, Coakley & Edwards, 1988; Koessler et al., 2001).

The learning effect may be particularly relevant when using a threshold device, as participants need to generate a specified inspiratory pressure before the valve opens to allow inspiratory airflow (LoMauro et al., 2014; Pedrosa, Silva, Azevedo, Forbes, Fregonezi, Dourado & Ferreira, 2015). It is extremely difficult to eliminate a learning effect and therefore Martin et al. (1986) cautioned that this should be considered when interpreting results. Only one study included in this review acknowledged that the learning effect could have caused a significant improvement in Pimax from baseline to three weeks (18 days) in the IMT group (Rodillo et al., 1989).

One study attempted to negate the learning effect when testing Pimax and Pemax by providing three to five trials of Pimax, but also found an improvement of inspiratory muscle strength in the control group performing unresisted breathing exercises (Yeldan et al., 2008). Rodillo et al. (1989) concluded that if learning effects were allowed for, their study did not convincingly show an improvement in pulmonary function (including Pimax), based on respiratory muscle training in patients with DMD. On the other hand, one of the excluded studies, based on study design, concluded that the improvement seen in inspiratory muscle strength and endurance (Pimax and 12sMVV) could not be attributed to a learning effect because there was not only an increase in early measurements but a continual rise until 10 months, whereafter a plateau was reached (Koessler et al., 2001).

3.7.6 Alternative measures of inspiratory muscle strength

Although the use of Pimax as an indicator of inspiratory muscle strength is a commonly used outcome measure (Fauroux, 2003), this assessment technique is effort dependent, can be demanding and several attempts might be needed to achieve reproducible results, particularly in patients with severe muscle weakness (Maillard, Burdet, van Melle & Fitting, 1998; LoMauro et al., 2014; Boentert et al., 2017). Other measures of inspiratory muscle strength that might be more reliable, valid and decrease the effect of learning should be considered including SNIP¹⁸, transdiaphragmatic pressure (Pdi) and non-volitional tests such as twitch mouth pressure (Wanke et al., 1994; Fauroux, 2003; Farrero et al., 2013; Hua, Liang, Xie, Liu, Zheng, Chen & Zhong, 2013; Caruso et al., 2015; Hulzebos et al., 2018).

Transdiaphragmatic pressure is an invasive technique where the differences between gastric and oesophageal pressures are measured; often using a maximum sniff manoeuvre (Pdimax) (Perrin et al., 2004; Nicot et al., 2006; Caruso et al., 2015).

¹⁸ The sniff nasal inspiratory pressure (SNIP) assessment technique is described in detail in Chapter 4

Twitch mouth pressure (P_{mo}, tw) is a non-invasive technique where magnetic phrenic nerve stimulation is used to determine diaphragmatic muscle strength. The advantage of this technique is that it is convenient, non-invasive, better tolerated than electrical stimulation, less effort dependent and non-volitional (Maillard et al., 1998; Hua et al., 2013; Farrero et al., 2013).

3.8 Clinical implications, recommendation and limitations of the study

In dystrophinopathies the risk of overexertion and muscle damage during exercise is higher than in other NMD due to the underlying pathophysiology influencing the structural proteins of the muscle membrane (Sander et al., 2000; Eagle, 2002; Finder et al., 2004; Goemans & Buyse, 2014). Future research should therefore aim to determine the safety, practicality and efficacy of respiratory muscle training among different NMD groups. Bulbar control may be impaired in several NMD (Laghi & Tobin, 2003; Panitch, 2006; Toussaint et al., 2018), and only one included study performed IMT with a face mask (Stern et al., 1989); therefore it is recommended that future research investigate the use of mask interface IMT when oral control is poor.

The variances in results of this review could be attributed to the heterogeneity of the included studies, as well as insufficient methodological information, which affects reproducibility. The IMT protocols varied regarding IMT device, intensity, repetitions, frequency and duration of training. The unclear risk of bias in most of the studies also creates uncertainty regarding methodological rigour and it is therefore not possible to determine which IMT protocol is more effective in children and adolescents with NMD. A recent Cochrane review on respiratory muscle training in children and adults with NMD (Silva et al., 2019) came to similar conclusions with regards to the paucity of evidence and the need for additional clinical IMT trials to be performed among patients with NMD. Long-term studies are necessary to determine if IMT can slow down the regression of pulmonary function and respiratory muscle strength in children with NMD (Winkler et al., 2000), whilst keeping in mind that VC is unlikely to improve in patients with near normal or normal P_{imax} values (Nève, Cuisset, Edmé, Carpentier, Howsam, Leclerc & Matran, 2013).

At the time when this review was performed, no other systematic reviews on respiratory muscle training in paediatric and adolescent NMD were available. An integrative review on the use of IMT in the paediatric population and a review on IMT in NMD, published subsequently, had similar findings and conclusions (Woszezenki et al., 2017; Hariza, Lasmitasari, Widjanantie & Nurdwinuringtyas, 2018).

A Cochrane protocol on respiratory muscle training in children and adolescents with NMD was published in 2015 (Pedrosa et al., 2015) and the completed systematic review was only published in 2019 (Silva et al., 2019). One RCT (Yeldan et al., 2008) included in this systematic review was published after the American Thoracic Society guidelines (Finder et al., 2004). The British Thoracic Society respiratory guidelines (2012) also cited a poor level of evidence to support respiratory muscle training in NMD (Hull et al., 2012). More rigorous RCT or cross-over studies on IMT among paediatric and adolescent patients with NMD are therefore needed.

It is suggested that future clinical trials increase the number of participants by conducting multi-centre trials among various institutions and hospitals. Further research could also investigate the effect of IMT on ventilated patients, and patients in acute/hospital settings. Studies in SA need to be conducted to collect relevant, context-specific data that can be applied in different contexts, including low- and middle-income countries. If IMT should prove safe and effective in children with NMD then the association between participants' functionality, ambulation and respiratory function should be assessed to determine the optimal time to start training for maximal clinical benefit. It is recommended that future systematic reviews include the use of the GRADE system for the quality assessment of included studies.

The limitations of this systematic review include the varied methodologies and IMT protocols, but the majority used threshold devices for medium to long term intervention. Limited information on IMT was available for the specific age range of 5-18 years and intervention was limited to specific NMD types, non-ventilated patients and those with oral control able to use a mouthpiece interface. The effect of IMT on secretion clearance was also not clarified. Only one study included in the final sample (Gozal & Thiriet, 1999) implemented both inspiratory and expiratory muscle strength training. Although respiratory muscle training is dose and type dependent, the confounding effect of expiratory muscle training on inspiratory muscle strength outcomes should be considered in future trials.

There is currently no consensus regarding optimal respiratory muscle training devices, protocols and methods to ensure clinically relevant changes in outcome for the wide pathophysiological scope of NMD (Haas et al., 2007; Núñez et al., 2014; Wenninger et al., 2019).

3.9 Conclusion

Respiratory muscle training has been incorporated into the management of NMD to enhance respiratory function and reduce respiratory morbidity and mortality, by improving respiratory muscle strength and/or endurance (Gozal & Thiriet, 1999; HO, 2005; Hull et al., 2012; Woszezenki et al., 2017; Wenninger et al., 2019).

Owing to controversy in the literature, especially regarding safety in patients with dystrophinopathies, more research is recommended before respiratory muscle training can be endorsed as a standard treatment strategy in this population (Finder et al., 2004). Limited new evidence has emerged on respiratory muscle training in NMD since the publication of the British and American Thoracic Societies' Guidelines (Finder et al., 2004; Hull et al., 2012).

This systematic review indicates that, although IMT might be beneficial for improving respiratory muscle strength in children with NMD, there are currently no published controlled studies investigating clinically relevant outcome measures of morbidity, such as hospitalisation rate, respiratory infections, adverse events and HRQoL. Similar results were reported in a recent systematic review on children and adults with NMD (Silva et al., 2019). Limited data is available on the safety and efficacy of IMT in children and adolescents (5-18 years) and there is currently no consensus regarding optimal IMT devices, protocols and methods to be followed in a wide variety of NMD (Woszezenki et al., 2017; Wenninger et al., 2019). In addition, the controversy regarding the safety of exercise specifically in patients with dystrophinopathies, warrants further investigation.

There is currently, therefore, no clear evidence for or against the use of IMT in children and adolescents with NMD and further clinical trials are recommended to determine safety, practicality, acceptability and efficacy of this intervention.

Chapter 4: HOW TO TRAIN YOUR DIAPHRAGM

The methods, outcome measures, inspiratory muscle training protocol and ethical considerations

4.1 Introduction

In the survey study (2.6.5.5) the majority of South African (SA) physiotherapists responding to the questionnaire supported the use of inspiratory muscle training (IMT) in children with neuromuscular disease (NMD), using devices that are available at a relatively low cost in SA. The systematic review (Chapter 3: 3.9) concluded that there is currently no clear evidence for or against the use of IMT in children and adolescents with NMD and clinical trials were recommended to guide clinical practice. It is important to measure the effect of an intervention on a patient's health (HMI, 2019) before implementing management strategies, especially in settings where healthcare resources are limited.

Clinical research studies were therefore designed to determine the safety and efficacy of IMT, using several, relevant outcome measures. This chapter describes the methods, outcomes measures, IMT protocol and ethical considerations used for the pre-experimental, pilot and cross-over IMT clinical studies.

4.2 Overview of methodology

4.2.1 Research settings and population

The SA public health care sector consists of primary, secondary and tertiary health facilities managed by the provincial Departments of Health (DoH) (https://www.who.int/workforcealliance/031616south_africa_case_studiesweb.pdf?ua=1).

Participants for this study (pre-experimental, pilot and cross-over randomised controlled trial) were recruited, in Gauteng and the Western Cape, from two tertiary public hospitals (Red Cross War Memorial Children's Hospital (RCWMCH) and Doctor George Mukhari Academic Hospital (DGMH)); schools for children with special needs; and the private health care sector. Permission was obtained from all relevant entities.

4.2.1.1 Pre-experimental study (Schools in Gauteng)

To ensure an adequate number of participants, the pre-experimental, pilot study was implemented at two schools for children with special needs in Pretoria, Gauteng¹⁹ (SA).

¹⁹ Names of schools withheld due to confidentiality

Permission from the Gauteng Department of Education (DoE), school boards, physiotherapy departments and principals were obtained before commencing with data collection. Eight children completed the six-week trial period (four participants from each school).

4.2.1.2 Randomised cross-over IMT study (RCWMCH, DGMAH and referrals)

The majority of participants in the cross-over RCT were recruited from RCWMCH (in Cape Town, Western Cape Province) and DGMAH, formerly known as Garankuwa Hospital (in Pretoria, Gauteng). Both settings manage children and adolescents with NMD who attend regular outpatient neurology/NMD clinic visits for assessment, monitoring and treatment during the year:

- Red Cross War Memorial Children's Hospital is a tertiary academic children's hospital associated with the University of Cape Town with 290 beds, situated in Rondebosch in the Western Cape and was the first specialised paediatric facility in SA.
- Doctor George Mukhari Academic Hospital is a tertiary academic hospital associated with the Sefako Makgatho Health Sciences University (previously known as Medunsa). The hospital consists of 23 departments and 1650 beds and is situated in Garankuwa in Gauteng.
- Medical superintendents/CEOs of both primary sites (RCWMCH; DGMAH) were made aware of the research and the permission protocol for each institution was followed.

Due to slow recruitment in the first year of data collection, additional sites, including private and public schools for children with special needs, and other clinics and public hospitals in Gauteng and Western Cape²⁰ were approached for eligible patients, with ethical approval²¹. Moreover, the Muscular Dystrophy Foundation (MDF) of SA distributed emails to their members to inform them about the study, and possible participants were recruited at a NMD workshop hosted by MDF (Gauteng).

²⁰ Names of institutions withheld due to confidentiality

²¹ Study amendments were approved by HREC

A paediatrician consultant at DGMAH (EH)²² also assisted with the identification of eligible patients from her patient records and additional participants were identified through word of mouth from parents of children who were already participating.

4.2.2 Study designs

A variety of study designs were used for the clinical phases of the study (Chapters 5 and 6), based on the objectives outlined in Chapter 1:

- As NMD are rare conditions, and SA does not have many large, specialised NMD centres; a convenience sampling frame was used for the recruitment of patients in the pre-experimental, pilot study. This was an observational pre-experimental (pre-test post-test) study where IMT was performed for six weeks to determine the practicality and acceptability of such an intervention in a specific patient cohort and obtain preliminary safety data for the IMT protocol (Chapter 5).
- Based on a systematic review of the literature (Chapter 3) and the results of the pre-experimental study (Chapter 5), a cross-over RCT (Chapter 6) was conducted where participants performed IMT or no training for three months, depending on group allocation, whereafter those that did not train during the first three months crossed over to the IMT programme. At the end of three months of IMT, training was ceased and all participants were monitored for a further three months to determine how long the effect of training lasted²³.

4.2.3 Eligibility criteria

The following criteria were applied to determine the eligibility of patients to participate in either the pre-experimental study or the cross-over RCT.

4.2.3.1 Inclusion criteria

Patients presenting with a documented/confirmed congenital or paediatric/adolescent NMD (Appendix Ci) between 5-18 years of age that were IMT naive.²⁴

²² This paediatrician has a special interest in genetics; consults at DGMAH once a week, but is full-time senior lecturer at the University of Pretoria; and assists with patients at Steve Biko Academic Hospital (SBAH).

²³ In order to comply with ethical principles of clinical research: if parents and participants opted to continue with IMT after the three-month monitoring period, they were provided with a device (Powerbreathe Classic ®) which they could keep.

²⁴ Early childhood intervention is important in order to prevent the long-term consequences of poor respiratory care. However, the use of the IMT devices require a certain amount of cooperation and understanding from the patient, therefore the lower age limit was set at five years.

4.2.3.2 Exclusion criteria

- Patients that were at the end of life period and/or presenting with cardiac failure.
- Patients presenting with acute respiratory infections and fever.
- Patients at risk of spontaneous pneumothorax or rib fractures, marked osteoporosis, undrained pneumothorax, large bullae on chest X-ray and/or history of recent (past 12 months) lung surgery (Hill et al., 2010).
- Patients presenting with vital capacity (VC) <25% predicted value, as this is an indication of severe disease progression (Koessler et al., 2001).
- Patients who were already participating in any other intervention trials beyond this study on IMT (for example an ongoing MI-E study or pharmacological trial), in order to minimise the burden of research on these patients as well as eliminate any cross-over effect.

The use of the handheld IMT device is contra-indicated in the following cases and these were therefore added as exclusion criteria ²⁵:

- A history of spontaneous pneumothorax or collapsed lung due to a traumatic injury, even if completely healed.
- A burst eardrum that had not completely healed, or any condition of the eardrum.
- Patients diagnosed with asthma, presenting with frequent severe exacerbations and low symptom perception.
- As IMT requires coordinated breathing efforts, children without sufficient cognitive ability to understand and follow basic instructions, or with insufficient coordination maturity to perform IMT with the Powerbreathe device.

Patients with decreased oral control, severe bulbar dysfunction or with a permanent tracheostomy were not excluded from participating, as the IMT device (Powerbreathe K3) can be used either with a mask or via a connector to a tracheostomy. The researchers demonstrated to the clinicians and caregivers how to obtain an adequate seal (to minimise air leakage) when the patient performed IMT. During recruitment, cognitive ability and breathing coordination were informally assessed by asking participants to follow simple commands (e.g. open your mouth, take a deep breath, hold your breath). The use of the Powerbreathe K3 device and IMT technique were explained and demonstrated to participants and their caregivers before training commenced. Participants were provided with the opportunity to “experience” the device for themselves, starting with a few deep unloaded breaths, followed by a few breaths against a low inspiratory resistance before setting the intensity according

²⁵ Powerbreathe® Kinetic user manual (KH1): pp1-37.

to the pre-determined resistance level.²⁶ Participants were asked to repeat the inspiratory breaths in the presence of the researcher/research assistants in order for their technique to be corrected where needed.

Uncoordinated breathing may lessen the efficacy of an IMT home programme, therefore if a patient was recruited for the study, but the researcher/research assistants/clinicians found that the children were unable to coordinate breathing with the assessment devices (Spirometer; MicroRPM) and/or IMT device, even after the demonstration and practise, they were withdrawn from the trial. These patients received the necessary explanation and/or counselling and the events were recorded. Patients who did not comply with eligibility criteria continued to receive standard care from the multi-disciplinary team at their specific institution.

4.2.4 Sample size

4.2.4.1 Pre-experimental study

The pre-experimental, observational study aimed to include a convenience sample of five to ten participants from two special schools in Pretoria. One patient was excluded based on her pulmonary function tests (VC <25% predicted), but four children from each school participated in the six-week IMT programme (total n=8). In retrospect, although not the primary purpose of this study, the sample size achieved was ultimately sufficient to achieve an 80% (1-beta) chance of detecting, at a significance level of 5% (alpha), a two standard deviation change in inspiratory muscle strength (maximum inspiratory mouth pressure (Pimax)) (SD:2) over six weeks for a pre-test post-test study design (Sample size calculators for clinical research: <http://www.sample-size.net/sample-size-study-paired-t-test/>).

4.2.4.2 Cross-over RCT

It was calculated that a sample size of 13 participants for a two-treatment cross-over trial was needed to achieve a 90% (1-beta) chance of detecting, at a significance level of 5% (alpha), a decrease in the primary outcome measure of two respiratory infections requiring antibiotics (SD:2), compared to no IMT (inactive control), over three months (Power calculation: <http://hedwig.mgh.harvard.edu>).

To ensure a sufficiently powered study, a sample size based on secondary outcome (Pimax), was also calculated (Power calculation: <http://hedwig.mgh.harvard.edu>).

²⁶ Determined by their pulmonary lung function tests and inspiratory muscle strength (30% of Pimax).

Based on the mean Pimax difference observed in the pre-experimental study (Chapter 5), a sample of 24 patients was calculated as being needed to detect a minimum mean Pimax difference of 10cmH₂O during the intervention period (IMT) compared to no IMT (inactive control), over three months, with a power of 90% (1-beta) and 5% significance level (alpha). Therefore, 24 children (12 from Gauteng and 12 from Western Cape) were recruited, over two years.

4.2.5 Recruitment procedure

4.2.5.1 Recruitment for the pre-experimental study

Two schools for children with special needs in Pretoria, Gauteng were approached to participate. After receiving permission from principals, school boards and theDoE, all eligible patients in the schools were identified by the clinicians. Patients were screened for suitability based on the eligibility criteria (4.2.3) and they and their parents/guardians were approached to provide informed consent and assent.

4.2.5.2 Recruitment for cross-over study

Recruitment was performed on days when patients and their caregivers attended the out-patient Neurology/NMD clinics as part of standard care; whilst patients referred by a specialist or colleague were recruited at their school, the doctor's office or home (according to individual circumstances). In some cases, the researcher contacted possible participants, based on referrals from doctors or families who were already involved in the study, while some patients volunteered to participate after being informed about the study by another participant. In addition to the referral system, the researcher (AH) and/or research assistants (LC, EL) attended NMD clinics to assist with screening for eligible patients.

- At RCWMCH patients were screened for eligibility by either the clinicians or the research assistant (LC) at weekly NMD clinics.
- At DGMAH the clinicians or primary researcher (AH) were informed of possible participants by the neurologist/paediatrician/geneticist managing the NMD clinic monthly. Patients were screened for eligibility by either the clinician or the primary researcher (AH). The paediatricians and specialists involved in the study as well as physiotherapy colleagues referred patients for recruitment (Appendix Cii) and information pamphlets were made available for use at the clinics (Appendix Ciii).

- Schools for children with special needs (Western Cape and Gauteng) were contacted to enquire about suitable patients and the Muscular Dystrophy Foundation (MDF, Gauteng branch) was asked to distribute information to their members and if anyone was interested in participating they contacted the primary researcher (AH) to arrange an appointment for screening/assessment.

The researcher (AH) and research assistants (LC, EL) received the necessary training for baseline and outcome assessment.

4.3 Outcome measures

4.3.1 Introduction

Most NMD present with multi-system involvement (Guglieri & Bushby, 2011; Goemans & Buyse, 2014; Ho et al., 2015) and therefore various outcome measures are needed to determine treatment effect. It has been suggested that clinical outcome measures should be relevant to both healthcare providers and the patient/family for effective co-management (Finder et al., 2004; Schechter, 2007). Clinically relevant, holistic assessment in patients with NMD should consider neuromuscular, social, cognitive and psychological functioning (Guglieri & Bushby, 2011; Mary et al., 2018; Toussaint et al., 2018).

The pre-experimental study and cross-over RCT, therefore, included both subjective and objective outcome measures of functional ability; health-related quality of life (HRQoL); the burden of disease (respiratory exacerbations and hospitalisations); perceived exertion (OMNI scale) and pulmonary function (lung volumes, flow, peak expiratory cough flow (PECF) and inspiratory muscle strength). Furthermore, participants and their parents/caregivers were allowed to provide open-text feedback on their experience of IMT. The primary outcomes for this study are depicted in Table 4.1 and the data collection sheet can be found in Appendix Civ.

Table 4.1: Primary outcome measures: inspiratory muscle training programme.

Description of information/data	Instrument	Units of measurement	Type of measurement
Any adverse events that might have occurred due to IMT intervention ²⁷	Patient data collection sheet	E.g. barotrauma (pneumothorax)	Categorical: Nominal
Hospital admissions (n)	Data collection sheet	Frequencies	Numerical
Acute respiratory infections & complications (n)	Data collection sheet	Frequencies	Numerical

The secondary outcome measures included pulmonary function (spirometry and measures of respiratory muscle strength and inspiratory flow), cough efficacy, HRQoL and adverse events (Table 4.2).

Table 4.2: Secondary outcome measures: inspiratory muscle training programme.

Description of information/data	Instrument	Units of measurement	Type of measurement
Lung volumes and flow (including spontaneous and forced spirometry)	MicroLoop Spirometer	L or L/min Z-scores	Numerical
Peak inspiratory flow*	Powerbreathe K3	L/second	Numerical
Cough efficacy (Peak cough flow)	Wright peak flow meter	L/min	Numerical
Inspiratory muscle strength: Maximum inspiratory mouth pressure	MicroRPM	cmH ₂ O % predicted	Numerical
Inspiratory muscle strength: Sniff nasal inspiratory pressure	MicroRPM	cmH ₂ O	Numerical
Inspiratory muscle strength: Strength-index*	Powerbreathe K3	cmH ₂ O	Numerical
Patient's functional level/ability	Based on ambulation and activities of daily living Vignos, Brooke & Motor Function Measure (Data collection sheet)	Scale (1-10; 1-6; /30)	Categorical: Ordinal
Health-related quality of life	Pediatric Quality of Life Inventory [®] (5-7 years, 8-12 years, 13-18 years)	Child & parent/ proxy questionnaires Total & subdomain score (%)	Numerical

*These values were only documented for the pre-experimental study and not the cross-over trial

²⁷ Including, but not limited to, mild to moderate adverse events such as chest pain/discomfort (hyperinflation/barotrauma), nausea/vomiting, fatigue and gastric distension; severe adverse events such as pneumothorax, desaturation, bradycardia, muscle damage, disease progression/muscle deterioration, cardiac arrest, respiratory failure, bleeding and death.

4.3.1.1 Measurement points for the pre-experimental, pilot study

For the pre-experimental study, pilot study inspiratory muscle strength (Pimax, sniff nasal inspiratory pressure (SNIP), strength-index (S-index) and peak inspiratory flow (PIF)) was measured at baseline and every two weeks during the six week IMT period.

The HRQoL questionnaire and pulmonary function tests (lung volumes, flows) and PEF were conducted at baseline and post-intervention (Figure 4.1)

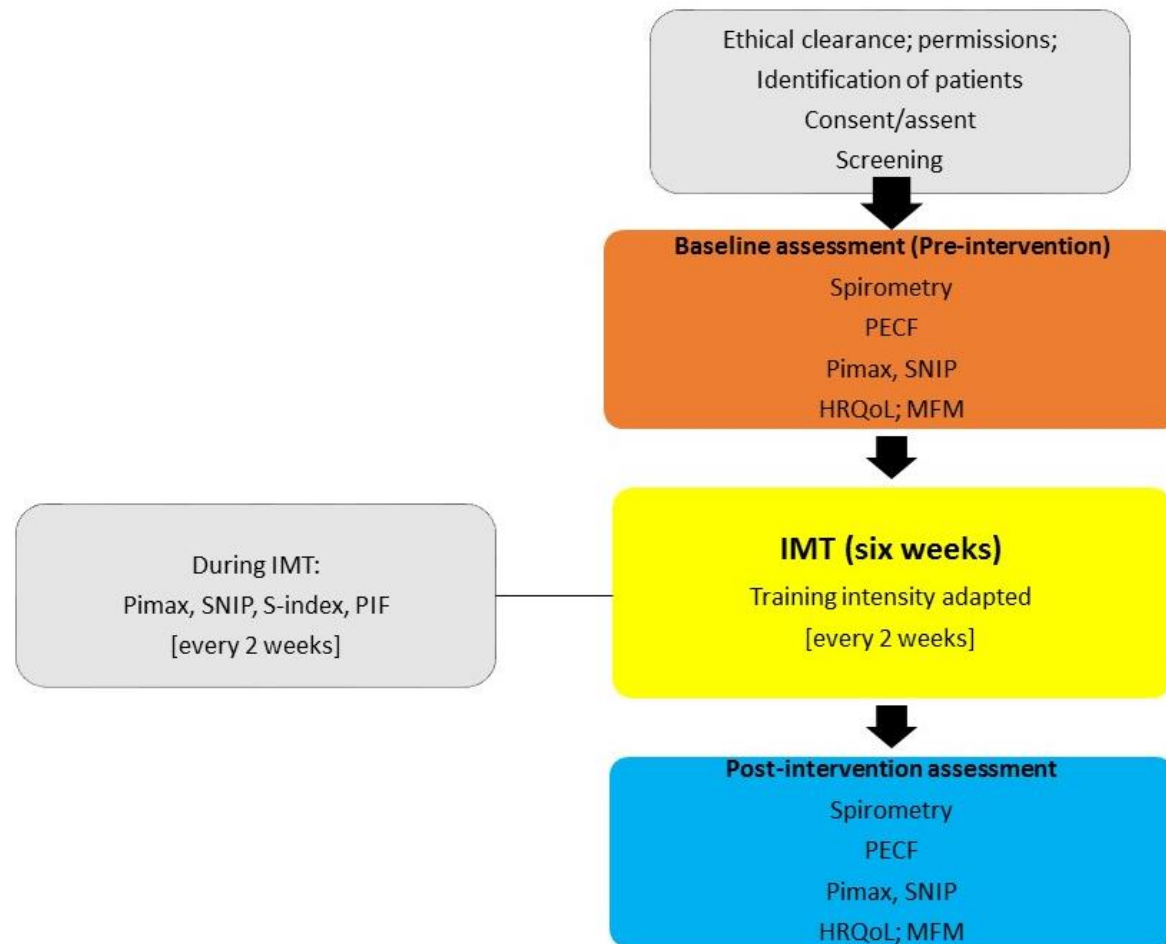


Figure 4.1: Data collection procedure pre-experimental study

4.3.1.2 Measurement points for the cross-over RCT

For the cross-over RCT, inspiratory muscle strength (Pimax, SNIP) was measured at baseline, every two weeks for three months during IMT and then monthly during the non-training/monitoring period. The HRQoL questionnaire and pulmonary function tests (lung volumes and flow), and PEF were conducted at baseline and/or pre-intervention, post-IMT and after three months of no training/monitoring (Figure 4.2).

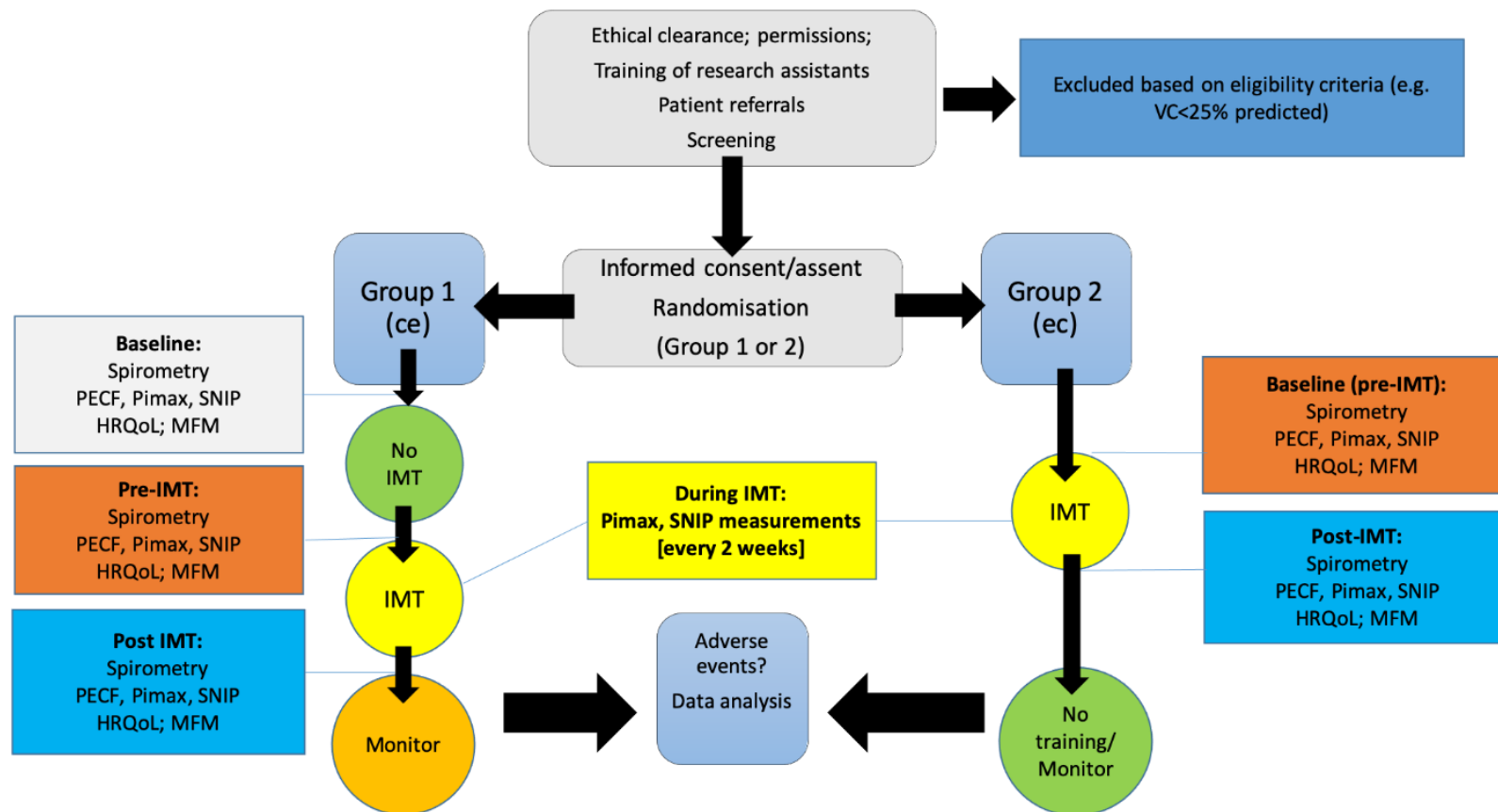


Figure 4.2: Inspiratory muscle training: randomised cross-over data collection process.

4.3.2 Anthropometric measures

Being overweight might influence general function, the excursion of the diaphragm and overall respiratory muscle function, due to increased respiratory effort caused by altered respiratory mechanics (Goemans & Buyse, 2014; MacBean, Wheatley, Lunt & Rafferty, 2017). Obesity can cause decreased chest wall compliance, increased work of breathing and increased oxygen need as the respiratory system is not as efficient, leading to dyspnoea, decreased exercise tolerance and poor HRQoL (ERS, 2002; Nici et al., 2006). Once patients with NMD become non-ambulant, together with cortisone usage (especially in Duchenne muscular dystrophy (DMD)), their weight initially increases, while weight loss might occur later during the course of disease due to oro-pharyngeal muscle weakness and swallowing problems (Perrin et al., 2004; Guglieri & Bushby, 2011; Goemans & Buyse, 2014; Wadman et al., 2020). In addition, cardiac and pulmonary complications might also influence a patient's weight, highlighting the importance of multi-disciplinary involvement in the management of children with NMD (Avendaño & Güell, 2003; Bushby et al., 2010; Guglieri & Bushby, 2011; Birnkrant et al., 2018).

A linear relationship between PEF and height and weight in children (4-18 years) has demonstrated the association between anthropometric measures and pulmonary function (Bianchi & Baiardi, 2008). Therefore, as part of the bio-demographic description of participants, standing height and weight were measured and these values were used for the calculation of Z-scores for the weight (WFA), height (HFA), body mass index (BMI)²⁸ and expected pulmonary function (forced vital capacity (FVC), forced expiratory volume in one second (FEV₁) Z-scores). Weight for age and BMI Z-scores were calculated with an electronic calculator (QuesGen: <http://www.quesgen.com/BMIPedsCalc.php>) and values were entered into an Excel spreadsheet for data analysis (Chapters 5 and 6).

Standing height

Height measurement is important to assess growth and predict pulmonary function in childhood (Gauld, Kappers, Carlin & Robertson, 2004). Standing height was measured in participants who were still ambulant or could maintain a standing posture with or without support (Stern et al., 1989). Participants were asked to remove their shoes and have their heels, buttocks and upper part of the back remain in contact with the stadiometer with their arms relaxed by their side. The researcher/research assistant lowered the slide until it reached the skull and recorded the reading from the height indicator, rounding off to the nearest 0.1 cm.

²⁸ Refer to operational definitions for a description of BMI

Height was measured twice and the average of the two readings was used for analysis. A third measurement was obtained only if the first two measurements were greater than 0.5 cm apart.

Ulna length

To compare to normative values and calculate Z-scores, left ulna length was recorded as a surrogate for height for those participants that could not maintain a standing posture and in those with spinal deformities (Gauld et al., 2004; Mayer et al., 2017; Birnkrant et al., 2018; Chiang et al., 2018; Kinane et al., 2018). Using ulna length or armspan as a surrogate for height to predict expected lung function values is supported by a strong level of evidence (2++) (Hull et al., 2012) and is recommended for non-ambulant patients (Stern et al., 1989; Mayer et al., 2015; Birnkrant et al., 2018; Chiang et al., 2018).

Ulna measurements were chosen for this study as they are reproducible and precise in school-aged children and might be superior to armspan measurements in NMD and patients that present with abnormal muscle tone as well as scoliosis and/or joint deformities caused by contractures (Gauld et al., 2004; Goemans & Buyse, 2014).

A conversion table based on sex and age was used to calculate height (Figure 4.3).

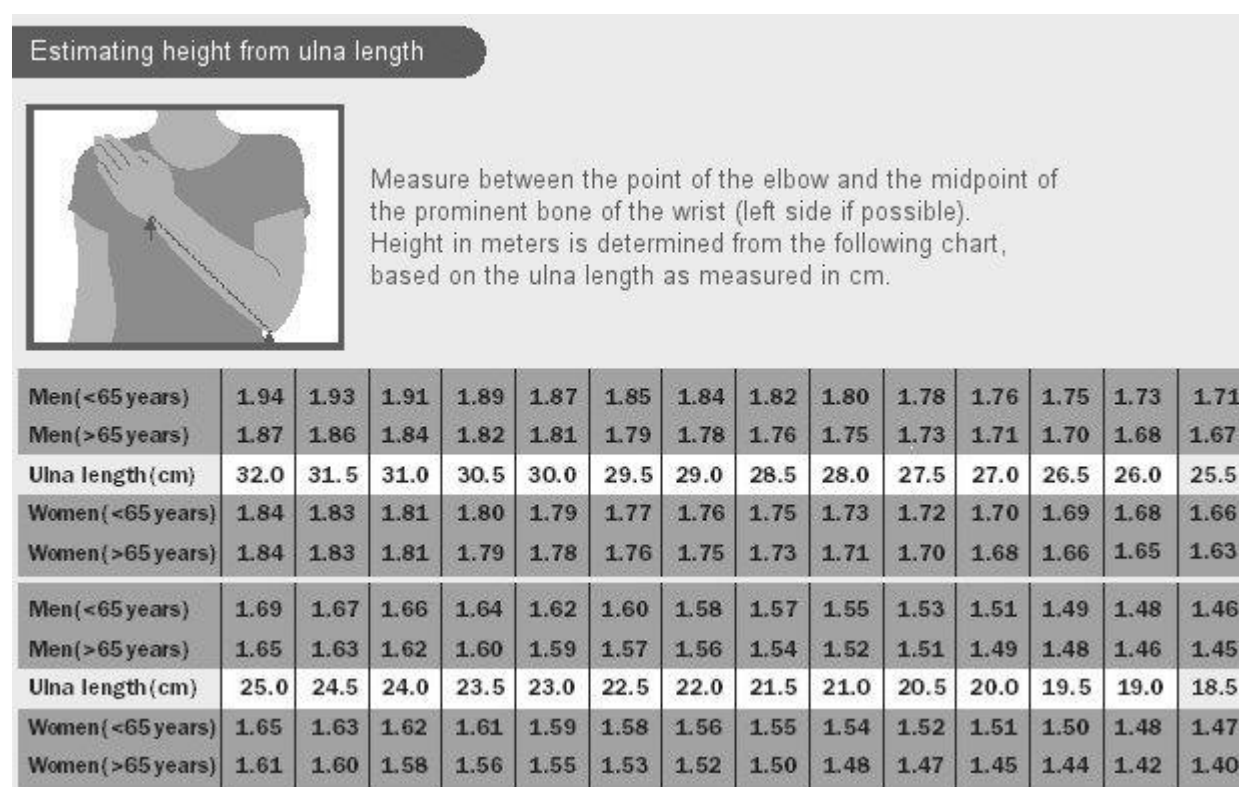


Figure 4.3: Ulna length conversion table (http://www.treatdiet.co.nz/media/ulna_height.jpg).

In some cases the converted ulna length height value was less than the last known standing height measure; in these cases, researchers recorded the most recent valid standing height measure for calculations of BMI and Z-scores (Mayer et al., 2015).

4.3.3 Pulmonary function

Lung function testing is routinely used as part of clinical assessment to determine pulmonary status and compare these values to normative data (reference values) (ATS, 1991). Pulmonary function assessment is commonly used to determine severity, functional impairment and progress of patients with recognised muscle weakness (ERS, 2002). Vital capacity (VC) specifically is useful in evaluating respiratory status at diagnosis, in monitoring disease progression, indicating cough efficacy and predicting the risk of post-surgery complications and survival in patients with NMD (Dohna-Schwake et al., 2006; Sharma, 2009; Chatwin et al., 2018; Chiang et al., 2018). The feasibility of performing pulmonary function testing among young school children has been confirmed (Bianchi & Baiardi, 2008; Nève et al., 2013). A variety of respiratory muscle strength tests might be useful in NMD, as the patterns of respiratory muscle weakness differ depending on the type of NMD (Nève et al., 2013; Boentert et al., 2017; Birnkrant et al., 2018; Finkel et al., 2018).

Pulmonary function testing in the pre-experimental and cross-over RCT, therefore, consisted of spirometry (relaxed and forced), as well as the measurement of cough ability (peak expiratory cough flow (PECF)) and inspiratory muscle strength (Pimax; SNIP) (Figure 4.4). Peak inspiratory flow and S-index were additional measures assessed with the Powerbreathe device during the pre-experimental study.

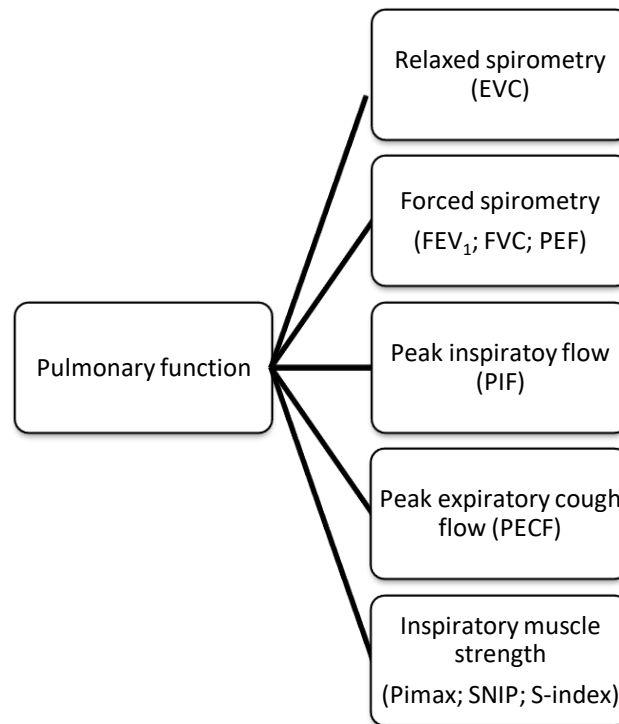


Figure 4.4: Pulmonary function outcome measures.

4.3.3.1 Spirometry (Relaxed and forced spirometry)

Spirometry (lung volumes and flow) can identify and quantify functional abnormalities of the respiratory system and can assess severity and progression of NMD, therefore these measures are recommended as part of standard assessment and can be measured from approximately six years of age (ERS, 2002; Bianchi & Baiardi, 2008; Nève et al., 2013; Mayer et al., 2015; Mary et al., 2018). Lung volume changes in NMD can be attributed to the progressive respiratory muscle weakness as well as a change in compliance of the lungs and chest wall (Avendaño & Güell, 2003; Servera et al. 2003; Birnkrant et al., 2018). Both relaxed and forced spirometry tests were performed in this study.

Spirometry is effort dependent and volitional and therefore a poor patient effort, due to physical or cognitive limitations, can lead to misdiagnosis and inappropriate treatment (Barreiro & Perillo, 2004; Nicot et al., 2006; Boentert et al., 2017; Chiang et al., 2018), which emphasises the need for encouragement when performing pulmonary function tests. In order to enhance patient performance, verbal and visual encouragement and careful instruction were provided during pulmonary function testing (Fauroux & Aubertin, 2007; Heinzmann-Filho & Donadio, 2015; Castrillo et al., 2019). The American Thoracic Society (ATS), European Community for Coal and Steel (ECCS) and European Respiratory Society have published guidelines to assist with standardisation and interpretation of spirometry and other pulmonary function tests (ATS, 1991).

Spirometry was performed in a relaxed upright sitting position, either in their wheelchair or a chair, similar to other studies (Winkler et al., 2000; Koessler et al., 2001; Dohna-Schwake et al., 2006; Birnkrant et al., 2018) and based on the guidelines of ATS/ERS for standardisation of lung function testing (Miller et al., 2005). Spontaneous/relaxed (slow VC measured on expiration (EVC)) and forced spirometry (VC, FEV₁ and peak expiratory flow (PEF)) were measured with a portable Carefusion, MicroLoop handheld spirometer at baseline (pre-intervention), post intervention (IMT) (either six weeks or three months) and in the cross-over RCT post monitoring, three months after IMT ceased.

To ensure validity of measurements, the best effort out of three technically acceptable and reproducible attempts were recorded for further analysis, similar to other studies and as recommended by spirometry guidelines (Miller et al., 2005; Nicot et al., 2006; Bianchi & Baiardi, 2008; Yeldan, Gurses & Yuksel, 2008; Park et al., 2010; Torres-Castro et al., 2016). In order to minimise variation between spirometry efforts, three satisfactory efforts were sought with acceptable variation <20% between these efforts (Fauroux & Aubertin, 2007). It is recommended that a manoeuvre should be repeated three to eight times and the highest value recorded for analysis (Farrero et al., 2013; Caruso et al., 2015). At least three successful spirometry, cough ability (PECF) and inspiratory muscle strength (Pimax; SNIP) attempts were recorded, but testing at times continued up to five repetitions (Szeinberg, Marcotte, Roizin, Mindorff, England, Tabachnik & Levison, 1987; Nicot et al., 2006; Meier et al., 2017; Kinane et al., 2018) in order to ensure the patient's maximum effort was captured and all three values recorded were within 20% of each other. This is aligned with other studies in DMD and spinal muscular atrophy (SMA) (Szeinberg et al., 1987; Stefanutti et al.; Takaso et al., 2010; Mayer et al., 2015).

Relaxed spirometry

One of the most frequently reported lung volumes in NMD is VC because this is a reliable, standardised, easy to measure with well-established reference values and can provide an estimation of disease progression in moderate to severe respiratory muscle weakness (inspiratory and expiratory muscle weakness) (ERS, 2002; Hull et al., 2012; Chiang et al., 2018). Participants were asked to perform a slow VC manoeuvre by breathing out for as long as possible after a full inspiration (EVC) (Hull et al., 2012; Nève et al., 2013; Chiang et al., 2018). An open circuit method as described by Miller et al. (2005) was used for all manoeuvres, as all patients had moderate to good oral control (based on speech and swallowing ability) and therefore no nose clip was needed to maintain optimal pressure and/or prevent air leakage (Farrero et al., 2013).

Forced spirometry

Forced spirometry (FVC, PEF, FEV₁) was performed by asking the participants to exhale as forcefully (hard and fast) as they could, after a maximum inhalation (TLC). In addition, visual incentive spirometry was used for these manoeuvres using the age-appropriate visual graphics function on the MicroLoop handheld spirometer.

Dynamic spirometry measures such as FVC, PEF and FEV₁ are well-established outcome measures in the assessment of restrictive pulmonary functional changes due to respiratory muscle weakness in patients with NMD (Auger et al., 2017; Mayer et al., 2017; Meier et al., 2017; Chiang et al., 2018; Ricotti, Selby, Ridout, Domingos, Decostre, Mayhew, et al. 2019). Forced vital capacity is a maximum expiratory manoeuvre performed during complete exhalation, after a full inspiration (Mayer et al., 2015), and is one of the most commonly used measures of pulmonary function in NMD (Nicot et al., 2006; Kinane et al., 2018). Forced vital capacity is a reliable general outcome measure for both inspiratory and expiratory muscle function and is indicative of general disease progression (Finder et al., 2004; Farrero et al., 2013; Boentert et al., 2017; Birnkrant et al., 2018; Morrow et al., 2019). However, a decrease in FVC and PEF% predicted might not be sensitive enough to highlight small changes between ambulatory and non-ambulatory patients (Mayer et al., 2015).

Peak expiratory flows can be obtained with portable devices (ERS, 2002) and is a reliable indicator of flow-related pulmonary function (Meier et al., 2017), but is one of the most effort dependent lung function tests measuring maximum voluntary flow during exhalation (Mayer et al., 2015). Assessment of FVC, PEF and FEV₁ are all volitional and effort dependent lung function measures, which could be difficult to perform in patients with advanced NMD (Nicot et al., 2006; Boentert et al., 2017). However, if a maximal effort is ensured by the patients, and the test is technically sound, these measures can be very useful clinically (Mayer et al., 2015; Meier et al., 2017). The percentage predicted values of FVC, PEF and FEV₁ are strongly correlated and show a linear decline as the child grows older (Meier et al., 2017). It stands to reason that PEF longitudinal change will be similar to that of FVC, as the ability to create a maximal flow during expiration (PEF) coincides with the ability to take a deep breath (maximal inspiration) and forcefully exhale (Panitch, 2006; Toussaint et al., 2009), producing a lower FVC with reduced PEF (Mayer et al., 2015). A study conducted in 41 children with NMD in SA also showed a strong, positive and significant correlation between PEF and PEFV₁ (Pearson's $r=0.81$; $p<0.0001$) and a moderate, significant association between FVC and PEFV₁ (Pearson's $r=0.61$; $p<0.0001$) (Morrow et al., 2019). This study also highlighted the potential utility of FVC and PEF measures as surrogates for cough efficacy (Morrow et al., 2019).

A similar correlation between PEF and PEF_{CF} was reported in a healthy Greece paediatric cohort (Pearson's $r=0.95$; $p<0.0001$) (Gogou et al., 2017). In addition, considering that PEF measurement might be more valuable than PEF_{CF} for patients with poor glottic closure (Bianchi & Baiardi, 2008), both these measures were included in the pulmonary assessment of this study.

Factors such as sex, age, ethnicity and growth can influence absolute spirometry values (Meier et al., 2017; Birnkrant et al., 2018; Chiang et al., 2018; Lumb & Thomas, 2020). Therefore reporting norm-adjusted percentage predicted values or Z-scores for pulmonary function (FVC, FEV₁ and PEF) is preferable to recording absolute values (Chapter 6). Accordingly, Z-scores for FVC and FEV₁ were calculated (Global Lung Function Initiative (GLI): <http://glgistransfer.org.au/calcs/spiro.html>) to describe data in terms of normative values and to compare the results from this study with other published studies. Although many studies in NMD have used percentage predicted FVC and FEV₁, the GLI multi-ethnic specific norm-referenced Z-score values were used in this study (Quanjer, Stanojevic, Cole, Baur, Hall, Culver, et al. 2012). The reasons are due to the lack of normative spirometry data for black African children prior to GLI and the inappropriateness of the historical reference equations for "African Americans" which might cause an underestimation of lung function. The expression of spirometry tests in standard deviations might therefore be more appropriate as it eliminates any age or ethnicity related bias and provides a better representation of normative lung function distribution (Stanojevic, Quanjer, Miller & Stocks, 2013; Da Rosa et al., 2017; Lumb & Thomas, 2020).

4.3.3.2 Inspiratory muscle strength

Pulmonary function can be reliably monitored by measuring FVC, Pimax and Pemax (Kinane et al., 2018; Wenninger, Stahl, Wirner, Einvag, Thiele, Walter & Schoser, 2020), as both inspiratory and/or expiratory muscles, may be affected in NMD (McCool & Rosen, 2006; Farrero et al., 2013; Bourke, 2014; Boentert et al., 2017). The most frequently used respiratory muscle strength tests in children are Pimax, Pemax and SNIP (Chiang et al., 2018; Hulzebos et al., 2018). A study by Gozal and Thiriet (1999), found a statistically significant difference between patients with NMD and their matched control groups for Pimax and Pemax ($p<0.01$). Kinane et al. (2018) also observed an annual decrease of 3.8% and 2.7% predicted Pimax and Pemax in patients with DMD. Sniff nasal inspiratory pressure is a useful measurement that can detect a decline in respiratory muscle strength in young children with DMD when VC values are still within normal ranges (Nève et al., 2013).

Respiratory muscle strength might therefore be a predictor of long-term outcome in patients with NMD (Schoser, Fong, Geberhiwot, Hughes, Kissel, Madathil, et al. 2017) and volitional respiratory muscle strength tests can add value to assessment in young patients with NMD (Nicot et al., 2006; Finkel et al., 2018).

Posture can affect respiratory muscle function assessment, especially when the diaphragm is involved and therefore, similar to another study performed in DMD and ATS/ERS recommendations, this study assessed patients in a sitting position (Martin et al., 1986; Miller et al., 2005).

Inspiratory pressure measured at the mouth (Pimax)

Maximum static inspiratory pressure is one of the most sensitive indicators of decreased inspiratory respiratory muscle strength and is determined by measuring the maximum inspiratory pressure during a maximal static contraction from residual volume (RV) or functional residual capacity (FRC) (Stefanutti et al., 2000; Sharma, 2009; Hull et al., 2012; Hulzebos et al., 2018). Measures of inspiratory pressure might provide a better indication of survival rate and be a better predictor of respiratory insufficiency than spirometric measures of VC and FVC (Nève et al., 2013; Eidenberger & Nowotny, 2014). Pulmonary function measures such as VC, PEF, Pimax and Pemax may have limited reliability and validity in patients with decreased oral control and pharyngeal weakness (Boentert et al., 2017). The disadvantages of using Pimax for inspiratory muscle strength assessment include the test being effort dependent, with wide variations among individuals and poor reproducibility (Gozal, 2000; ERS, 2002; Caruso et al., 2015). Despite its variability, Pimax is still viewed as a valuable assessment of respiratory muscle strength in children (Tomalak, Pogorzelski & Prusak, 2002; Heinzmann-Filho & Donadio, 2015; Hulzebos et al., 2018).

While Pimax measures the force created by the respiratory muscles, it is also dependent on lung volumes, as the greatest pressures are achieved near FRC and RV. This relationship between pressure and volume indicates the diaphragm's force-length properties and mechanical coupling with the chest wall (McCool, 1992). Measuring Pimax from RV is considered the method of convention and preference (Fauroux & Aubertin, 2007; Hill et al., 2010; Heinzmann-Filho & Donadio, 2015; Hulzebos et al., 2018; Verma et al., 2019). Although Pimax is commonly used and clinically relevant, interpretation of low Pimax values can be difficult (ERS, 2002; Nicot et al., 2006). For example, low Pimax may be a result of poor technique or air leaks rather than reflecting true muscle weakness (Nicot et al., 2006).

Therefore, maximum inspiratory pressure tests should be performed by an experienced operator; participants should be encouraged to perform a maximum manoeuvre and careful instructions are essential to ensure ultimate performance (Fauroux & Aubertin, 2007; Heinzmann-Filho & Donadio, 2015).

For this study, inspiratory muscle strength was measured in the sitting position using an electronic handheld mouth pressure meter (Carefusion, MicroRPM); similar to the technique described by (Dohna-Schwake et al., 2006; Yeldan et al., 2008; Park et al., 2010; Meier et al., 2017; Chiang et al., 2018). Maximum mouth pressure (Pimax) was measured after full expiration (until RV) followed by a maximal inspiratory effort, through a cylindrical mouthpiece without a nose clip (Szeinberg et al., 1987) which was held for at least one second (ERS, 2002; Fauroux, 2003; Fauroux & Aubertin, 2007; Park et al., 2010). The use of nose clips is not mandatory when testing respiratory muscle strength (Fauroux & Aubertin, 2007; Verma et al., 2019), but has been used in some studies (Gozal & Thiriet, 1999; Stefanutti et al., 2000; Dohna-Schwake et al., 2006; Yeldan et al., 2008).

Pimax % predicted was calculated and based on the formula suggested by Wilson et al. (1984) and referenced in Kinane et al. (2018) for boys and girls 7-17 years old
[Boys $44.5 + (0.75 \times W(\text{kg}))$; Girls $40 + (0.57 \times W(\text{kg}))$].

Sniff nasal inspiratory pressure (SNIP)

A reliable alternative to Pimax which might be more natural and easier to perform and does not require practice or oral control is the SNIP (Gozal, 2000; Nicot et al., 2006; Fauroux & Aubertin, 2007; Nève et al., 2013).

Sniff nasal inspiratory pressure (Carefusion, MicroRPM) was therefore also measured in this study as an alternative indicator of global inspiratory muscle strength (Stefanutti et al., 2000; Ratnovsky et al., 2008; Farrero et al., 2013; Boentert et al., 2017; Chiang et al., 2018). The method used was similar to that described in the ATS/ERS statement on respiratory muscle strength testing and testing in children (ERS, 2002; Fauroux & Aubertin, 2007). Measuring SNIP does not require a mouthpiece and is a non-invasive, volitional manoeuvre measuring global inspiratory muscle strength, with narrower reported variability than Pimax (Stefanutti et al., 2000; ERS, 2002; Fauroux & Aubertin, 2007; Caruso et al., 2015; Chiang et al., 2018).

Furthermore, this technique has been validated in NMD and can easily be performed by most patients, including those with DMD, severe respiratory muscle weakness and young children (Wanke et al., 1994; Maillard et al., 1998; Gozal, 2000; Fauroux, 2003; Fauroux & Aubertin, 2007; Nève et al., 2013).

It is important to note that Pimax and SNIP are usually measured at different lung volumes (RV and FRC respectively). At RV, passive recoil pressure of the chest wall is present which could provide an overestimation of the patient's inspiratory muscle strength, whereas at FRC the chest recoil is zero which might be a more specific indication of true inspiratory muscle strength (McCool, 1992; Fauroux & Aubertin, 2007). The sniff manoeuvre has also been shown to be more reproducible, easy to perform and an alternative to Pimax, especially in patients with decreased oral control (Wanke et al., 1994; Boentert et al., 2017), but is still effort dependent and submaximal efforts can occur in patients who are ill or breathless (Gozal, 2000). Measures of Pimax and SNIP are therefore not interchangeable, and SNIP should be measured in addition to Pimax (Stefanutti et al., 2000; Caruso et al., 2015).

In this study, SNIP was assessed with participants in an upright, relaxed sitting position. in a chair or wheelchair, performing a sniff manoeuvre at the end of tidal volume (FRC) (Ratnovsky et al., 2008; Nève et al., 2013), with the mouth closed. The left/right nostril (depending on the participant's preference) was occluded with a nasal probe size that ensured complete nasal passage closure, while the contralateral nostril remained open to allow the passage of air (Stefanutti et al., 2000; Ratnovsky et al., 2008). The same nasal passage side was occluded and the same size probe was used with each follow-up assessment every two weeks.

Pulmonary function measures such as VC, PEF, Pimax, Pemax and SNIP are volitional and effort dependent tests and therefore reproducible results might not always be possible. Alternative methods such as phrenic nerve studies are valuable but are not readily available (Nicot et al., 2006; Farrero et al., 2013; Boentert et al., 2017). Limited research is available for normative values of SNIP in children and adolescents and more research is encouraged to explore the use of this test in this subpopulation (Chiang et al., 2018; Verma et al., 2019).

Peak inspiratory flow, strength-index and volume

One of the assessment functions of the Powerbreathe K3[®] inspiratory muscle training threshold device include measuring PIF, S-index and lung volume when taking a deep breath from RV.

All three of these measurements are rated very poor to excellent based on the mean and standard deviation for patients with a similar height, weight, age and sex (predicted population values). While sitting, patients were asked to breathe out as far as they could (to RV); and then to take a deep, fast breath through the Powerbreathe device. The data for PIF, S-index and volume on inspiration were recorded, based on a single breath effort. Peak inspiratory flow as a function of inspiratory muscle strength, refers to the amount of airflow that can be created when taking a deep breath, relating to the force-velocity relationship of the inspiratory muscles (<https://www.powerbreathe.com/powerbreathe-k3>; Gozal, 2000).

The S-index, as measured by the Powerbreathe K3 device is derived from the participant's PIF and based on the muscle force-velocity relationship during inspiration. Peak inspiratory flow and strength can be reduced at all lung volumes in the presence of inspiratory muscle weakness. In addition to the S-index and Pimax measures, lung volume was also measured (litres) when the patient performed a deep breath manoeuvre with the Powerbreathe K3[®]. The S-index was assessed, during every contact session with the participants of the pre-experimental study, at baseline and every two weeks.

4.3.3.3 Cough ability (PECF)

The efficacy of a cough is dependent on the peak flow created during the expulsive phase of a cough after the opening of the glottis with a release of compressed air, with assistance of the expiratory muscles (Servera et al., 2003; Dohna-Schwake et al., 2006; Toussaint et al., 2009; Farrero et al., 2013). The measurement of PECF, therefore, provides an objective measure of cough efficacy (Gauld, 2009; Rose et al., 2018). Correlation between PECF and lung volumes (FVC, FEV₁ and PEF) has been shown in children four to 18 years of age (Bianchi & Baiardi, 2008), six to 13 (Gogou et al., 2017) and correlates well with the ability to clear the airways (Finder et al., 2004; Panitch, 2006; Gauld, 2009). In addition to PEF, which was measured with the MicroLoop handheld spirometer, the participants' unassisted cough ability (PECF) was measured. Similar to spirometry testing, three PECF efforts were recorded with the participant in the sitting position using a Paediatric Wright peak flow meter with a mouthpiece, but without a nose clip as participants found this uncomfortable and it caused anxiety (Dohna-Schwake et al., 2006; Park et al., 2010; França, Camargos, Vieira, Pereira & Parreira, 2015; Chiang et al., 2018).

Early identification for patients at risk of pulmonary complications through measurement of cough ability can lead to earlier intervention strategies such as cough augmentation that can improve patient outcome (Boitano, 2006; Rose et al., 2018; Morrow et al., 2019). Although recommended by international guidelines, measuring PEF is not routinely performed in children with NMD in the SA healthcare setting (Morrow et al., 2019), similar to Canada and the UK (Rose et al., 2018).

4.3.4 Functional ability (level of ambulation and upper limb function)

The assessment of functional ability in NMD is important for use in clinical practice as well as clinical trials as it is related to independence and HRQoL

(Bérard, Payan, Hodgkinson, Fermanian, Group, et al. 2005; Janssen et al., 2016).

4.3.4.1 Level of ambulation

As part of the subjective assessment, participants were asked about their level of ambulation, if they were using a manual or electric/power wheelchair and/or how much assistance was needed. In Chapter 5, the functional level of participants is indicated as ambulant (A), partially ambulant (PA) or non-ambulant (NA) and in Chapter 6 these categories are described as either ambulant (A) or non-ambulant (NA).

The annual rate of decline of forced vital capacity percentage predicted (FVC%p) is higher in patients who become non-ambulant at an earlier age (Mayer et al., 2017), hence maintaining mobility for longer is advantageous for independence as well as respiratory function. Assessing functional outcomes in patients with the progressed disease, and especially those who are already non-ambulant is important for determining the long-term efficacy of interventions

(Mazzone, Vasco, Palermo, Bianco, Galluccio, Ricotti & Mercuri, 2012). The fact that pulmonary function is associated with functional ability is of clinical relevance and can assist clinicians with proactive management strategies. For example, at an upper limb function Brooke score of 2 and 3, pulmonary function decline becomes apparent; and a Brooke score of 5 (inability to raise their hands to their mouth) could indicate that FVC%p has decreased to less than 50%. This clinical loss of pulmonary function can indicate the need for NIV and mechanical cough assistance (Mayer et al., 2017; Meier et al., 2017; Birnkrant et al., 2018; McDonald & Mercuri, 2018).

Because pulmonary function decline correlates with the general disease stage of patients with NMD (Mayer et al., 2017; Meier et al., 2017), this study assessed upper limb function (Brooke scale), lower limb function (Vignos scale), and ten items of upper limb function and coordination (Motor Function Measure (MFM)) to determine if there was an association between these values and pulmonary function (Figure 4.5).

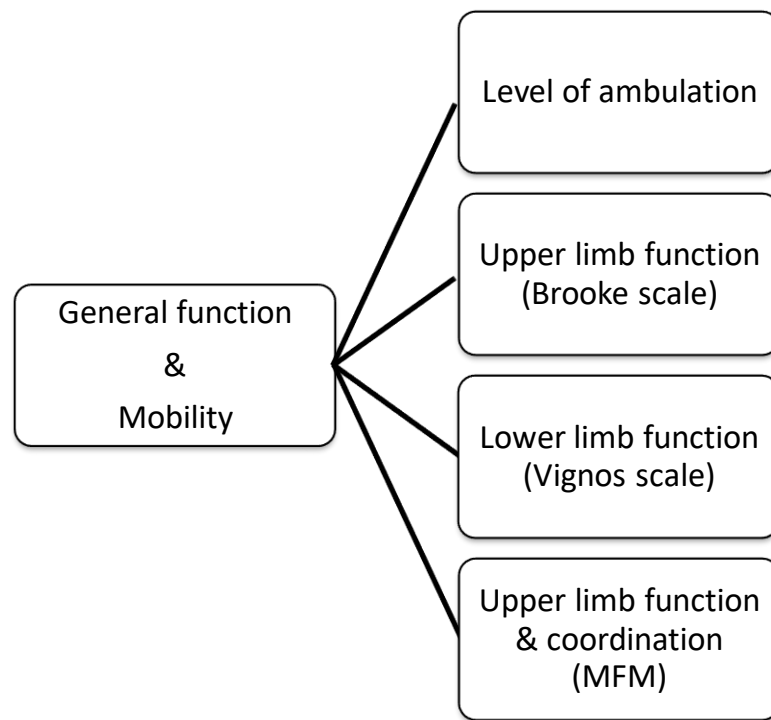


Figure 4.5: Outcomes for general function and mobility.

4.3.4.2 Upper limb and lower limb function (Brooke and Vignos scales)

The Brooke and Vignos ordinal scales were developed to describe the functional ability (upper and lower limbs) and disease progression of patients with DMD, but has been implemented in clinical practice for a variety of NMD (Lue, Lin, Chen & Lu, 2009; Mazzone et al., 2012; Lu & Lue, 2014; Janssen et al., 2016).

The Brooke scale describes upper limb function on a six-point scale (Table 4.3), where six is the lowest functional value and one the highest. A score of six indicates that “hands cannot be raised to the mouth” and a score of one indicates that the “patient can abduct arms into a full circle until they touch above the head” (Lue et al., 2009; Lu & Lue, 2014; Janssen et al., 2016).

The Brooke scale is a valid instrument of upper limb function in severely progressive NMD, such as DMD, but could be insufficient to distinguish severity levels in slowly progressive conditions such as BMD, LGMD, FSHMD owing to a large floor effect, especially in BMD (Lue et al., 2009; Lu & Lue, 2014). The loss of upper limb function is associated with pulmonary function loss (Mayer et al., 2017), which therefore has clinical implications for activities of daily living (ADL) as well as respiratory morbidity.

Table 4.3: Brooke scale (upper limb function).

Grade	Description
1	Starting with arms at the sides, the patient can abduct the arms in a full circle until they touch above the head
2	Can raise arms above head only by flexing the elbow (shortening the circumference of the movement) or using accessory muscles
3	Cannot raise hands above head, but can raise an 8-oz glass of water ²⁹ to the mouth
4	Can raise hands to the mouth, but cannot raise an 8-oz glass of water to the mouth
5	Cannot raise hands to the mouth, but can use hands to hold a pen or pick up pennies from the table
6	Cannot raise hands to the mouth and has no useful function of hands

For lower limb function, the 10-point Vignos scale was used, where 10 indicates the lowest possible functional score and one the highest. A score of 10 shows that a “patient is confined to a bed” and one indicates that the patient “walks and climbs stairs without assistance” (Lue et al., 2009; Lu & Lue, 2014) (Table 4.4).

Table 4.4: Vignos scale (Lower limbs).

Grade	Description
1	Walks and climbs stairs without assistance
2	Walks and climbs stairs with aid of railing
3	Walks and climbs stairs slowly with aid of railing
4	Walks unassisted and rises from a chair but cannot climb stairs
5	Walks unassisted but cannot rise from a chair or climb stairs
6	Walks only with assistance or walks independently with long leg braces ³⁰
7	Walks in long leg braces but requires assistance for balance
8	Stands in long leg braces but is unable to walk even with assistance
9	Is in a wheelchair
10	Is confined to a bed

²⁹ ±180ml of water

³⁰ Long leg braces are not commonly used in the NMD population in South Africa

The Brooke and Vignos scales provide global descriptions of functional ability whereas the MFM for NMD is a reliable, validated and disease specific, comprehensive scale that caters for ambulant and non-ambulant patients (Bérard et al., 2005; Mercuri et al., 2012). For these reasons, and because of the assessment of distal motor function, which could be relevant for more severe DMD and SMA, the MFM was also included as part of the functional assessment of participants.

4.3.4.3 Upper limb function and coordination (Motor Function Measure)

The Motor Function Measure (MFM-32) is a reliable, validated general observer-rated scale developed to monitor the progression of disease in a wide variety of NMD (6-62 years of age). This measurement includes 32 items in three domains: i) standing and transfers (13 items); ii) axial and proximal (12 items) and iii) distal motor ability (7 items) (Bérard et al., 2005; Bushby & Connor, 2011; Mazzone et al., 2012; Iwabe et al., 2014).

The advantage of observer-rated instruments is the use of standardised procedures, instructions and materials (Mazzone et al., 2012). The MFM has been well received by patients, who have reported appreciating the “playful” aspect of some of the tasks and discovering the ability to perform certain functional activities they were unaware of. In addition, no special equipment is required (Bérard et al., 2005). The agreement coefficients of the MFM items (inter-rater reliability) were moderate to excellent (0.51-0.94), and intra-rater test re-test was good to excellent (0.61-0.94) with high internal consistency for the global scale as well as subdomains (Bérard et al., 2005). Very strong correlations have been reported between the total MFM score and other outcome measures such as Brooke ($r=0.85$) and Vignos scales ($r=0.91$) (Bérard et al., 2005).

Ten self-selected items of MFM-32 (items 14-23) (Bérard et al., 2005) were performed in sitting in a wheelchair or chair (Table 4.5), to assess upper limb function and coordination. These items were selected so that all participants could be tested similarly, regardless of their level of ambulation and so that the test could be performed in approximately 10 minutes, to minimise fatigue (Chapter 1: 1.1.2; 1.1.4.2). The ten items included four from the D2 (axial and proximal) and six from the D3 (distal motor function) domains. The advantages of the upper limb functional components of the MFM is that they include assessment from shoulder ability to distal function and can be performed by participants that are ambulant or non-ambulant (Bushby & Connor, 2011; Mazzone et al., 2012). The distal function of MFM has been reported to be more a more stable indicator of functional ability, as proximal function is usually affected before distal function in NMD (Jansen et al., 2013). The maximum score for each item was three, therefore participants’ scores in this study were expressed out of 30.

Table 4.5: Selected Motor Function Measure (MFM) items for upper limb function and coordination.

MFM 10 selected items (sitting) [Items 14-23]³¹	
Item number	Description
14	<u>SEATED ON THE CHAIR OR IN THE WHEELCHAIR, HEAD IN FLEXION:</u> From head in complete flexion, raises the head then maintains it raised for 5 seconds, the head stays in midline position throughout the movement and the holding position. ³²
15	<u>SEATED ON THE CHAIR OR IN THE WHEELCHAIR, FOREARMS ON THE TABLE BUT NOT ELBOWS:</u> Places both hands on top of the head at the same time while the head and trunk remain in midline position.
16	<u>SEATED ON THE CHAIR OR IN THE WHEELCHAIR, THE PENCIL ON THE TABLE:</u> Without moving the trunk, reaches the pencil with one hand, forearm and hand off the table, with the elbow in full extension at the end of the movement.
17	<u>SEATED ON THE CHAIR OR IN THE WHEELCHAIR, 10 COINS ON THE TABLE:</u> Successively picks up and holds 10 coins in one hand during the 20-second period.
18	<u>SEATED ON THE CHAIR OR IN THE WHEELCHAIR, ONE FINGER PLACED IN THE CENTER OF THE FIXED CD:</u> Goes round the edge of the CD with the same finger without hand support on the table.
19	<u>SEATED ON THE CHAIR OR IN THE WHEELCHAIR, THE PENCIL ON THE TABLE:</u> Picks up the pencil and draws a continuous series of loops inside the frame and over its full length touching the top and bottom line of the frame.
20	<u>SEATED ON THE CHAIR OR IN THE WHEELCHAIR, HOLDING THE SHEET OF PAPER:</u> Tears the sheet of paper folded in 4, beginning from the folded edge.
21	<u>SEATED ON THE CHAIR OR IN THE WHEELCHAIR, THE TENNIS BALL ON THE TABLE:</u> Picks up the ball, and turns the hand over completely holding the ball.
22	<u>SEATED ON THE CHAIR OR IN THE WHEELCHAIR, ONE FINGER PLACED IN THE CENTER OF THE DIAGRAM:</u> Raises the finger and places it successively on the 8 drawings without touching the lines.
23	<u>SEATED ON THE CHAIR OR IN THE WHEELCHAIR, UPPER LIMBS ALONG THE TRUNK:</u> Places the two forearms and/or the hands on the table at the same time without moving the trunk.

Each item on the MFM is scored on a four point scale, with zero if the participant is unable to perform the task or cannot maintain the starting position whilst performing the task, where three is the ability to perform the task with a controlled (normal) movement pattern

(Iwabe et al., 2014; MFM user manual: <https://mfm-nmd.org/obtenir-un-manuel-utilisateur/>).

³¹ Tasks were assessed as outlined by the MFM instructional manual (English version)

³² Participants were asked to focus on a hand puppet while in neck flexion, and follow the hand puppet into neck extension and thereafter maintaining a neutral head position for 5 seconds

4.3.5 Health-related quality of life (PedsQL)

The availability of resources, long-term care and patient comfort must be considered in the chronic management of patients with NMD, to reduce hospitalisations, improve HRQoL and life expectancy as well as reducing the burden of disease on the patient and their family (McCool & Rosen, 2006; Wang et al., 2007; Farrero et al., 2013; Auger et al., 2017; Boentert et al., 2017). Health can be influenced by individual, social and environmental determinants (Bircher & Kuruvilla, 2014) and is, therefore, a multidimensional concept associated with the condition's physical presentation and impact, psychological/emotional effect and social functioning, including elements of meaning and fulfilment (Varni, Seid & Rode, 1999; Eiser & Morse, 2001; Hull et al., 2012; Finkel et al., 2018). The use of HRQoL as an end-point in clinical trials is recommended for participants of all ages (McCool & Rosen, 2006; Iannaccone, Hynan, Morton, Buchanan, Limbers & Varni, 2009; Auger et al., 2017). Although patient and caregiver perceived HRQoL might be underestimated and could differ, patient preference and perceptions are important in making clinical decisions (Varni, Seid & Kurtin 1999; Finder et al., 2004; Finkel et al., 2018; Toussaint et al., 2018). Few studies have investigated HRQoL in children in NMD, especially considering the effect of decreased physical and respiratory function (Kohler et al., 2005; McDonald, Henricson, Abresch, Florence, Eagle, Gappmaier, et al. 2013).

The impact of a chronic condition on the lives of children can be described by assessing their HRQoL (Gold, Mahrer, Yee & Palermo, 2009), but aspects such as cognitive development needs to be considered when choosing an HRQoL instrument, especially in children (Varni et al., 1999; Eiser & Morse, 2001). Measurements of HRQoL can be either generic or disease specific (Eiser & Morse, 2001; Iannaccone et al., 2009; Messina, Vita, Sframeli, Mondello, Mazzone, D'Amico, et al. 2016). Although disease/condition specific measures have been shown to be feasible, valid and reliable in children with specific NMD conditions such as DMD and SMA (Iannaccone et al., 2009; Messina et al., 2016), generic HRQoL instruments are valuable in that they can be benchmarked against normative values and compared to other studies conducted in other, heterogenous, acute and chronic paediatric conditions (Varni et al., 1999; Varni, Seid & Kurtin, 2001; Varni, Burwinkle, Katz, Meeske & Dickinson, 2002).

The generic 4.0 PedsQL child report and proxy scales have well-established validity and reliability in the paediatric population (Varni et al., 1999; Bastiaansen et al., 2004; Iannaccone et al., 2009; Hull et al., 2012; McDonald et al., 2013) and can be used in different research study designs and within a variety of settings such as schools, hospitals and community environments (Varni et al., 1999; Varni et al., 2001). Internal consistency (Cronbach alpha coefficients) for total PedsQL score as well as subdomains of physical and psychosocial health summary score for child and proxy have been shown to be acceptable for group comparisons (Core measures: alpha 0.83 and 0.86 for patient and proxy respectively) (Varni et al., 1999; Eiser & Morse, 2001; Varni et al., 2001). This instrument has also shown reliability and validity in languages other than English, including Spanish (suitable indicators of criterion and construct validity) (Amaya-Arias, Alzate & Eslava-Schmalbach, 2017); Dutch (Bastiaansen et al., 2004) and Chinese (Yang, Xiao & Yan, 2011).

Age-appropriate outcome measures for self-reported HRQoL are recommended (Varni et al., 1999) and understanding HRQoL as reported by the patient can assist in shared decision making with the healthcare professionals and caregivers (Eiser & Morse, 2001; Hull et al., 2012). Measurement of the parent's (proxy) perspective of their child's HRQoL is also important as it will influence healthcare provided for the child (Varni et al., 1999). Children and adults also might have different concerns when it comes to HRQoL and utilising proxy reports are therefore recommended (Varni et al., 2002; Messina et al., 2016). Due to variance seen between the child and parent's perspective of HRQoL (Varni et al., 1999; Varni et al., 2002; Iannaccone et al., 2009; Hull et al., 2012) both the child and proxy generic Pediatric Quality of Life InventoryTM (PedsQL), and not the NMD disease/condition-specific questionnaires, were used in this study (Varni et al., 1999; Iannaccone et al., 2009).

The PedsQL questionnaire (parallel patient self-report and parent proxy report) (Appendix Cv; Appendix Cvi) is a multi-dimensional scale that consists of 23 items (15 core items and 8 supplemental) clustered as four specific domains on physical (8 items), emotional (5 items), social (5 items) and school functioning (5 items) (Varni et al., 1999; Eiser & Morse, 2001; Varni et al., 2001; Bastiaansen et al., 2004; Iannaccone et al., 2009; McDonald et al., 2013). The age range for PedsQL is from five to 18 years for patient self-report and two to 18 years for parallel parent proxy-report and these can be compared across ages (Varni et al., 1999). The PedsQL can be self-administered by older children and parents, and children five to seven years of age can complete the questionnaire with assistance (Varni et al., 1999). For ages five to seven, a three-point Likert scale is used for each question and for eight to 18 years of age a five-point Likert scale applies (Eiser & Morse, 2001).

The total PedsQL Score is suitable as a summary score for the primary analysis of HRQoL outcome in clinical trials and other group comparisons; while the Physical and Psychosocial (emotional, social and school functioning subscales) health scores are recommended for secondary analyses and young children (5-7 years), only for descriptive and exploratory analysis, until further testing has been performed (Varni et al., 2002). In many studies on HRQoL in children, age differences are not always considered, or mostly older children are included (13-18 years) (Eiser & Morse, 2001). In this study, PedsQL was chosen as an outcome measure as it provides age-appropriate questionnaires for 5-7 years, 8-12 (Messina et al., 2016) and adolescents (13-18 years) respectively (Appendix Cv; Appendix Cvi). Additional information on the PedsQL instrument is available (Varni et al., 1999; Eiser & Morse, 2001; Bastiaansen et al., 2004).

4.3.5.1 Translation of PedsQL for South African context

MapiTrust provided permission to use the PedsQL for research purposes. The following translations for five to 18 years were available or conducted (by professional language experts) for the purposes of this study (Table 4.6). The generic PedsQL was already translated into SA English, as well as another official language (Afrikaans), which is commonly used in Western Cape and Gauteng.

Table 4.6: PedsQL™ Generic Core Scales translations for South Africa.

	Adolescent (13-18)		Child (8-12)		Young Child (5-7)	
	Child self-report	Parent proxy-report	Child self-report	Parent proxy-report	Child self-report	Parent proxy-report
Afrikaans for SA	X	X	X	X	X	X
English for SA	X	X	X	X	X	X
Setswana for SA	T	T	T	T	T	T
Xhosa for SA	X	T	X	X Local translation	X	X Local Translation

X = translation already available; T = translated for the purposes of this study

[Personal communication, MapiTrust (2016)]

4.3.5.2 Calculation of PedsQL scores

The possible answers for each question range from 0 to 4 which includes 'never a problem' (scored 0), 'almost never a problem' (scored 1), 'sometimes' (scored 2), 'often' (scored 3) and 'almost always a problem' (scored 4).

All these scores were linearly transformed to 0-100 score for standardised interpretation (e.g. 0=100; 1=75; 2=50; 3=25; 4=0). An average of the four subsections (sum of items divided by the number of items completed) provides a total PedsQL score, with higher scores indicating better HRQoL levels (Varni et al., 1999; Varni et al., 2001; Iannaccone et al., 2009).

In the case of participants who were non-ambulatory, the first two questions under the Physical domain were not applicable. For these patients, the total PedsQL score was calculated on 21 items, whereas those who were still ambulant were scored on 23 items in total. All four subsections were calculated and the total PedsQL score, as well as the subscale for Physical and Psychosocial scores, were expressed as a percentage. The Psychosocial domain consists of the combined score of emotional, social and school functioning domains (Varni et al., 2001; Bastiaansen et al., 2004). Subscale scores were calculated based on the total score divided by the number of items answered; if more than 50% of the items were not answered, then a subscale score was not calculated.

4.3.6 OMNI scale

As a precautionary measure, participants' level of perceived exertion was monitored by asking them to rate on the OMNI pictorial scale how tired they felt on a scale of one to 10 before and after each training session; where zero was not tired at all and 10 indicated being extremely tired. The OMNI scales makes use of a series of pictures (cyclist, walk/running, person using a wheelchair) that aligns with a verbal descriptor (Pfeiffer, Pivarnik, Womack, Reeves & Malina, 2002; Utter, Robertson, Nieman & Kang, 2002) (Figure 4.6).

At baseline and before each training session, if needed, the level of perceived exertion and its correlation with the OMNI pictorial scale was explained to participants, in a similar fashion as Utter et al. (2002). In addition, the researcher/research assistants asked the participants how tired they felt when performing IMT, on average over two weeks, with every follow-up visit.

In an IMT study by Gozal and Thiriet (1999), participants were asked about their respiratory load perception (RLP) during specific Pimax intensities, using a Borg scale. The Borg scale is a good indicator of the degree of physical strain experienced, but the reliability and validity in children and adolescents has not been determined (Pfeiffer et al., 2002; Wenninger et al., 2019) and it is considered unsuitable for young children (Utter et al., 2002). The OMNI visual scale was shown to be a valid and reliable indication of perceived exertion in adolescent girls while performing treadmill exercises, superior to the Borg scale, and was developed for participants from multiple ethnicities (Pfeiffer et al., 2002).

A significant correlation between the OMNI pictorial walk/running scale and physiological measurements in six to 13-year-old children has been reported, confirming that children can translate the pictures/description in the OMNI into numbers (perceived level of exertion) (Utter et al., 2002). Limited evidence is however available on the use of the OMNI pictorial scale in patients with NMD specifically.

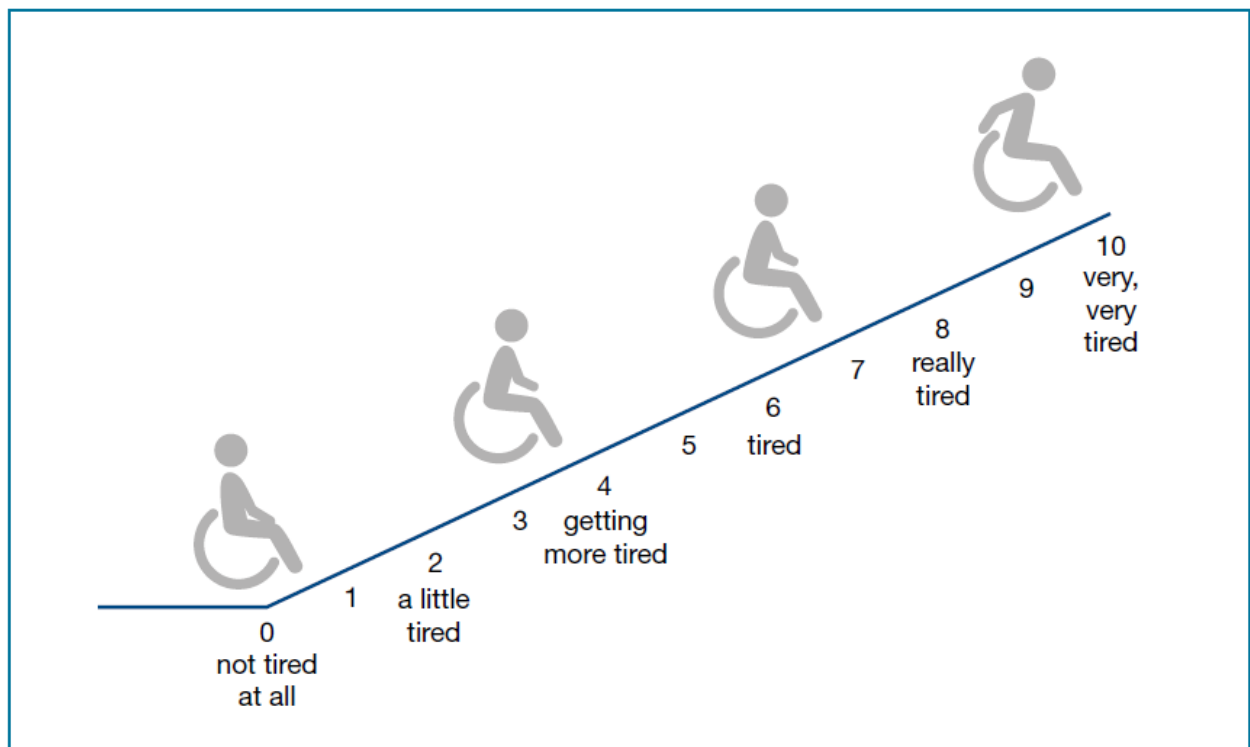


Figure 4.6: OMNI scale for perceived exertion.

(Human A, Honey E, Morrow B (2019) Inspiratory muscle training in severe spinal muscular atrophy: a case report. *Int J Ther Rehabil* [online] 26(4):1–19.<https://doi.org/10.12968/ijtr.2017.0108>)

The OMNI scale is visually represented in various ways, in order to be sensitive regarding the participants' level of ambulation. For this study images of a “man running up the hill” were used for those that were ambulant, and a “girl going up a hill with a wheelchair” (similar to Figure 4.6) was used for non-ambulant participants.

4.4 Study process and procedures

4.4.1 Randomisation for pre-experimental study

For the pre-experimental, pilot study there was no control group and randomisation was not performed.

4.4.2 Randomisation for cross-over RCT

Eligible participants (4.2.3) and their parents/caregivers were provided with information leaflets and the applicable consent and assent forms (Appendix Cvii; Appendix Cviii; Appendix Cix) and the study explained to them. If the children and their parents/caregivers agreed to participate, they were randomly allocated to groups using a sealed opaque envelope system.

Participants were allocated to either Group 1 (ce) (starting with no IMT) and crossing over to IMT after three months, or Group 2 (ec) starting with IMT. Depending on group allocation, participants were either involved in the study for nine months (Group 1) or for six months (Group 2), as depicted in Figure 4.7.

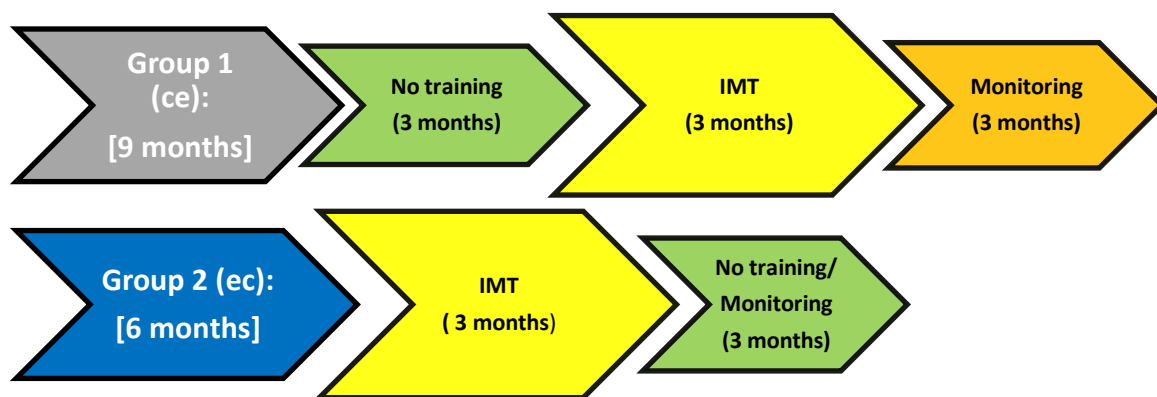


Figure 4.7: Duration of participation in cross-over randomised controlled trial based on group allocation.

4.4.3 Inspiratory muscle training protocol

4.4.3.1 Training device (Powerbreathe, K3)

When prescribing respiratory muscle training for a patient presenting with respiratory muscle weakness, the type of device (resistance, flow or threshold) should be considered (Aboussouan, 2009; Woszezenki et al., 2017; Wenninger et al., 2019). The IMT protocol for this study was developed based on the systematic literature review (Chapter 3) and clinical expertise (Tables 4.7 and 4.8). Inspiratory muscle training was performed at school or home with an electronic handheld tapered-flow threshold device (Powerbreathe K3, HaB International Ltd, Southam, UK) and monitored by clinicians or parents/caregivers (Figure 4.8).

The Powerbreathe K3[®] device was chosen because, despite the initial cost, these devices can be used for data collection in a variety of patient populations. Besides the advantages of a threshold, tapered flow training experience, additional features such as storing of training data, additional tests such as PIF, S-index and volume and being able to monitor the patient's progress in a scientific manner made it the ideal choice of research investment in SA. In addition, the Powerbreathe K3[®] device also provides a visual stimulus for training, as every breath is counted down from 30 (if breath quality is adequate), with an audible beep indicating when the patient can take another breath (pacing function), which provides motivation and improved breathing quality. Manual mode on the Powerbreathe[®] allowed for the training intensity (cmH₂O) to be adjusted in order to optimise training, based on the two-weekly Pimax assessment during the training period.

Another advantage of the electronic device is that test results (inspiratory muscle strength, PIF and volume) and up to 36 IMT sessions (Load, power and volume) can be stored on the device. In addition, the training index describes the efficacy (%) of each training session and up to 36 training sessions can be presented as graphical history from which trends of training can be observed (<https://www.powerbreathe.com/powerbreathe-k3>). The training data were recorded on the data collection sheet every two weeks at patient follow-up and could be compared to the training diary kept by participants and caregivers/clinicians. The training diary was also kept in order for parents/caregivers/clinicians and researcher/research assistants to monitor the number of training sessions, the sets of training, level of perceived exertion or any adverse events and the results/measurements for each training session.



Figure 4.8: Powerbreathe K3 ® device (<https://www.powerbreathe.com/powerbreathe-k3>).

Training load for IMT was set according to the participant's ability in order to be effective, but safe. A training load (intensity) of 50-70% of a patient's maximum Pimax value is advocated by manufacturers for effective training, however, this is not specified for patients with NMD. It has been recommended that if a patient cannot complete either 30 breaths consecutively or three sets of 10 breaths, the training intensity should be lowered to 30-40% until the patient becomes accustomed to training (Power breathe Kinetic, user manual, 2010). To minimise the risk of muscle damage and improve participant adherence, an intensity of 30% of Pimax was implemented in this study (Topin et al., 2002; Cup et al., 2007; Woszezenki et al., 2017; Hariza et al., 2018). The hypothesis was that this training intensity would provide an effective training stimulus, while not overexerting the patient. The intensity level was based on literature and manufacturer guidelines (Powerbreathe ®) suggesting that this is the minimum intensity required for improved inspiratory muscle strength (Löftters et al., 2002; Hill et al., 2010; Woszezenki et al., 2017). The two pooled studies in the systematic review (Chapter 3: 3.6.7) used similar IMT protocols for their participants.

The training was performed in sitting, without a nose clip, as all participants could maintain a good mouth seal and the majority did not tolerate the nose clip well when attempting to use it during pulmonary function testing. Correct breathing technique is essential to ensure effective training and therefore the physiotherapists and researchers assisted participants and their parents in explaining how the device should be used and correcting their technique if needed.

Performance and motivation were improved through visual feedback (counting down the breaths) provided on the screen of the Powerbreathe K3[®] as well as an audible beep after each breath, with a double beep at the end of 30 breaths. To improve adherence to the training programme and ensure safety by monitoring levels of perceived exertion and reporting of any adverse events, participants and their parents/caregivers were asked to keep a training diary. The diaries were also monitored by the physiotherapists at the school or researcher/research assistants (DiMarco et al., 1985; Topin et al., 2002).

4.4.3.2 Training intensity, sets, duration and frequency

When allocated to Group 1 (ce), participants received standard medical and physiotherapy management during their first three months of no IMT (inactive control period) whereafter they crossed over to three months of IMT in addition to standard care (intervention period). Once training ceased their pulmonary function was monitored for three months post-intervention (Figure 4.7). Participants in Group 2 (ec) started with IMT for the first three months, as an adjunct treatment to their standard care (intervention period) and once IMT was completed after three months, they were monitored for another three months (control period). It has been suggested that improved functional outcomes and the benefits of IMT might only last for a short period once training ceases (Eagle, 2002), therefore both groups were monitored for three months post-IMT intervention to determine how long the effect of IMT would last (Aslan, Gurses et al., 2013). The suggested training protocol for the pre-experimental and cross-over studies are depicted in Tables 4.7 and 4.8.

The six-week threshold IMT programme for the pre-experimental, pilot study was based on the results from the systematic review (Chapter 3) and literature on children and adolescents with DMD and SMA (Wanke et al., 1994; Gozal & Thiriet, 1999; Topin et al., 2002; Zupan, 2004; Takaso et al., 2010) (Table 4.7).

Table 4.7: Inspiratory muscle training protocol for the pre-experimental, pilot study.

Device	Intensity	Repetitions	Rest period (between sets)	Frequency	Duration
Threshold, Powerbreathe K3 [®]	30% of Pimax	10 breaths (3 sets); 30 breaths (1 set)	20-60s (if needed)	Twice a day	6 weeks

Participants started their training with 10 breaths, three sets twice a day until they could perform 30 breaths consecutively. Depending on the number of rest periods needed between sets, if any, training (30 breaths) took less than five minutes in the morning and in the afternoon. The level of perceived exertion was determined by the OMNI scale, recorded before and after every training session, as well as on average over every two weeks during the intervention. In order to monitor IMT performance (quality of breaths performed, safety) and note any adverse events, training was performed at the school from Mondays to Fridays, twice a day, under the supervision of one of the physiotherapists. Training five days per week was a pragmatic arrangement in order to ensure the safety and correct performance of the training technique.

Since no adverse events related to IMT³³ were observed or reported after the pre-experimental, pilot study, the cross-over study followed a similar training programme. During the cross-over study, IMT was performed twice daily, at school (five days a week) or at home (five to seven days a week) for a duration of three months. (Table 4.8).

Table 4.8: Inspiratory muscle training protocol for the cross-over randomised controlled trial.

Device	Intensity	Repetitions	Rest period (between sets)	Frequency	Duration
Threshold, Powerbreathe K3 ®	30% of Pimax	10 breaths (3 sets); 30 breaths (1 set)	20-60s (if needed)	Twice a day	12 weeks (3 months)

Training intensity (cmH₂O) for both the pre-experimental and cross-over RCT was adjusted based on the patients' Pimax values, measured every two weeks, during the intervention period.

³³ Including, but not limited to, mild to moderate adverse events such as chest pain/discomfort (hyperinflation/barotrauma), nausea/vomiting, fatigue and gastric distension; severe adverse events such as pneumothorax, desaturation, bradycardia, muscle damage, disease progression/muscle deterioration, cardiac arrest, respiratory failure, bleeding and death.

4.4.3.3 Safety and precautionary measures

The following precautionary measures were considered while using the Powerbreathe K3[®] handheld IMT device³⁴:

- Breathing out slowly to prevent dizziness due to hyperventilation. If the patient felt lightheaded or dizzy whilst training, they were asked to slow down their breathing rate or pause until they had fully recovered.
- The IMT training device was not used whilst the patient suffered from a cold, sinusitis or respiratory tract infection until the symptoms had disappeared. Patients that did develop a cold either stopped or decreased their training for a few days until they were no longer symptomatic.
- Participants could experience slight ear discomfort when training with the IMT device, especially after recovering from a cold (equalisation of pressure). However, in this study, none of the participants presented with these symptoms.
- Participants were reminded that training with the device should feel a bit difficult, but not painful.

The following infection control measures were implemented:

To prevent transmission of infections, participants were instructed not to share their Powerbreathe[®] kinetic mouthpiece(s) or valve head(s) with other users, including family members. After every training session, the mouthpiece of the filter was wiped with an alcohol swab or similar. The filter was replaced every two weeks during the intervention and the valve head was soaked in warm soapy water for at least 10 minutes, rinsed with warm water, whilst opening and closing the valve to clean the valve surfaces, after every three-month training.

4.4.4 Data collection procedure for pre-experimental and cross-over randomised controlled trial

The pre-experimental, pilot study and cross-over RCT data were collected by the primary researcher (AH), physiotherapists (schools and hospitals) and research assistants (LC, EL) in the various research settings (4.2.1).

³⁴ Powerbreathe Kinetic[®] user manual (KH1): pp 1-37.

Demographic data, medical history and background information were extracted from the medical and physiotherapy files of participants and a paediatrician (EH³⁵) was consulted if anything regarding the diagnosis was unclear. Information was captured on hard copies of the relevant data collection forms at recruitment and follow-up assessment (Appendix C iv). The patient/proxy HRQoL was completed at baseline, pre-and post-intervention (Appendix C v; Appendix C vi). Clinicians, participants and caregivers recorded daily outcome measures such as repetitions, sets and level of perceived exertion (OMNI scale) in provided training diaries. The researcher and research assistants recorded baseline, pre and post-intervention assessment values as well as the data stored on the Powerbreathe K3[®] (Load, power, volume and training index). All training diaries and data collection sheets were coded and stored securely in the researcher's office. All electronic data were stored on password protected computers, with external hard drive back-up, by the researcher and supervisor. All the information from the data collection sheets and questionnaires were confirmed and thereafter collated by the primary researcher (AH). The researcher entered the data into an Excel spreadsheet for analysis and data were checked for completeness and correctness by a colleague (HH).

Similar measurements were taken in both the pre-experimental and cross-over studies, but randomisation was only performed for the cross-over study. The data collection procedure and measurement points for the pre-experimental and RCT cross-over study are depicted in Figures 4.1 and 4.2.

4.4.5 Data analysis

STATISTICA (Data Analysis Software System, Version 13, www.statsoft.com), STATA (StataCorp, www.stata.com) and Statistical Package for the Social Sciences (SPSS v24 & 25) were used for data analyses. Depending on the normality of data (tested using the Shapiro Wilks W and Kolmogorov-Smirnov tests), the relevant parametric or non-parametric statistical tests were applied.

Descriptive statistics were expressed, for continuous variables, as mean $\pm$ standard deviation (SD) or median, interquartile ranges (IQR), depending on the distribution of data; and frequency distributions where appropriate. Depending on the normality of data, associations between variables were calculated using either Chi-square (categorical variables), Pearson's correlation or Spearman's rank tests (continuous variables). Depending on the distribution of the outcome measure, significant differences in continuous variables between IMT (experimental) and no IMT (control) periods were tested using the student t-test for independent variables or Mann-Whitney U tests.

³⁵ Engela Honey

The dependent student t-test and Wilcoxon matched pairs tests were used to test within group changes (compare pre-and post IMT variables). Change over time (during the IMT period) was analysed using repeated measures ANOVA (multiple points). Between and within group analyses (IMT vs no IMT) were performed using two-way ANOVA tests. Statistical significance was accepted as $p < 0.05$.

4.5 Ethical considerations

Respect, scientific merit and integrity, distributive justice and beneficence are core ethical principles that apply to research with human subjects (Department of Health, 2015), and were adhered to in this study.

Ethical considerations were based on the Belmont Report for Ethical Principles and Guidelines for the Protection of Human subjects of Research as well as the Declaration of Helsinki (World Medical Association: Declaration of Helsinki, Fortaleza, Brazil, 2013). In clinical trials of airway clearance techniques (ACT) in children, control groups are often difficult to define and sham treatments are either inappropriate, unethical or impossible to perform (Auger et al., 2017). For these reasons and sample size considerations, a cross-over study design was implemented.

Inspiratory muscle training was provided as an adjunct to the participants' home programmes. There were therefore no additional costs to the hospitals, as the research-related expenses were covered by the research grants and sponsors.

The three basic ethical principles of autonomy (respect for persons), beneficence (non-maleficence) and justice were applied.

4.5.1 Autonomy

Parents/caregivers/clinicians and patients received an information leaflet that was available in Afrikaans, English, Xhosa or Setswana, explaining the aim of the study and requesting the child's participation (Appendix Cvii). A verbal explanation was provided and where needed an interpreter was arranged. Parents/caregivers and patients were provided with the opportunity to ask questions and raise any concerns they might have. Parents/caregivers and physiotherapists were not blinded to group allocation, as they attended the assessment and treatment sessions.

On completion of the study, a post-intervention information form will be distributed to parents/caregivers, physiotherapists (healthcare NMD teams at both hospitals) and participants.

Informed consent (Appendix Cvii) was sought from parents/caregivers and assent (affirmative agreement to participate in the study) from children five to 17 years (<18 years) (Appendix Cviii; Appendix Cix) before enrolment. Simplified versions of the assent form and information leaflet were provided to children five to seven years and seven to twelve years of age. In addition, a verbal explanation was given in an age-appropriate manner and the parents/caregivers were encouraged to be present during assessment and treatment. Adolescents (13 years and older) were able to read and understand the documentation provided, however, they were assisted by their parents/caregivers or the researcher/research assistant if needed.

Parents/caregivers attending the RCWMCH NMD clinic received information leaflets on their clinic attendance day, which contained the contact details of the researchers, safety and institutional ethics committee. They could read these leaflets and ask questions while waiting to see the neurologist. This measure was taken to decrease the burden on patients as they usually have numerous consultations and appointments during a single hospital visit. Parents/caregivers and children were asked questions to ascertain their understanding before signing consent/assent.

Once parents/caregivers and patients agreed to participate they were reminded that their participation was entirely voluntary and they could withdraw from the study at any time without providing reasons and without affecting further therapy or medical treatment. Contact details of the researcher/research assistant/supervisor were provided if they had any questions or concerns. All participants and their parents/caregivers were assured that all information collected would be treated as confidential, but the results may be published without disclosure of the participant's identity.

4.5.2 Beneficence

Equipoise was relevant in this study as researchers did not know for certain whether IMT as an adjunct would be superior to standard care in children with NMD (Chapter 3).

Therapeutic research was performed in this study, as there was the prospect of direct health-related benefit for the participant (Regulation 135) (Department of Health, 2015) by using IMT as an adjunct treatment.

Children and adolescents in SA are entitled to improved healthcare services based on rigorous research conducted in this population, but should not unnecessarily bear the burden of research, therefore minors should only participate in research where their participation is indispensable (Department of Health, 2015). This was the case in this study, as results of IMT in adult patients cannot be extrapolated to children and the safety, practicality, acceptability and efficacy of IMT for children with NMD need to be determined to guide clinical practice.

4.5.2.1 Risks and benefits

It is hoped that the results from this study will improve physiotherapy services delivered to paediatric and adolescent patients at hospitals and clinics throughout SA.

The researchers hypothesised that IMT may improve pulmonary function and cough ability, decrease dyspnoea, slow down the weakening of inspiratory muscles and improve overall HRQoL among participants, however, there may also be no individual benefit. Although some studies have found IMT successful, others found the opposite. A possible reason for this contradiction may be due to the lack of (or minimal amount) of dystrophin and in addition the defective nitric oxide release mechanism in dystrophinopathies that is responsible for the protection of an exercising muscle (Chapter 1). Therefore, the main risk during IMT was likely to be overexertion, and in order to prevent this, the perceived level of exertion of the patient was monitored using the OMNI (modified Borg) scale and participants were provided with rest periods when needed. The level of perceived exertion was monitored daily as well as on average over two weeks during the six week or three-month period. In addition, to ensure the safety of participants when performing IMT and prevent overexertion during IMT, certain exclusion criteria were applied (e.g. patients with the severely progressed disease were excluded). Any other adverse events, potentially related to IMT, were documented in either the training diaries (daily) or on the data collection sheets (every two weeks), for example, chest pain or abdominal discomfort. Pulmonary function tests (such as lung volumes, flows and Pimax) could cause fatigue, dizziness and shortness of breath, but these are not usually harmful.

There was no direct financial benefit for participants and their parents/caregivers, however for monitoring and assessment parents/caregivers were reimbursed for their travelling expenses to bring their child to the hospital for follow-up assessment.

Following this research, participants and other children with NMD may benefit from improved physiotherapy management at the hospitals that they attend, guided by evidence-based practice based on the results of this research. If participants opted to continue with IMT after the study has ceased, they were provided with a Powerbreathe Classic ® training device.

4.5.2.2 Safety monitoring committee

A safety monitoring committee was appointed to oversee the research in the two provinces, monitor the patient's progress and ensure their safety by identifying adverse events that might be related to IMT. Parents/caregivers were asked to make the clinicians and/or researcher/research assistants aware if any adverse events occurred during the intervention or related to IMT. Adverse events were monitored on a daily basis by clinicians or parents/caregivers and noted in the training diaries. The researcher/research assistants also enquired regarding adverse events from participants, clinicians or parents/caregivers every two weeks when the follow-up assessments were performed, during the three-month intervention period.

Every hospital (RCWMCH; DGMAH) had two appointed safety committee members, one physiotherapist and one medical doctor/specialist (Appendix Cii). Clinicians at RCWMCH and DGMAH were aware of the safety protocol to be followed. If any adverse event was reported or noted during the research period, the respective safety committee members at the institutions as well as the research supervisor (BM) and researcher (AH) had to be informed. As a safety measure, an interim analysis was conducted by the researcher and supervisor after ten participants (Group 1 and 2) completed the cross-over trial. This analysis showed a statistically significant improvement in the participants' inspiratory muscle strength (Pimax), as well as cough ability (PECF), irrespective of group allocation, and no adverse events related to IMT, were reported. Hence the study was permitted to continue.

Overexertion was prevented by monitoring levels of perceived exertion using the OMNI scale, providing a rest period in-between sets if needed and adjusting training intensity accordingly (4.3.6). Precautionary measures for IMT were considered throughout the intervention period (4.4.3.3).

In cases where multi-disciplinary support services or counselling were needed, patients and parents/caregivers were referred to the relevant departments.

4.5.2.3 Post-trial care

Most participants and their parents/caregivers included in the pre-experimental and cross-over studies reported the perceived value of IMT as an adjunct to standard management. Participants and their parents/caregivers were therefore offered the option to continue with IMT at the end of the study period. The Powerbreathe K3 ® devices used for training and data collection was funded by a PhD development grant and will be used for other studies in near future. In order to provide continuity of care among research participants, a few factors had to be considered: The high cost of the K3 and other electronic devices which have to be imported to SA; the socio-economic context of many of the participants where electricity might not always be readily available; illiteracy and an inability to work with electronic devices, high maintenance and the durability of an electronic device vs a manual IMT device. For these pragmatic reasons participants were provided with an alternative, easy to use, durable, non-electricity dependent and more cost-effective, manual constant load IMT device (Powerbreathe Classic ®). If the different types of devices (threshold, tapered flow vs constant load) will provide a similar training stimulus and outcome is currently unknown and should be considered in future trials. All participants indicated that they would like to continue with IMT as part of their home programme for long-term use. The devices were provided to the participants at no cost as they were sponsored.

4.5.2.4 Privacy, confidentiality and anonymity

To ensure confidentiality and privacy of the participants' data, all documents, data sheets and questionnaires were coded and de-identified. Data were safely stored in a locked cabinet in the researcher's office and electronic information was safe-guarded on a password protected computer and external hard drive. The key to the data code is kept in a separate location than the coded data collection sheets/questionnaires and access to these records are limited to researchers involved in the study. No identifiers will appear in any outputs or communications arising from this research.

4.5.3 Justice

To obtain an adequate sample size as well as make results more generalisable to the paediatric and adolescent population of SA, a multi-centre trial was conducted and all eligible patients were invited to participate. Patients participating in any other trials were excluded in order to minimise the research burden and eliminate cross-over effects. Both primary sites (RCWMCH & DGMAH) are public hospitals which could suggest that the burden of research in this study was carried by the low socio-economic groups.

However, it is noted that patients in private care also attend clinics at the primary study site (RCWMCH) and through referral processes, patients from schools for children with special needs (private and public funded), private healthcare and members of MDF were also included in the study.

Evidence-based practice based on research in the adult population cannot be extrapolated and used in children due to significant anatomical and physiological differences (Schechter, 2007). Allowing children to participate in clinical trials provides them with the opportunity to be part of research and reap the benefits of the outcomes. Furthermore, researchers need to obtain data on the effects of interventions on children to determine safe and effective practices for this vulnerable population. Several NMD present substantially differently in children, owing to the natural progression of the disease, along with anatomical changes occurring with growth and maturation. To assess beneficial interventions for children with NMD, research should be conducted in the population of interest (Toussaint et al., 2018).

4.5.4 Ethical clearance and permissions obtained for data collection

The following permissions were obtained to conduct this study:

- Ethical approval from the Human Research Ethics Committee, University of Cape Town was obtained (513/2015) (Appendix Di).
- Participants signed an assent form, based on age, and their parents/caregivers signed a consent form (Appendix Cvii; Appendix Cviii ; Appendix Cix).
- Permission from MapiTrust (developers) was obtained to use the generic PedsQL questionnaires and the user agreement was signed (Appendix Dii). Permission to translate the proxy version (13-18 years) into isiXhosa, as well as all year groups (5-18 years) and their proxies into Setswana, was also provided (Translation agreement).
- Permission to conduct the pre-experimental 6-week IMT study was obtained from: Heads of physiotherapy departments, school boards as well as Gauteng Department of Education (DoE) (Appendix Diii).
- Permission to conduct the cross-over 3-month IMT study was obtained from:
Western Cape: Head of physiotherapy department (RCWMCH), CEO, medico-legal advisor and research committee of RCWMCH, Western Cape Department of Education (WCED) (Appendix Div).
Gauteng: CEO of DGMAH, Gauteng Department of Education (DoE) (Appendix Dv).

4.6 Funding

Funding for this research was provided by the URC Equipment Grant (Western Cape); Sefako Makgatho Health Sciences University Research Development Grant; and the SA Society of Physiotherapy (SASP) (PhD grant).

The inspiratory muscle training electronic devices (Powerbreathe K3[®]), which are capable of storing training data, were purchased by Sefako Makgatho Health Sciences University (SMU) PhD research development grant and were loaned to participants for the duration of the study. The assessment devices, Powerbreathe[®] consumables, travelling costs for parents and researchers, refreshments and researcher fees were covered by the URC WC equipment grant and SMU PhD research development grant. The SASP funding was utilised for consumables and translation of the PedsQL questionnaires.

4.7 Conclusion

The methods and outcome measures used to answer the research objectives were provided in this chapter and the ethical principles underpinning this clinical research were described. The main components of pulmonary rehabilitation include muscle training (including respiratory muscle training), education and ACT, adapted according to individual patient presentation and preference (Aboussouan, 2009; Rous et al., 2014; Birnkrant et al., 2018; Finkel et al., 2018; Toussaint et al., 2018; Castrillo et al., 2019).

The focus of this thesis is therefore to assess the effect of IMT on clinical outcomes and HRQoL in NMD, whilst implementing precautionary measures to ensure that participants do not overexert themselves.

In Chapter 5 the results of the pre-experimental, pilot IMT study will be presented.

Chapter 5: TESTING, TESTING 1,2,3...

Pre-test post-test IMT pre-experimental, pilot study

5.1 Introduction

Inspiratory muscle training, as an adjunct treatment in the management of patients with neuromuscular disease (NMD), could ameliorate the decline of inspiratory muscle strength, thereby preserving pulmonary function for longer and delaying the onset of respiratory muscle failure, however supporting evidence in children is limited and inspiratory muscle training (IMT) remains controversial (McCool & Tzelepis, 1995; Servera et al., 2003; HO, 2005; Wang et al., 2007; Finder, 2010; Hull et al., 2012; Aslan et al., 2013) (Chapter 1: 1.1.4.2). The effect of IMT is variable and likely to be influenced by the type; nature and severity of NMD; disease stage; associated pathophysiology; degree of respiratory involvement and the specificity and intensity of the training regime (Gozal, 2000; Eagle, 2002; Aboussouan, 2009; Woszezenki et al., 2017) (Chapters 1 and 3).

The systematic review (Chapter 3) demonstrated that IMT might be beneficial for improving inspiratory muscle strength in patients with NMD, however, no literature related to the effect on respiratory morbidity, adverse events and/or health-related quality of life (HRQoL), could be found. Inspiratory muscle training devices are relatively inexpensive and readily available in South Africa (SA), and the survey study (Chapter 2) suggested that SA physiotherapists favour using IMT in clinical practice for patients with NMD. There is, however, currently insufficient evidence to guide clinical practice on IMT in children with NMD. The paucity of evidence is mainly due to the limited number, small sample sizes, data heterogeneity and high risk of bias of existing studies as well as the potential safety concerns of IMT, particularly in patients with dystrophinopathies (Eagle, 2002; Woszezenki et al., 2017; Chapters 1 and 3).

5.2 Study design

A pre-experimental, observational pre-test post-test study design was implemented to determine the practicality of performing IMT in children with NMD; the acceptability of the intervention, to inform any adaptations needed to the IMT protocol; and to provide preliminary safety data for IMT, before implementing a randomised controlled trial (RCT) (Chapter 6). The pre-experimental, pilot study aimed to recruit five to ten participants.

The STROBE guidelines for observational studies (STROBE statement/checklist: <https://www.strobe-statement.org>) were used as a reference for reporting the results of this pilot study.

5.3 Methods

Eight participants from two different schools for children with special needs in Pretoria (Gauteng, SA) participated. To describe holistic and inclusive effects of IMT, participants were assessed in four main areas: adverse events (including hospitalisation and/or respiratory tract infections), pulmonary function, functional ability, and health related quality of life, as described in Chapter 4 (4.3). The subsections of assessment/measurements are outlined:

- a) Bio-demographic data including height, weight and body mass index (BMI),
- b) Adverse events related to IMT, hospitalisation and/or respiratory tract infections,
- c) Pulmonary function including lung volumes flow, inspiratory muscle strength and cough efficacy,
- d) Functional ability including the level of ambulation and upper limb function,
- e) Health related quality of life,
- f) Participant and physiotherapist subjective feedback on their IMT experience.

5.4 Adverse events related to inspiratory muscle training

At baseline and every two weeks, participants and clinicians were asked if they had experienced any adverse events related to IMT³⁶. Adverse events were classified as mild or moderate which could include nausea/vomiting; pain/discomfort and gastric distension/aerophagia while severe adverse events included bradycardia; desaturation or barotrauma such as pneumothorax.

5.5 Pulmonary function

As described in Chapter 4 (4.3.3) pulmonary function testing in the pre-experimental study consisted of spirometry (relaxed and forced), peak inspiratory flow (PIF), peak expiratory cough flow (PECF), and inspiratory muscle strength (maximum inspiratory mouth pressure (Pimax); sniff nasal inspiratory pressure (SNIP) and strength-index (S-index). The Z-scores for forced vital capacity (FVC) and forced expiratory volume in one second (FEV₁) were calculated using an electronic calculator (GLI: <http://gligasttransfer.org.au/calcs/spiro.html>). The predicted Pimax values were calculated based on the weight-related formulae for boys and girls (7-17 years) outlined by Wilson et al. (1984).

³⁶ Including, but not limited to, mild to moderate adverse events such as chest pain/discomfort (hyperinflation/barotrauma), nausea/vomiting, fatigue and gastric distension; severe adverse events such as pneumothorax, desaturation, bradycardia, muscle damage, disease progression/muscle deterioration, cardiac arrest, respiratory failure, bleeding and death.

Researchers minimised the number of repetitions during the assessment to reduce the risk of fatigue and muscle damage (Chapter 1: 1.1.2; 1.1.4.2). As a precautionary measure, every participant was asked, after each pulmonary function test, if they were tired and/or, could continue and was provided with the opportunity to rest in-between tests if needed. Wherever possible, three repeatable measurements for spirometry, Pimax and SNIP were performed and the best value was used for analysis.

5.6 Functional ability (level of ambulation and upper limb function)

The objective outcome measures used to assess functional ability were level of ambulation, Vignos and Brooke scales as well as ten items of the Motor Function Measure (MFM) (Chapter 4: 4.3.4).

5.7 Health-related quality of life

Health-related quality of life was measured using the generic Pediatric Quality of Life Inventory (PedsQL)TM (Chapter 4). The patients and their primary caregivers were asked to complete the PedsQL prior to the intervention (baseline) and after six weeks (post-intervention). The total PedsQL score was used for primary analysis and the subscales (Physical, Psychosocial) for secondary analysis. The higher the score, the higher the perceived HRQoL (Varni et al., 2002; Bastiaansen et al., 2004; Iannaccone et al., 2009) (Chapter 4).

5.8 Inspiratory muscle training programme and participant adherence

Inspiratory muscle training was performed with the Powerbreathe K3[®], twice a day, five days a week, for six weeks, unless the child was absent from school or could not train due to sports events or other school-related activities. The training was performed at school under the supervision of the physiotherapists and the intensity for training was set at 30% of the patient's best Pimax value; measured at baseline and every two weeks (4.4.3). The participants' perceived exertion due to IMT was also determined by making use of the OMNI scale before and after training. The data collection procedure and measurement points for this pre-experimental study was outlined in Chapter 4 (4.3.1.1).

5.9 Analysis

The analysis was performed as outlined in Chapter 4. For the majority of spirometric measures, PEF, PIF, inspiratory muscle strength (Pimax, SNIP & S-index) and HRQoL, the student t-test for dependent samples was performed as appropriate to normally distributed data.

Peak expiratory flow was, however, not normally distributed, therefore the Wilcoxon matched pair test was used to compare values before and after IMT. To express change over time, analysis of variance (ANOVA repeated measures) was performed for Pimax, SNIP, intensity (load) of IMT (cmH₂O), S-index and PIF. Weight for age and BMI Z-scores for bio-demographic data were calculated using an electronic calculator (QuesGen: <http://www.quesgen.com/BMIPedsCalc.php>).

5.10 Results

5.10.1 Bio-demographic description of participants

Eight children (4 boys and 4 girls; median age (IQR) 12.21 (9.63-16.05)) with a variety of NMD (mostly Duchenne muscular dystrophy (DMD) and spinal muscular atrophy (SMA)) from two schools for children with special needs (Gauteng, SA) participated from February to June 2017. Baseline bio-demographic data including age in years, weight for age (WFA) and BMI Z-scores were normally distributed, but due to the small sample size, are presented as median (IQR) values (Table 5.1).

Diagnosis of NMD was based on clinical presentation, assessment by a geneticist, muscle biopsy and genetic testing. Two patients presented with cardiopulmonary co-morbidity, including right ventricular hypertrophy and pulmonary hypertension; while one patient had a confirmed diagnosis of attention deficit hyperactivity disorder (ADHD) and mild cognitive impairment, but was still able to follow instructions. Four presented with spinal deformities, of which three had a thoracic scoliosis and one a thoracic kyphosis. Three participants had undergone previous surgical procedures including scoliosis repair, bilateral hip surgery for correction of dislocation and muscle lengthening/tendon release procedures.

The weight of participants varied greatly with a median (IQR) WFA Z-score of -3.40 (-4.63 to -0.08). Participants were either within the normal range or severely underweight (lower than three standard deviations). Median (IQR) was -6.86 (-10.90 to -2.52), with most participants (n=6) classified as being severely wasted and only two were within the normal range (Table 5.1).

Table 5.1: Baseline bio-demographic data, mobility levels and pulmonary function (n=8).

<i>Participant</i>	<i>Sex (M/F)</i>	<i>Age (years)</i>	<i>NMD type</i>	<i>Weight for age (Z-scores)</i>	<i>BMI (Z-scores)</i>	<i>Mobility</i>	<i>VC (L)</i>	<i>FVC (Z-scores)</i>	<i>FEV₁ (Z-scores)</i>	<i>Pimax (cmH₂O)</i>	<i>Pimax (% pred.)</i>
1	f	17.58	Myopathy	-3.31	-4.61	PA	1.85	-3.07	-3.03	33	53.22
2	m	11.25	DMD	0.51	-0.42	A	2.56	-2.71	-2.63	37	49.07
3	f	9.83	SMA	-5.62	-22.86	NA	0.94	-5.69	-4.73	23	47.37
4	f	9.42	Mild degen. neuropathy	1.06	0.04	NA	0.73	-5.45	-4.62	40	64.63
5	m	15.42	DMD	-5.95	-14.28	NA	1.62	-4.45	-3.49	51	79.13
6	m	16.67	DMD	-3.64	-7.51	NA	1.95	-4.50	-3.72	20	27.06
7	f	13.17	SMA	-3.49	-7.29	NA	0.92	-5.67	-5.07	34	61.07
8	m	8.33	SMA	-0.66	-6.42	NA	0.91	-2.92	-3.41	65	103.75

A=Ambulant; DMD=Duchenne muscular dystrophy; FVC=Forced Vital Capacity; NMD=neuromuscular disease; PA=partially ambulant; Pimax=maximum inspiratory mouth pressure; NA=Non-ambulant; SMA=Spinal muscular atrophy

5.10.2 Home programme of participants

Participants were asked if they followed any specific home programme. Two indicated that they were performing range of motion (ROM) exercises, which included passive movements and stretches daily or at least twice a week.

For respiratory therapy, one participant was performing thoracic expansion exercises with the use of a green theraband for resistance; she ceased with these exercises once IMT started. Half of the participants performed some form of breathing exercise at least once a day. Most used manually assisted cough (MAC) techniques during acute infections. None of the participants used mechanical insufflation-exsufflation (MI-E), lung volume recruitment (LVR) techniques, or other cough augmentation techniques such as glossopharyngeal breathing (GPB) or breath-stacking with a resuscitation bag/ventilator; which correlates with survey study findings (Chapter 2).

5.10.3 Adverse events, hospitalisations, respiratory tract infections and precautionary measures

No adverse events related to IMT during the six week intervention period were reported. One participant was hospitalised for three days, during week two and four of intervention, due to an acute respiratory tract infection and the same participant used antibiotics twice over the first four weeks. One more participant used antibiotics for an upper respiratory tract infection during the first two weeks of IMT. These events were not considered by independent clinicians to be related to the use of IMT.

The median (IQR) OMNI values are presented in Table 5.2. The OMNI scores were not recorded at baseline, as participants had not trained as yet, and the first measurement was therefore only recorded after two weeks of IMT (average score over the preceding first two weeks). On average, over the first two weeks of IMT, the majority of participants reported a low OMNI score out of 10, indicating a low level of perceived exertion. Only one child, which presented with an upper respiratory tract infection during the intervention period, reported high values of eight (really tired) and 10/10 (very, very tired). The OMNI scores increased significantly between week two and six ($p=0.04$), with increasing levels of perceived fatigue (getting more tired).

Table 5.2: OMNI scale averages during two-week intervals of inspiratory muscle training (n=8).

Timepoint	After two weeks of IMT	After four weeks of IMT	After six weeks of IMT
OMNI score	1 (0-4)*	4.5 (2.5 – 6.5) [#]	3.5 (1.5 – 6) ^{\$*}

Values are expressed as median (IQR); p-values Wilcoxon matched pairs test. # comparing 2 and 4 weeks ($p=0.05$); \$ comparing 4 and 6 weeks ($p=0.20$); * comparing 2 and 6 weeks ($p=0.04$).

5.10.4 Pulmonary function

At the time of intervention, none of the participants was using either nocturnal or daytime ventilation. One patient with asthma mentioned that she used nebulised bronchodilators, if and when needed. Although baseline X-rays are indicated to provide a reference point for patients (Wang et al., 2007; Goemans & Buyse, 2014), no chest X-rays were available for assessment for any of the participants. With relaxed spirometry (slow vital capacity (VC)), all participants performed good blows, with five meeting the British Thoracic Society (BTS) quality criteria pre-intervention and seven meeting the criteria post-intervention. With forced spirometry measurements at baseline, four performed good blows and one met the BTS quality criteria, whereas post-intervention five performed good blows and three met the criteria. Based on the American Thoracic Society (ATS) interpretation, all participants presented with a restrictive pulmonary pattern of varying degrees (evident from the FEV₁/FVC ratio (Tiffeneau index); between 80-100% (Meier et al., 2017; Chiang et al., 2018), which remained unchanged pre and post-intervention (Table 5.3).

Table 5.3: Pre-post variables for pulmonary function and inspiratory muscle training load (n=8).

<i>Variable</i>	<i>Baseline</i>	<i>Post-intervention</i>	<i>p-value</i>
VC (L)	1.44 (±0.66)	1.56 (±0.83)	0.18
FEV₁ (L)	1.37 (±0.56)	1.37 (±0.65)	0.99
FEV₁ Z-scores	-3.84 (±0.87)	-3.94 (±0.96)	0.62
FVC (L)	1.54 (±0.62)	1.55 (±0.62)	0.98
FVC Z-scores	-4.31 (±1.26)	-4.33 (±1.07)	0.94
FEV₁/FVC (%)³⁷	93.38 (±5.50)	92.00 (±5.55)	0.65
PEF (L/min)*	150.5 (98.5-168)	161 (121-196)	0.05 [#]
Pimax (cmH₂O)	37.88 (±14.60)	48.13 (±16.45)	0.01*
Pimax % predicted	60.66 (±23.02)	76.38 (±24.70)	0.01*
SNIP (cmH₂O)	37.13 (±20.68)	40.38 (±20.07)	0.60
PIF (L/s)	1.20 (±0.60)	2.24 (±0.98)	0.02*
S-index (cmH₂O)	23.88 (±9.88)	41.88 (±16.15)	0.02*
PECF (L/min)³⁸	198.13 (±100.43)	214.38 (±102.42)	0.63
Training load (cmH₂O)	11.38 (±4.47)	13.38 (±4.37) (at 4 weeks)	0.12

*All continuous variables are mean (±SD) unless otherwise stated; *Median (IQR); # Wilcoxon*

FEV₁=forced expiratory volume in one second; FVC=forced vital capacity; PECF=peak expiratory cough flow; PEF=peak expiratory flow; PIF=peak inspiratory flow; Pimax= maximum inspiratory mouth pressure; S-index=strength index; SNIP=sniff nasal inspiratory pressure; VC=vital capacity

³⁷ When FVC and FEV₁ are decreased, the distinction between an obstructive and restrictive ventilatory pattern depends on the absolute FEV₁/FVC ratio (Tiffeneau index)

³⁸ It has to be noted that some participants had more difficulty in performing cough flow (PECF) manoeuvres than spirometry.

There was no significant change in relaxed or forced spirometric measurements of VC, FVC or FEV₁ post-intervention. The change in peak expiratory flow (PEF) tended towards significance ($p=0.05$), while the unassisted cough ability (PECF) did not show a statistically significant change after the intervention ($p=0.63$) (Table 5.3). As can be seen from Table 5.3, global inspiratory muscle strength measures (Pimax) ($p=0.01$), S-index ($p=0.02$) and PIF ($p=0.02$) showed a statistically significant improvement from baseline. The mean ($\pm$ SD) change in absolute Pimax (Δ Pimax) post-IMT was $10.3 (\pm 8.63)$ cmH₂O.

Based on repeated measures ANOVA (Figures 5.1 to 5.4), Pimax, PIF and S-index changed significantly over the intervention period, whilst there was no significant change in SNIP ($p=0.39$). *Post hoc* t-tests were performed to indicate where significant changes occurred over the six weeks' intervention for Pimax, PIF and S-index respectively. Individual patient data are provided in Appendix Ei.

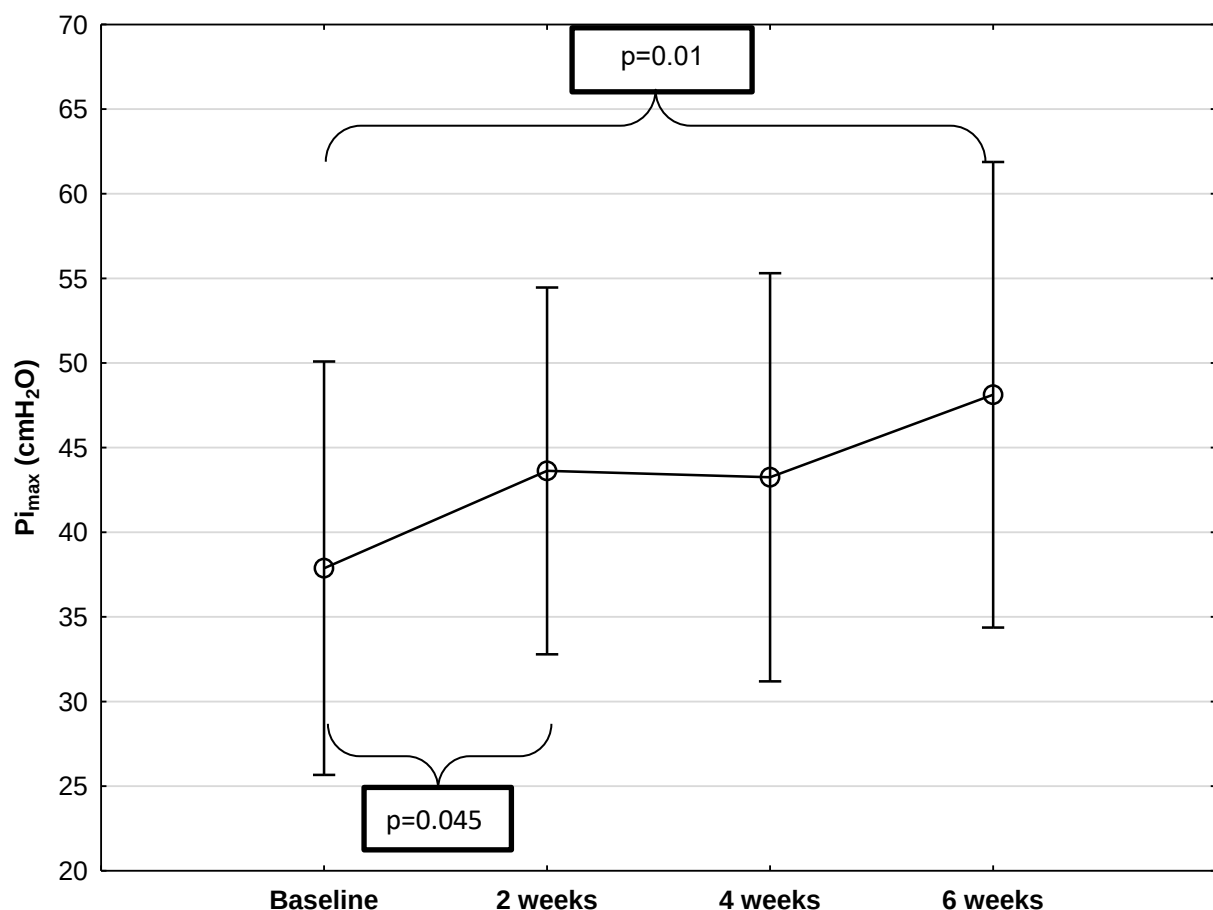


Figure 5.1: Change in mean inspiratory muscle strength (Pimax) throughout intervention (ANOVA $p=0.02$). The vertical bars denote 0.95 confidence intervals. Significant *post-hoc* bivariate dependent tests between measurement points are indicated.

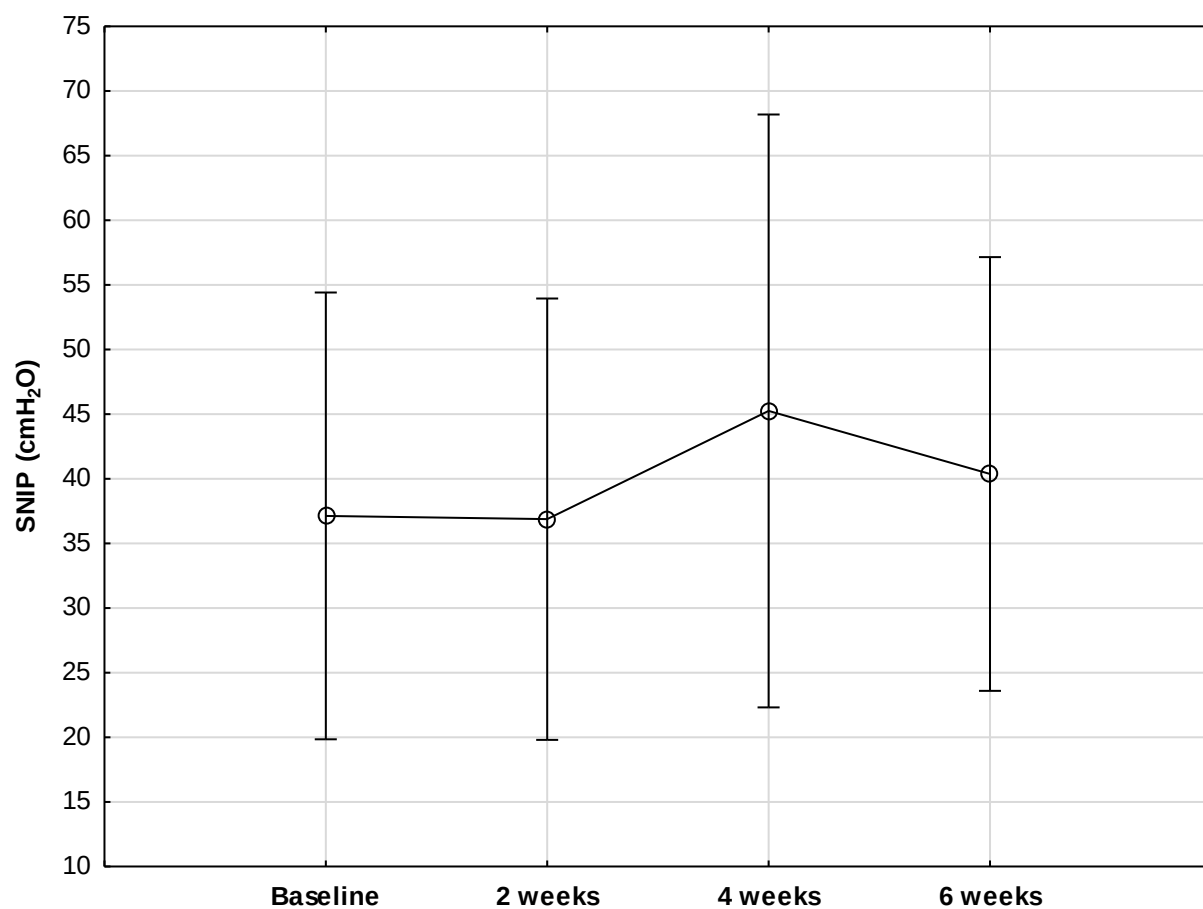


Figure 5.2: Change in mean inspiratory muscle strength (SNIP) throughout intervention (ANOVA $p=0.39$). The vertical bars denote 0.95 confidence intervals. No significant differences between measurement points on *post hoc* analysis.

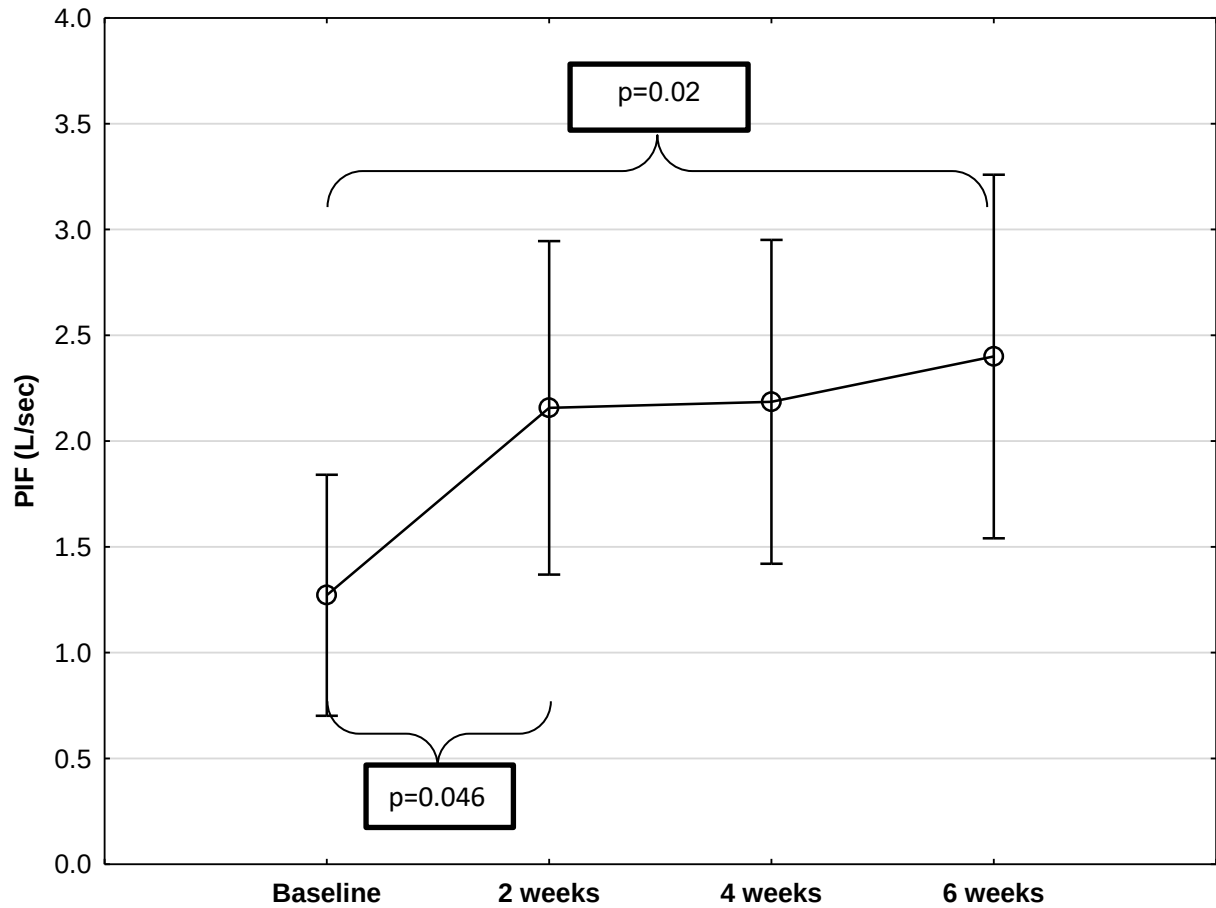


Figure 5.3: Change in mean peak inspiratory flow (PIF) values throughout intervention (ANOVA $p=0.007$). The vertical bars denote 0.95 confidence intervals. Significant *post-hoc* bivariate dependent tests between measurement points are indicated.

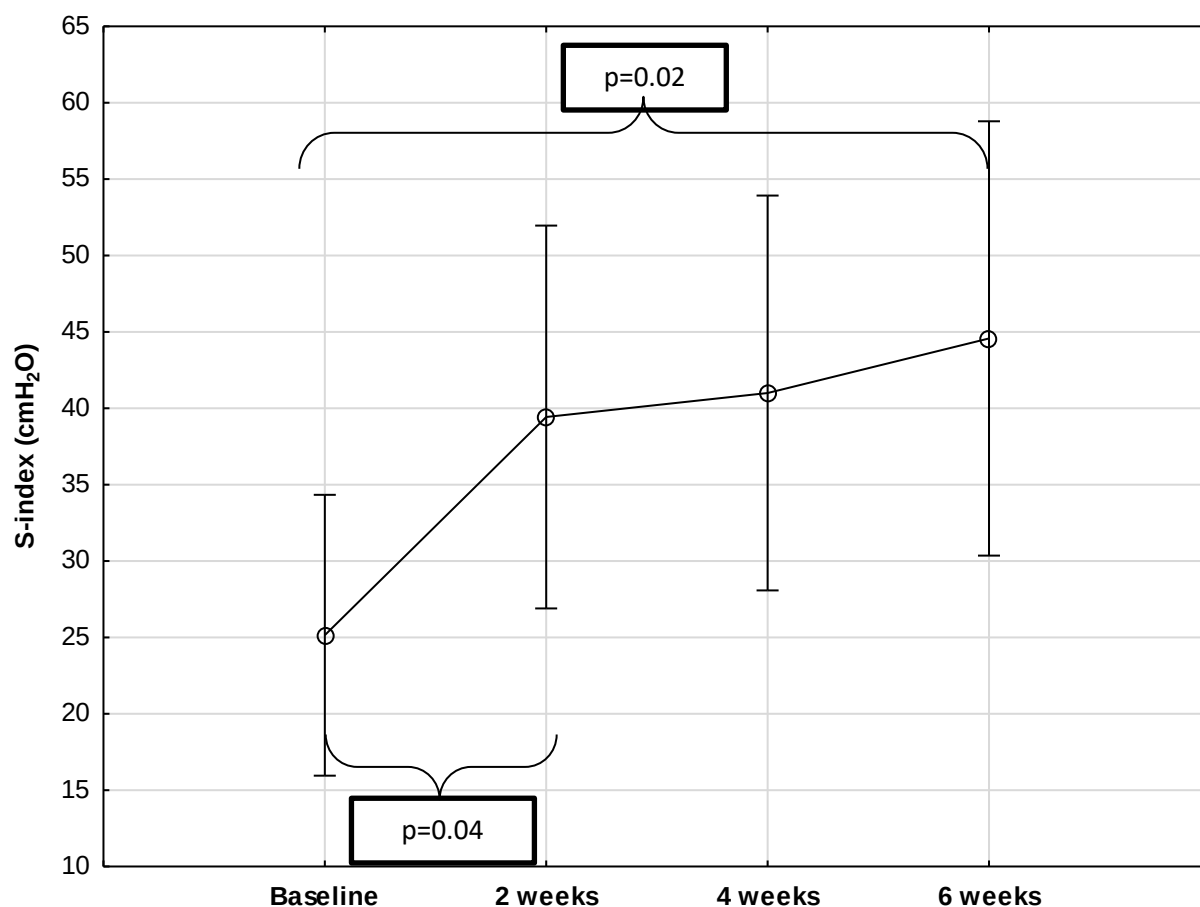


Figure 5.4: Change in mean strength-index (S-index) throughout intervention (ANOVA $p=0.005$).
The vertical bars denote 0.95 confidence intervals. Significant *post-hoc* bivariate dependent tests between measurement points are indicated.

For other pulmonary function measures such as unassisted cough ability (PECF) the change post six-week IMT was non-significant (Table 5.3). This study did not find any association between any of the bio-demographic data (age, sex, height and BMI) or any pulmonary function measure (spirometry, PECF and inspiratory muscle strength).

5.10.5 Functional ability, level of ambulation and upper limb function

Participant level of mobility, upper and lower limb function (Brooke & Vignos scales) (4.3.4) at baseline are depicted in Tables 5.1 and 5.4. Mobility was described as partially ambulant (PA) if a participant could still walk short distances with support or the use of a mobility aid and non-ambulant if they were making use of a wheelchair only.

The majority of participants were non-ambulant and using a wheelchair (manual, electric or both) (Meier et al., 2017). One boy with DMD was still ambulant and one participant was partially ambulant as she could walk short distances with support and splints.

Upper limb function on the Brooke scale was fair, with a median of three out of six (ability to raise a glass of 180ml water to the mouth, but unable to raise hands above their heads) and a slight improvement post intervention. Lower limb function was more affected at baseline, with a median of nine out of 10 on the Vignos scale (using a wheelchair) (Table 5.4).

Neither the Brooke ($p=0.11$) nor Vignos ($p=1.00$) scales showed any statistically significant change over the six week IMT intervention period based on the Wilcoxon matched pair test (Table 5.4).

Table 5.4: Mobility and upper limb function and coordination (n=8).

Variable	Baseline	Post-intervention	Wilcoxon (p-value)
Brooke (/6)	3 (2.5-3)	2.5 (1.5-3)	0.11
Vignos (/10)	9 (8-9)	9 (8-9)	1.00
Motor Function Measure (/30)	25.75 (± 1.83) [#]	26.75 (± 1.39) [#]	0.03*

MDN (IQR) unless otherwise indicated; [#]mean ($\pm$ SD)

Upper limb function and coordination (based on ten items of the MFM) (Chapter 4: 4.3.4.3) improved significantly ($p=0.03$) from pre-to post-intervention (Table 5.4; Figure 5.5).

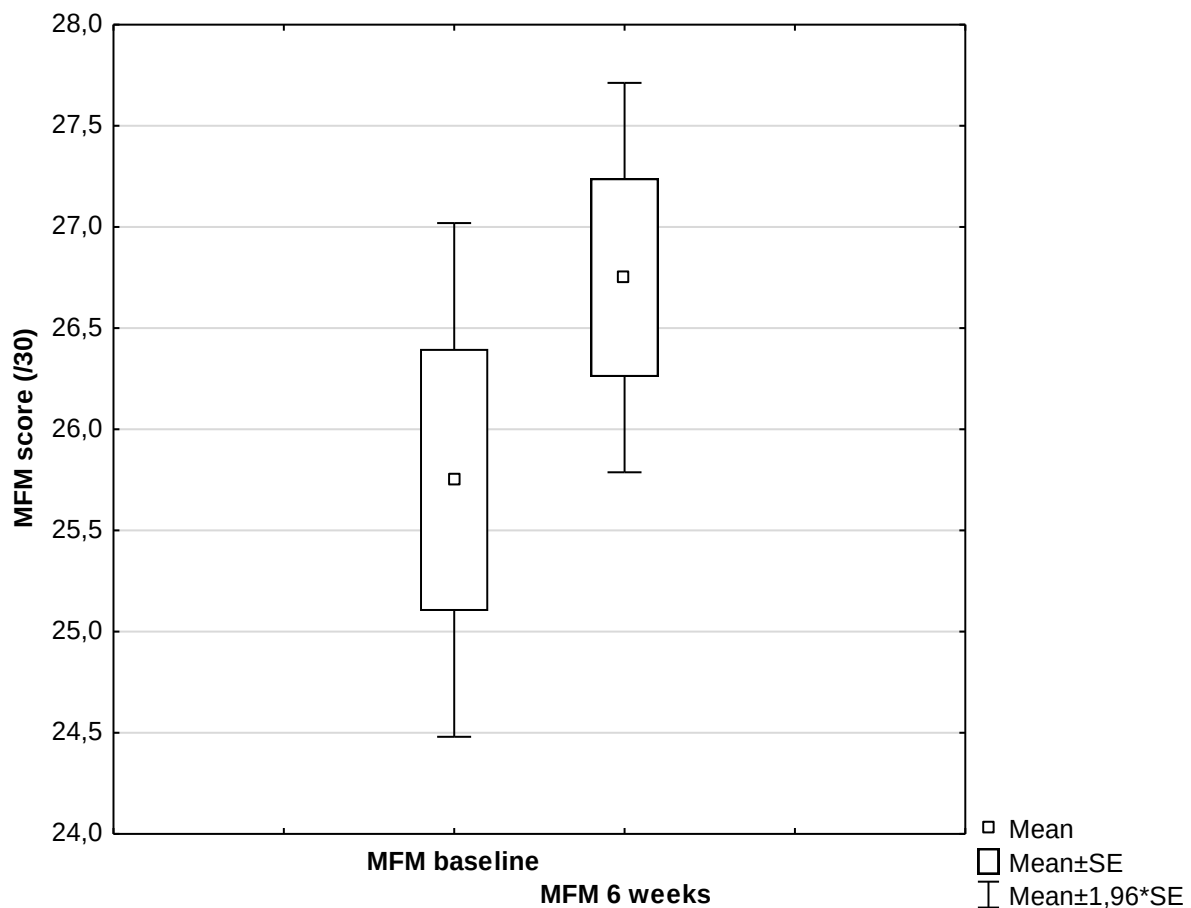


Figure 5.5: Upper limb function and coordination (MFM) pre-post inspiratory muscle training (n=8).

5.10.6 Health-related quality of life

Health-related quality of life was measured with the PedsQL (child and proxy) (Chapter 4: 4.3.5). Although there was a slight improvement in the self-reported HRQoL from baseline to post-intervention, based on the total PedsQL scale (%), this was not statistically significant ($p=0.15$) (Table 5.5). The total PedsQL, Physical and Psychosocial (social, emotional and school performance) domains post intervention showed a mean ($\pm$ SD) change (Δ PedsQL scores) of 8.58 (± 15.06), 0.28 (± 17.49) and 12.29 (± 18.36) respectively. The pre-post intervention changes for the Physical and Psychosocial domains were also not statistically significant ($p=0.97$; $p=0.10$) (Table 5.5).

Effect sizes were calculated to determine the possible clinical relevance of the changes observed (Jansen et al., 2013). When calculating Cohen's d for effect sizes (<https://www.statisticshowto.datasciencecentral.com/cohens-d/>), the Child PedsQL total score showed a medium effect size (0.52) and the Psychosocial domain a large effect size (0.81).

Table 5.5: Health-related quality of life measurements: total scores, subdomains for child (n=8) and proxy (n=4).

Variable	Baseline	Post-intervention	p-value
Child PedsQL total (%) n=8	64.99 (± 16.04)	73.56 (± 16.97)	0.15
Child PedsQL (Physical domain) (%)	65.23 (± 30.45)	65.50 (± 23.0)	0.97
Child PedsQL (Psychosocial domain) (%)	64.80 (± 12.83)	77.08 (± 17.10)	0.10
Proxy PedsQL total (%) n=4	56.19 (± 18.19)	64.20 (± 16.78)	0.12

Values are expressed as mean ($\pm$ SD); PedsQL=Pediatric Quality of Life Inventory

Only four parents/caregivers completed the proxy PedsQL questionnaire: two parents/caregivers did not complete a proxy form, one parent changed the subheadings of the questionnaire rendering her responses invalid, and one parent never returned the questionnaire. The descriptive values of the four individual responses (total PedsQL proxy score, physical and psychosocial) are provided in Table 5.6.

Table 5.6: Proxy PedsQL scores (n=4).

Proxy	PedsQL (total %) (Pre-post test)	PedsQL (physical %) (Pre-post test)	PedsQL (psychosocial %) (Pre-post test)
1	81.0; 89.3	83.3; 83.3	80; 91.7
2	42.9; 72.6	38.0; 45.8	45; 83.3
3	27.4; 40.5	37.5; 37.5	23; 41.7
4	48.9; 58	25.0; 20.8	62; 73.3

PedsQL=Pediatric Quality of Life Inventory

5.10.7 Inspiratory muscle training adherence, intensity, power and volume

The baseline training intensity for each participant was set at 30% of their baseline Pimax. All participants in this pre-experimental study were IMT naïve and had not previously performed any threshold respiratory muscle training. Participants commenced training with three sets of 10 breaths, with a rest-interval of less than 60s between sets (10-40 seconds), twice a day, five days a week. More than half of the participants (5/8) managed to perform one set of 30 breaths, twice a day, five days a week by the second week of intervention (at 13 training sessions) and the majority (7/8) could do so by the fourth week.

The baseline intensity set for IMT was 11.38 (± 4.47)cmH₂O and at four weeks of intervention was 13.38 (± 4.37)cmH₂O ($p=0.12$)(Table 5.3). Along with the change in Pimax, there was a proportional change ($p=0.04$) in training intensity over the three measurement points, with the main change occurring during the first two weeks ($p=0.02$)(Figure 5.6).

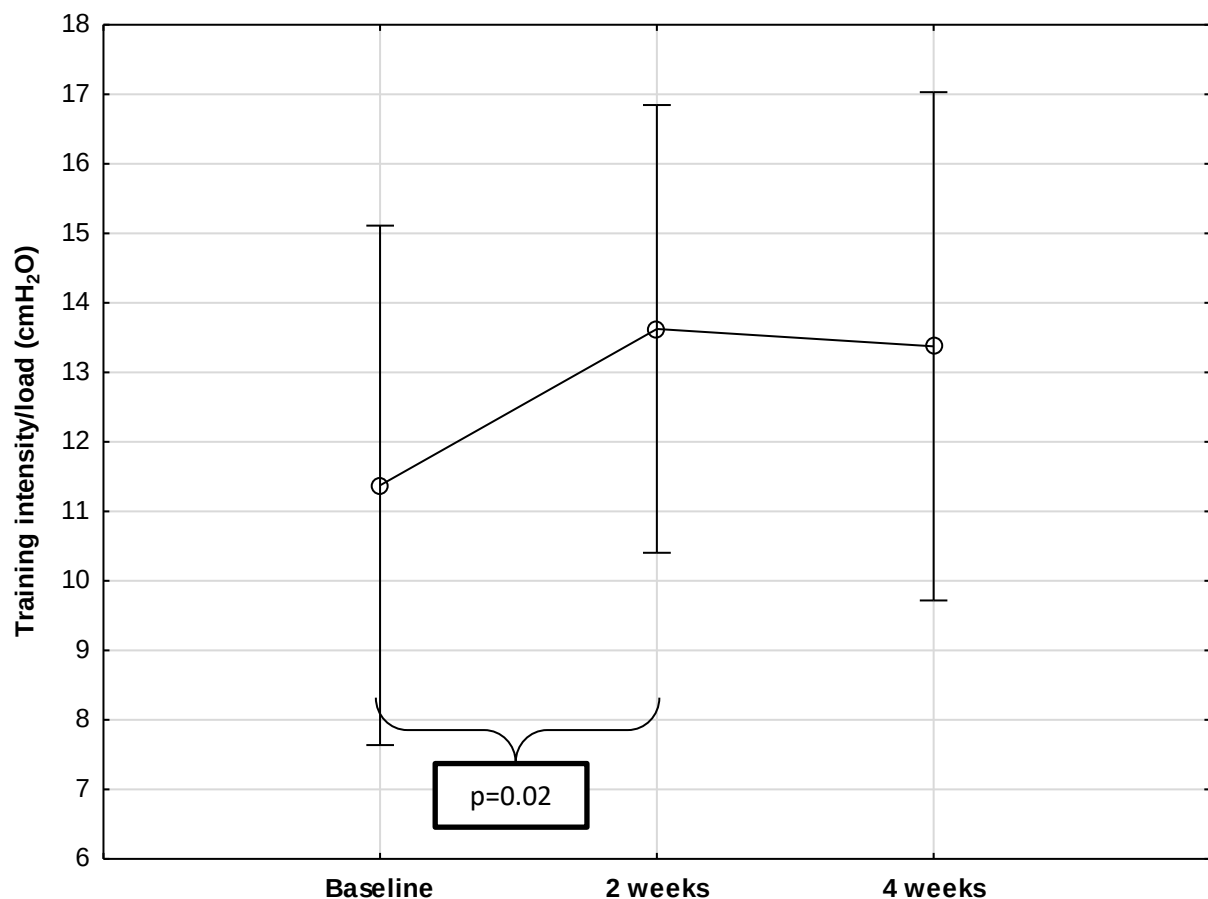


Figure 5.6: Change in mean inspiratory muscle training intensity (load) throughout the intervention period (weeks) (ANOVA $p=0.04$). The vertical bars denote 0.95 confidence intervals. Significant *post-hoc* bivariate dependent tests between measurement points are indicated.

The total training sessions for participants, as noted in the training diaries by the clinicians, ranged from 38 to 60. Although the data were normally distributed, due to the short training period (6 weeks) and small sample size, these descriptive values are reported as median (IQR). The MDN (IQR) number of training sessions over the six-week intervention period, as recorded by physiotherapists at the school, was 52 (47-56) out of a possible, maximum of 60 training sessions. The adherence rate therefore was high and ranged from 85-87%. The number of training sessions recorded on the Powerbreathe[®] device (dependent on the quality of breaths) was similar at 51 (47-53) ($p=1.00$). There was no statistically significant correlation between change in Pimax (ΔP_{imax}) over the six week IMT intervention and the number of training sessions measured using either training diaries or recorded sessions.

The training intensity (load), based on the data captured for each training session on the Powerbreathe K3[®], showed a statistically significant change over the intervention period ($p=0.00005$), with *post hoc* t-tests showing significant improvements between session 10 and 20 ($p=0.008$), and from the first to last training sessions ($p=0.015$) (Figure 5.7).

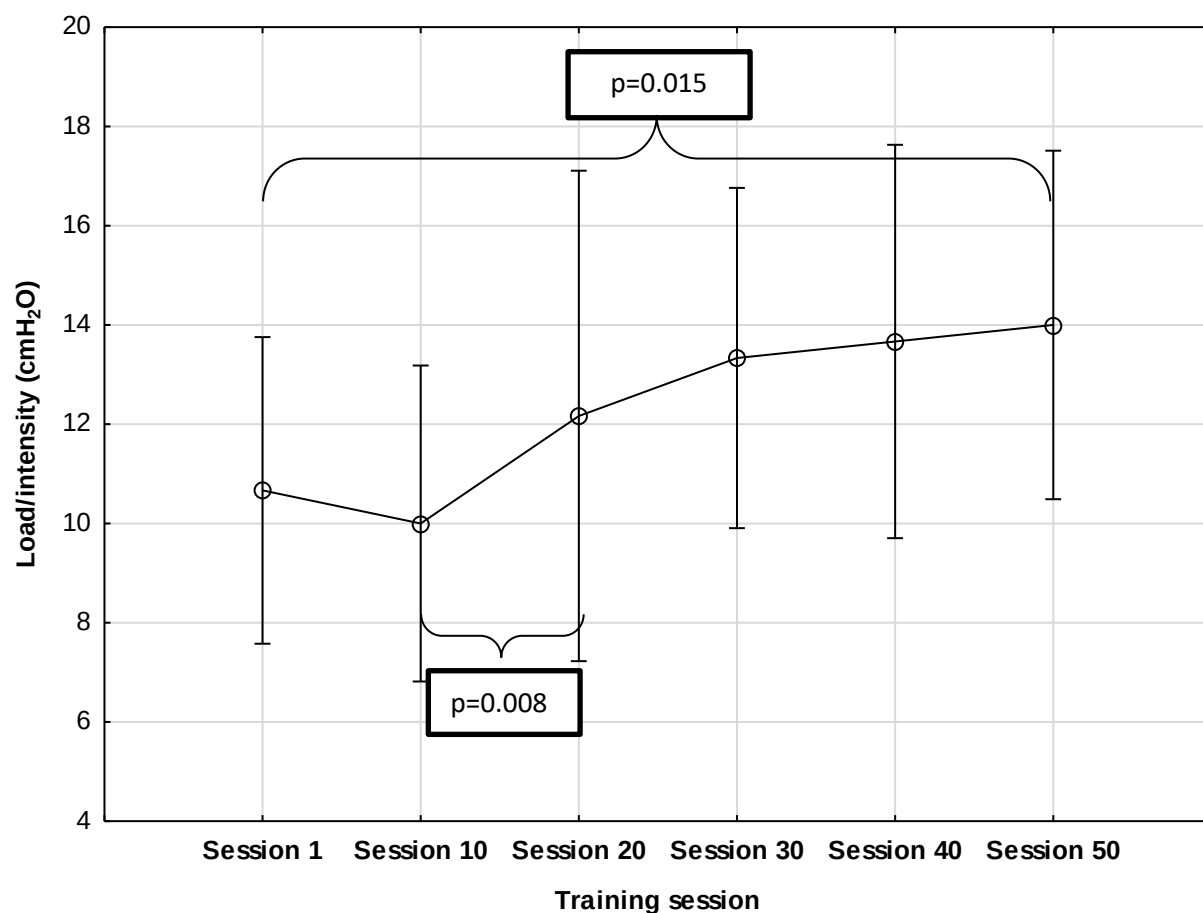


Figure 5.7: Change in mean inspiratory muscle training intensity (load) over the intervention period (Powerbreathe K3 ®)(ANOVA $p < 0.001$). The vertical bars denote 0.95 confidence intervals. Significant *post-hoc* bivariate dependent tests between measurement points are indicated.

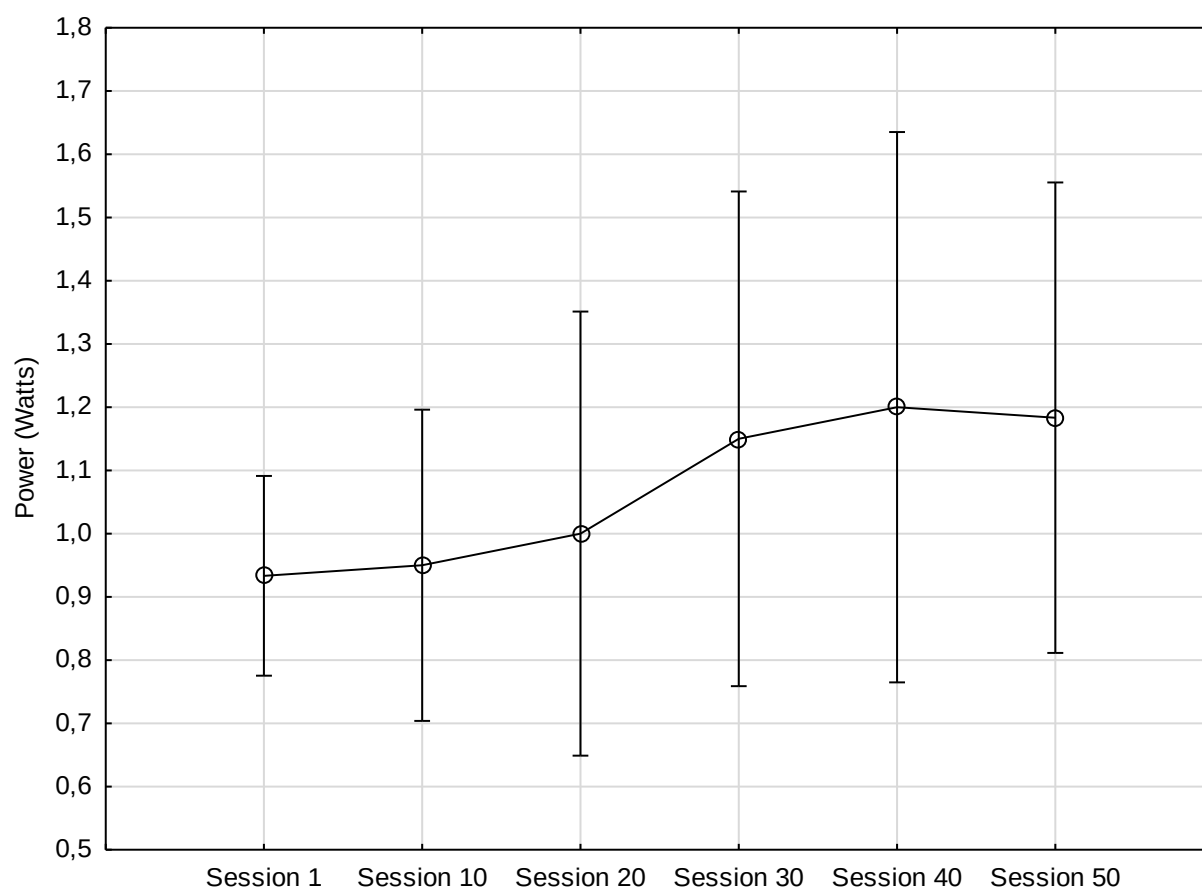


Figure 5.8: Change in mean power (Watts) over the intervention period (Powerbreathe K3 ®) (ANOVA $p=0.18$). The vertical bars denote 0.95 confidence intervals. There were no significant differences between measurement points on *post hoc* analysis.

The power (in Watts) and the volume (in litres) values captured by the Powerbreathe K3 ® device overtime was not normally distributed (although the residuals were normally distributed allowing ANOVA analysis), and neither showed a statistically significant change over the intervention period ($p=0.18$ and $p=0.20$ respectively) (Figures 5.8 and 5.9), or between baseline and the 50th training session for power ($p=0.18$) and volume ($p=0.068$) respectively.

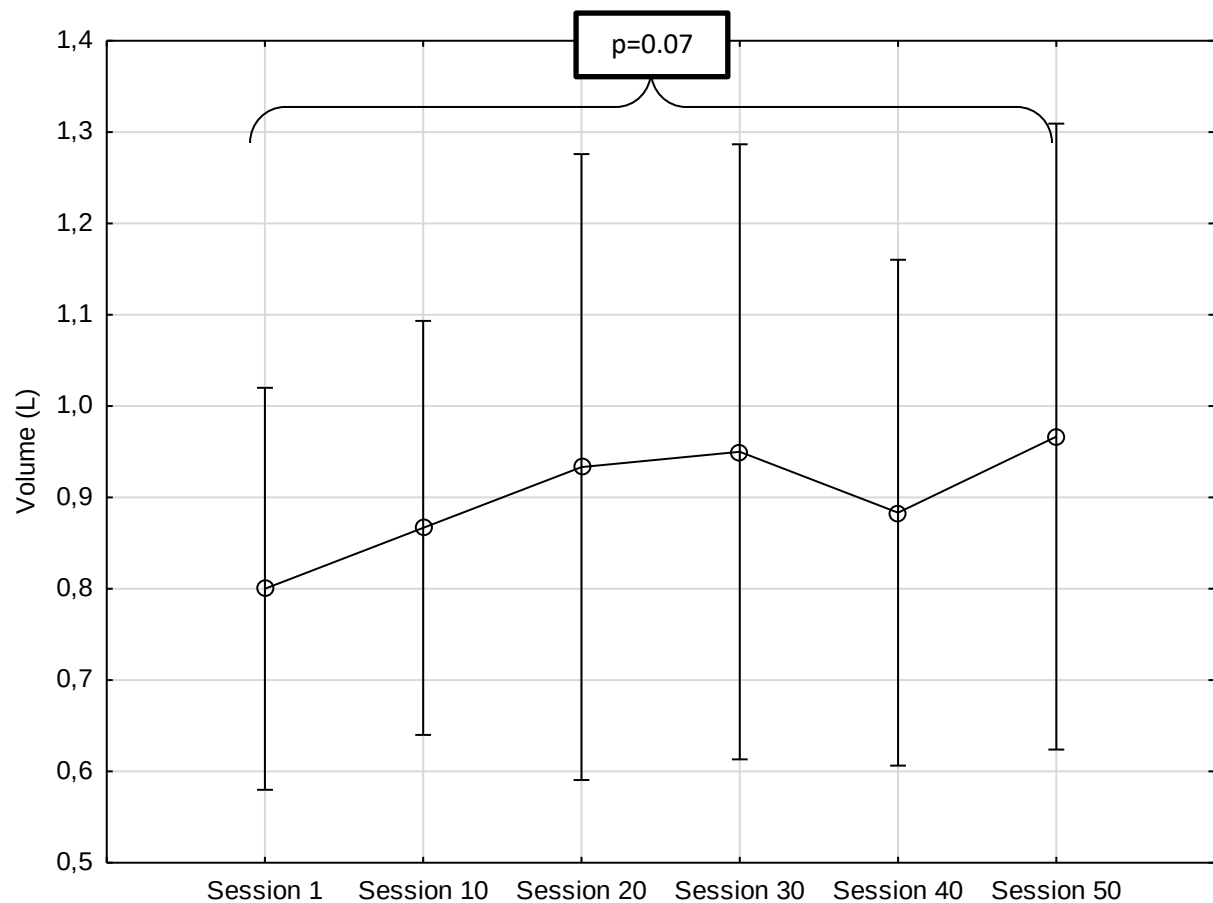


Figure 5.9: Change in mean volume (L) over the intervention period (Powerbreathe K3 ®) (ANOVA $p=0.20$). The vertical bars denote 0.95 confidence intervals. There were no significant differences between measurement points on *post hoc* analysis.

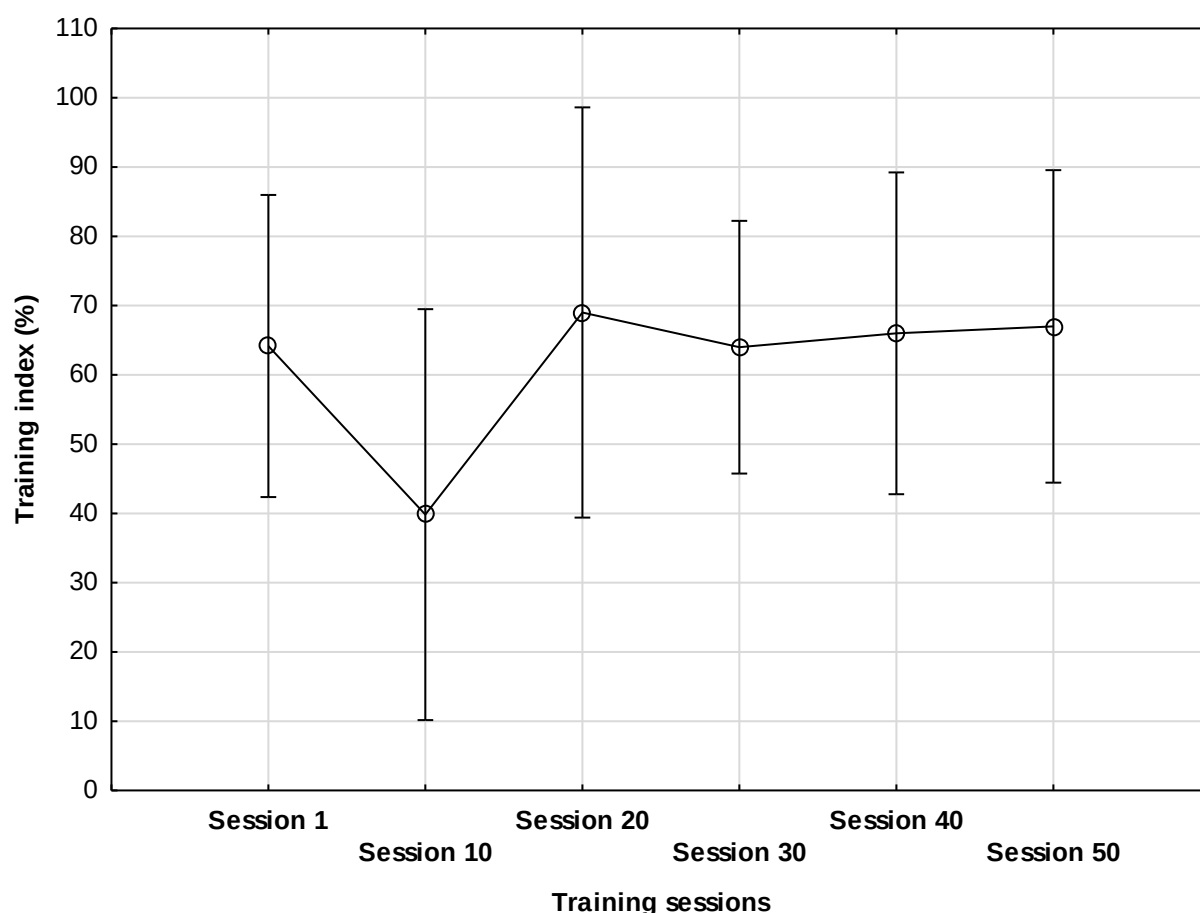


Figure 5.10: Change in mean training index (%) over the intervention period (Powerbreathe K3 ®) ($p=0.053$). The vertical bars denote 0.95 confidence intervals. There were no significant differences between measurement points on post hoc analysis.

The change over time in training index (%), a measurement of contraction and speed as well as energy expenditure, tended toward significance ($p=0.053$) (Figure 5.10), but there was no significant change between baseline and the 50th IMT session as determined by *post hoc* dependent t-test ($p=0.75$).

5.10.8 Feedback from participants and physiotherapists

Overall patient satisfaction with the IMT programme, on a 10-point visual analogue scale, was extremely high, with a median (IQR) of 9 (9-10) reported by the participants themselves. When further asked about their experience of IMT the participants and the physiotherapists involved provided the following responses (Table 5.7).

Table 5.7: Open-text verbatim responses from participants and physiotherapists about inspiratory muscle training (n=8).

Participant number	What did the participants have to say about IMT?	What did the physiotherapists have to say about the experience of IMT with each participant?
1	It is nice and relaxing!	Improvement was noticed in his posture, breathing pattern and endurance.
2	It helps me with breathing, I am less out of breath and my lungs work better.	Improved posture, confidence he even corrected others that participated in the study. He also presented with improved endurance and academic performance.
3	My lungs are better, I breathe better (more normal) and I can sing louder in the choir!	Improved posture, confidence and increase in voice volume/projection, as she speaks and sings louder. Decreased use of asthma medication (cortisone) since she started with IMT. Regarding morbidity, she presented with a decreased frequency of respiratory illness during the winter period: only one upper respiratory tract infection and one case of gastro-enteritis during the six-week training period.
4	Liked the training, it was nice.	When he started training he was sick and had difficulty with IMT, after he received medication he was much better and could start with training again. He was not sick again after he started training and his morbidity during winter time decreased (frequency of respiratory illness).
5	Helps me to improve and keeps me healthier. I can go shopping with my mother and come to the physiotherapy department without having to stop every now and again because I am short of breath.	Inspiratory muscle training will be more beneficial in some patients as compared to others. For this patient specifically, it was clinically relevant, and she was very dedicated and will continue with training (patient adherence has a positive influence on the outcome of the intervention).
6	It was fun, and now I can run faster and longer!	Similar to the previous participant: certain patients might benefit more from IMT than others, depending on their diagnosis, clinical presentation and motivation. This patient was very dedicated, motivated to exercise and seems to benefit from the intervention (clinical presentation).
7	It makes my lungs better.	Any effort of maintenance is valuable for these patients and making them aware of effective breathing is to their advantage/provides clinical benefit for them.
8	Liked the training, it helps me with my breathing.	Any effort of maintenance is valuable for these patients and making them aware of effective breathing is to their advantage/provides clinical benefit for them.

5.11 Discussion

This is the first SA study to investigate the potential utility of IMT in children with NMD. This was a short-duration pre-experimental, pilot study with a small, heterogenous convenience sample from one region, limiting internal and external validity. Despite these limitations, the findings support the suitability of the proposed objective outcome measures and IMT protocol in children and adolescents with NMD in SA. The intervention also seemed safe, practical and acceptable to implement within the planned context, with good adherence to training and positive outcomes for pulmonary function and HRQoL, similar to other studies (Wanke et al., 1994; McCool & Tzelepis, 1995; Winkler et al., 2000; Human et al., 2019; Wenninger et al., 2019).

5.11.1 Bio-demographic description of participants

Most of the participants were in their pre-adolescent or adolescent phase (median age of 12.2) and the majority were already non-ambulant, similar to other studies (Nicot et al., 2006; Nève et al., 2013; Landfeldt et al., 2015; Meier et al., 2017; Katz et al., 2019). Children and adolescents in this sample presented with a variety of NMD, but the majority had DMD, as expected in this age group (Table 5.1). Most participants presented with low PEF values (<270 L/min) which place them at high risk of secretion retention during respiratory infections and therefore airway clearance techniques (ACT), including cough augmentation, are indicated (Bach et al., 1997; Gauld & Boynton, 2005; Panitch, 2006; Farrero et al., 2013; LoMauro et al., 2014; Chiang et al., 2018). The majority of participants in this pre-experimental study used MAC techniques during acute infections but did not receive routine cough augmentation therapy and none were familiar with the broader range of cough augmentation techniques recommended for this patient group (including LVR, breath-stacking, GPB and MI-E) (Finder et al., 2004; Bushby et al., 2010; Finder, 2010; Wang et al., 2010; Hull et al., 2012; Birnkrant et al., 2018; Chatwin et al., 2018; Toussaint et al., 2018; Castrillo et al., 2019). This finding concurs with the results of the study surveying SA physiotherapy NMD practice (Chapter 2).

Similarly, although most participants were already in the non-ambulatory phase and all presented with decreased pulmonary function (FVC <60% predicted; Pimax <60cmH₂O), none were receiving night-time ventilation nor were any participants performing lung volume recruitment to preserve lung and chest wall compliance, as recommended (Kang & Bach, 2000; Sejerson & Bushby, 2009; McKim et al., 2012; Birnkrant et al., 2018; Chiang et al., 2018). These findings may relate to a lack of knowledge among both patients and physiotherapists, which correlates with the results from the survey (Chapter 2: 2.6).

Although SA physiotherapists reported that they were aware of internationally recommended pulmonary management guidelines for children with NMD, they preferred the use of conservative physiotherapy techniques that might not always be effective in NMD and have a limited evidence base (Panitch, 2006; Chatwin et al., 2018; Finkel et al., 2018; Toussaint et al., 2018). Lack of available resources (financial, equipment, human) may also be a contributing factor.

Interpretation of anthropometric measures such as weight, height and BMI, based on standard growth charts, are not ideal in patients with NMD due to their altered body composition and therefore WFA percentiles and Z-scores are recommended (Wang et al., 2007; Birnkrant et al., 2018). This study made use of alternative height measures such as ulna length (Hull et al., 2012; Mayer et al., 2015) to calculate Z-scores for WFA and BMI as the majority of participants were non-ambulant, and half presented with either scoliosis or kyphosis, similar to other research (Nicot et al., 2006; Marques et al., 2014; Janssen et al., 2016). Valid weight and height measures were also needed to compare pulmonary function tests with normative values.

Most participants, despite having reasonable oral control, were severely underweight based on their WFA (median=-3.40) and BMI (median=-6.86) scores. Marques et al. (2014) also found similar BMI alterations in a study among children and adults (7-23 years) with congenital muscular dystrophy (CMD) and SMA (n=18); as four of their participants younger than 20 years were underweight, while only one was overweight and one obese. In a study by Nève et al. (2013), 33 children with DMD also presented with low median (range) BMI raw and Z-scores (16.5 (12.5-33.8); -0.1 (-4.8 to 6.3)). As patients with NMD grow older, their BMI might also decrease, especially once feeding difficulties such as dysphagia arise (Janssen et al., 2016; Birnkrant et al., 2018; Wadman et al., 2020). Caution must be taken when interpreting anthropometric findings, as calculated WFA and BMI derived from ulna length may not accurately reflect participants' true height.

5.11.2 Adverse events and precautionary measures

No adverse events directly attributable to IMT were reported in this study, but the primary aim of this pre-experimental, pilot study was to determine if the proposed outcome measures, assessment techniques and performance of IMT was viable, did not overexert the participants and if IMT was acceptable in children and adolescents with NMD in SA and could proceed to a cross-over RCT.

Previous studies in NMD have also not shown adverse events related to IMT (Wanke et al., 1994; McCool & Tzelepis, 1995) even in advanced disease progression and severe respiratory muscle weakness (Winkler et al., 2000; Human et al., 2019).

Caution needs to be taken when exercising in patients with NMD, especially those with dystrophinopathies, such as DMD, as these patients potentially have reduced cardiopulmonary exercise capacity and are at risk of muscle damage (Chapter 1: 1.1.4.2). For these reasons, high intensity resistance and eccentric contraction exercises should be avoided (Eagle, 2002; Goemans & Buyse, 2014) and submaximal aerobic exercise, avoiding overexertion and providing adequate periods of rest, is recommended (Avendaño & Güell, 2003; Birnkrant et al., 2018; Voet et al., 2019).

Respiratory muscle training intensity in most studies is guided by the patients' Pimax values, starting at 30% of Pimax (Lötters et al., 2002; Takaso et al., 2010; Woszezenki et al., 2017; Hariza et al., 2018), but there are varying reports of continuous training ranges increasing this intensity. Studies have reported up to 70-80% (Koessler et al., 2001; Woszezenki et al., 2017) and interval-based training up to 95% of baseline Pimax (Hill, Jenkins, Hillman & Eastwood, 2004; de Freitas Fregonezi, Resqueti, Güell, Pradas & Casan, 2005) and even 100% of Pimax (Wenninger et al., 2019). For safety sake, researchers applied the lowest intensity that can still provide clinical benefit, which was 30% of Pimax, throughout this study. As an additional safety and precautionary measure, the OMNI scale was used on a daily basis during training and as an indication of exertion on average over every two weeks, to monitor that participants did not overexert themselves (4.4.3.3). None of the participants indicated very high OMNI values, however, average OMNI values did increase during the second two weeks of IMT training, and subsequently decreased, but not returning to baseline levels. This could either indicate that participants perceived a higher level of exertion as the training intensity (cmH₂O) increased and started adapting physiologically towards the end of the training period. The clinical relevance or implications of these findings have to be confirmed in larger long-term trials. The validity and reliability of the OMNI scale in children with NMD in SA has not been determined, and this might impact the results.

Based on pulmonary function measurements, feedback and observation it seems that 30% of Pimax is a safe and suitable IMT intensity for children and adolescents with NMD in SA, but this requires confirmation with larger RCT.

5.11.3 Pulmonary function

Anthropometric measures have been associated with pulmonary function among children six to 10 years, especially FVC and FEV₁ (Torres, Martinez & Manço, 2003).

Despite the majority of the eight participants in this pre-experimental study being non-ambulant, overweight was not identified as a confounding factor that could influence pulmonary function. Contrary to (Bianchi & Baiardi, 2008), this study did not find any association between age, sex, height and BMI, PEF or any other pulmonary function measures (FVC, FEV₁ and PEF) including inspiratory muscle strength (Pimax, SNIP). The lack of association may be attributed to the majority being classified as underweight and/or the difference in ethnicity as compared to other studies as well as the small sample size and the study being underpowered to determine such an association.

5.11.3.1 Spirometry

Spirometry tests such as VC, FVC, FEV₁ and PEF indicate disease progression and predict pulmonary morbidity (Hull et al., 2012; Farrero et al., 2013; Meier et al., 2017; Chiang et al., 2018; Morrow et al., 2019). The loss of pulmonary function, especially FVC, correlates with the progressive loss of upper limb function in NMD (Brooke scale) (Mayer et al., 2017). Pulmonary function tests such as spirometry (including VC, FVC), peak flows (PECF) and respiratory muscle strength (Pimax, Pemax) should therefore form part of the assessment and monitoring of patients with neuromuscular weakness as they can predict outcomes and inform management strategies in NMD (Birnkrant et al., 2018; Finkel et al., 2018; Toussaint et al., 2018; Dassios & Dimitriou, 2019; Stephan et al., 2020).

All participants in this study presented with a restrictive disease pattern ranging from mild to very severe, predisposing them to respiratory complications. This restrictive pattern is evident from the low absolute and Z-score FVC values reported, despite normal (>0.7) FEV₁/FVC ratios (Barreiro & Perillo, 2004; Meier et al., 2017; Chiang et al., 2018). Forced manoeuvres such as PEF and FVC are volitional and effort dependent, and could be very difficult to perform for patients with NMD, especially as they grow older and with advancing disease (Nicot et al., 2006; Mayer et al., 2015; Meier et al., 2017; Birnkrant et al., 2018). This explains the finding that baseline spirometric ranges of FVC (0.78-2.36L), FEV₁ (0.71-2.04L) and PEF (94-196L/min) were at the lower range of normative values for children (Bianchi & Baiardi, 2008; Heinzmann-Filho et al., 2012; Da Rosa et al., 2017). In addition, due to the respiratory muscle weakness causing decreased expiratory airflow, in proportion to the decrease in FVC, can lead to normal or high values of FEV₁/FVC (Meier et al., 2017; Chiang et al., 2018).

It was notable that measures of relaxed spirometry more often met ATS quality standards in study participants than forced spirometry. Relaxed vital capacity manoeuvres may be easier for patients with NMD to perform compared to forced manoeuvres, due to underlying respiratory muscle weakness (Hull et al., 2012) and should be considered in future studies. Both FEV₁ and FVC are usually decreased in patients with NMD due to decreased inspiratory and/or expiratory muscle strength as well as decreased chest wall and lung compliance (Avendaño & Güell, 2003; Birnkrant et al., 2018; Chiang et al., 2018). Other factors to consider that may influence pulmonary function test performance is the presence of concomitant learning difficulties and co-morbidities such as attention-deficit disorder, autism spectrum disorders and anxiety, particularly in patients with dystrophinopathies, especially DMD (Ho et al., 2015; Birnkrant et al., 2018; Chiang et al., 2018). In this study, the quality of the blows as well as the number of participants that met the BTS quality criteria improved slightly for both slow VC and forced manoeuvres from pre to post intervention. However, there was no significant change pre-post intervention, similar to previous reports in adults with slowly progressive NMD (Aslan et al., 2013; Wenninger et al., 2019) and findings from paediatric studies as reported in the systematic review (Chapter 3: 3.6). Mean lung volume values pre-post intervention either remained the same or showed slight improvement, although the overall change was not significant, as previously reported (Hull et al., 2012). The fact that lung function did not decline during the study period may reflect the short duration of the study; however, the potential utility of respiratory muscle training in slowing progression of pulmonary disease, as suggested by (Aslan et al., 2013; Wenninger et al., 2019) in adults with slowly progressive NMD, requires further investigation over a longer duration.

5.11.3.2 Inspiratory muscle strength, peak inspiratory flow and training tolerance

In this study, the Pimax values measured at baseline and even after intervention were far below what is expected for healthy children in the same age range (Fauroux & Aubertin, 2007). The Pimax values in this study are similar to previous studies reporting mean ($\pm$ SD) Pimax ranging from 22.7 $\pm$ 14.3cmH₂O to 64.5 $\pm$ 24.7cmH₂O in mixed populations (children, adults and adolescents with a variety of NMD) (Suárez, Pessolano, Monteiro, Ferreyra, Capria, Mesa & De Vito 2002; Chatwin et al., 2003; Kinane et al., 2018). Normative values for Pimax in children are limited (Chiang et al., 2018; Da Rosa et al., 2017; Hulzebos et al., 2018), but a study by Tomalak et al. (2002) reported significant differences between Pimax in boys and girls ($p < 0.001$) in both sitting and standing positions. In this study, no significant association between sex and change in Pimax (Δ Pimax) was found, which could be attributed to the small sample size ($n=8$).

Despite the low baseline values, this study found a statistically significant improvement in inspiratory muscle strength (Pimax, S-index) over the intervention period of six weeks. Similar to the findings from this pre-experimental study (Δ Pimax): $10.3 \pm 8.63 \text{ cmH}_2\text{O}$), a change in Pimax over time was also observed in a study by (Gozal & Thiriet, 1999), with a mean ($\pm$ SD) change of $19.8 (\pm 3.8) \text{ cmH}_2\text{O}$ ($p < 0.02$) in the six-month IMT training group with NMD (DMD and SMA type III), while no change was seen in the control group receiving no training. Load perception, based on a modified Borg scale, was also significantly decreased in the training group ($p < 0.01$) compared to the controls (Gozal & Thiriet, 1999). A RCT in adult patients with Myasthenia gravis showed that an eight-week, threshold (20-60% of Pimax) IMT programme led to significant improvement in Pimax, thoracic mobility and upper chest wall expansion (de Freitas Fregonezi et al., 2005). Similarly, another RCT investigating an eight-week IMT threshold training programme among adults with slowly progressive NMD, reported a statistically significant improvement in Pimax ($p = 0.002$) and SNIP ($p = 0.04$) when compared to sham training (Aslan et al., 2013). A feasibility IMT study among adult patients with late-onset Pompe disease ($n = 11$) also reported a statistically significant improvement in Pimax post-intervention ($p = 0.02$) (mean increase of $7.6 \text{ cmH}_2\text{O}$; with a moderate effect size) (Wenninger et al., 2019).

Although SNIP does not require practice, might be easier to perform and more reproducible than other inspiratory muscle strength tests (Stefanutti et al., 2000; Fauroux & Aubertin, 2007; Nève et al., 2013; Verma et al., 2019), children in this pre-experimental, pilot study expressed a subjective preference for performing the Pimax test rather than SNIP. Limited literature on normative values is available for SNIP. In children a mean ($\pm$ SD) SNIP of $93 (\pm 23) \text{ cmH}_2\text{O}$ in healthy girls and $104 (\pm 26) \text{ cmH}_2\text{O}$ in boys (Fauroux & Aubertin, 2007) has been reported; while the mean reported value of SNIP among children, adolescents and adults with a variety of NMD was much lower ($56 \pm 26 \text{ cmH}_2\text{O}$) (Stefanutti et al., 2000), as was the median (range) values for children with DMD ($48 (22-80) \text{ cmH}_2\text{O}$) (Nève et al., 2013). The SNIP values in this pre-experimental, pilot study were lower than normal ranges, but well correlated with those reported in children with NMD (Stefanutti et al., 2000; Chatwin et al., 2003). Low SNIP values can be attributed to severe ventilatory restriction caused by respiratory muscle weakness and atrophy (Fauroux & Aubertin, 2007) especially with fast progressing NMD or later in the disease. The SNIP and Pimax values at baseline were similar, but SNIP was lower than Pimax after IMT, similar to the findings by Aslan et al. (2013). Similarly, SNIP did not improve with IMT, despite the improvement in Pimax.

In this study, there was a marked increase in inspiratory muscle strength (Pimax, S-index) and training intensity between baseline and the second week of intervention. None of the subsequent measurement intervals (2 to 4 weeks; 4 to 6 weeks) showed such a marked increase. This improvement could therefore be attributed to a learning effect (Eagle, 2002), caused by improved respiratory muscle action and coordination with threshold training (Winkler et al., 2000; Tomalak et al., 2002) and may not necessarily reflect true IMT efficacy (Rodillo et al., 1989). The IMT and Pimax measurements in this pre-experimental, pilot study were both performed at residual volume (RV), implying that measurement and training were of the same motor unit. Therefore, true strengthening of inspiratory muscles may have occurred and the effects seen may not solely be due to a learning effect. This could also explain why SNIP values did not improve significantly, as measurements for SNIP are taken at FRC. The observation that Pimax continued to improve in this pre-experimental study after the first two weeks of training, albeit at a slower rate, suggests that besides the learning effect a true inspiratory muscle training effect also may occur with IMT. Longer RCT might therefore indicate if IMT can have a training effect and if improved pulmonary function outcomes are merely due to a learning effect. A previous experimental, long-term IMT study (24 months) showed that IMT improved inspiratory muscle strength and endurance (Pimax and 12sMVV), justifying the use of this intervention in children and adolescents with DMD and SMA (Koessler et al., 2001).

Threshold load training, as was used with this study, provides both pressure and flow load as a training stimulus. This explains the observed improvement in both inspiratory muscle strength and inspiratory flow. Peak inspiratory flow (PIF) indicates the ability of the inspiratory muscles to rapidly contract and overcome the inherent elastance and resistance of the respiratory system, which in NMD becomes more difficult as restrictive lung disease develops with age (Gozal, 2000; Ioss et al., 2004; Yang & Finkel, 2010; Birnkrant et al., 2018). The S-index is also a global indicator of inspiratory muscle strength measured by the Powerbreathe device[®] and is derived from the PIF, which explains their similar p-values outlined in Table 5.3. Even though all participants presented with restrictive lung disease of varying degrees, a significant improvement in the ability to create airflow in taking a deep breath was observed. This improved ability could potentially minimise dyspnoea, decrease work of breathing, maintain lung and thoracic compliance and improve cough ability in children with NMD.

Evidence for IMT in patients with NMD is contradictory and therefore remains controversial (Vilozni et al., 1994; Koessler et al., 2001; Eagle, 2002; Avendaño & Güell, 2003; Finder et al., 2004).

The different outcomes of IMT studies in NMD could be attributed to methodological differences, duration, specificity and intensity of training as well as the nature and severity of the condition (Eagle, 2002; Aboussouan, 2009). Although it has been suggested that slowly progressive disease, with lung volume preservation, might show more benefit from IMT (Wanke et al., 1994; Winkler et al., 2000; Koessler et al., 2001; Eagle, 2002), this study did not find a significant association between indicators of disease progression such as baseline VC, FVC, FEV₁ and PEF and change in Pimax (Δ Pimax). The lack of association might be attributed to the small sample size (n=8) and being underpowered to determine any associations.

5.11.3.3 Cough ability (PECF)

Pulmonary function such as VC and maximum inspiratory capacity (MIC) are related to assisted and unassisted PECF, i.e. the patient's ability to expel secretions, the higher the inspiratory capacity the greater the PECF (Dohna-Schwake et al., 2006; Toussaint et al., 2018; Castrillo et al., 2019). In the study by Gauld & Boynton (2005), children with DMD could perform spirometry easier than cough flow manoeuvres possibly because PECF requires glottis closure (Bianchi & Baiardi, 2008). Decreased oral control and poor glottis closure are commonly found in patients with NMD, and in particular in SMA (Wang et al., 2007; Bianchi & Baiardi, 2008).

Although this pre-experimental, pilot study found a significant improvement in inspiratory muscle strength (Pimax, S-index), PECF did not change significantly despite a statistical tendency towards improvement (p=0.05). The lack of clear PECF improvement was unexpected as an increased inspiratory lung volume, due to improved inspiratory muscle strength, should translate into an improved cough ability (PECF) as outlined in Chapter 1. These findings do however correlate with a RCT in adults with NMD by Aslan et al. (2013) which reported statistically significant improvement in Pimax after eight weeks of IMT (p=0.002) compared to sham, but no change in PECF (p=0.07). A possible explanation for this phenomenon could be that PECF requires the use of different muscle groups, glottis closure and good oral control (Marques et al., 2014), whilst PEF does not require glottis closure. Oral control might have influenced the PECF readings in this study, however, participants appeared to have good oral control and acceptable bulbar function.

Cough ability (PECF) is an indicator of the patient's disease progression, ability to clear secretions and the risk for developing respiratory complications (Kang & Bach, 2000; Bianchi & Baiardi, 2008; Gauld, 2009).

This pre-experimental study had similar baseline PEF values as previously reported for children and adults with NMD (Chatwin et al., 2003) and normative values for children Bianchi & Baiardi (2008). Post intervention, the mean ($\pm$ SD) PEF in this pre-experimental study was 214.38 ($\pm$ 102.42) while PEF was 179.25 ($\pm$ 86.61) L/min, similar to other studies on normative values in children (Bianchi & Baiardi, 2008). Similar to the study by Bianchi & Baiardi (2008), male participants in this pre-experimental study also had a tendency of higher PEF values than females, but this association was not significant and the sample size was small. Although this study's values for PEF were within the normal ranges for children (Bianchi & Baiardi, 2008; Gogou et al., 2017), it is of interest to note that the mean PEF throughout the study period even after IMT, fell below the recommended 270L/min threshold value recommended for adult patients. This tendency could indicate the possible need for cough augmentation and potentially reduced resilience to respiratory infections (Bach et al., 1997; Gauld & Boynton, 2005; Hull et al., 2012; Farrero et al., 2013). For children under 12 years of age, predictor PEF threshold values (equivalent age-adjusted) indicative of the need for cough augmentation are unknown, as normative PEF values for children with NMD are limited, and might be lower than that of adults (Dohna-Schwake et al., 2006; Panitch, 2006; Hull et al., 2012). Children only reach adult PEF values of 400L/min and higher at 12 to 13 years of age (Bach & Saporito, 1996; Bianchi & Baiardi, 2008; Chiang et al., 2018). The participants in this study presented with a median age of 12.2, suggesting that some might not have reached adult PEF values due to pulmonary immaturity. Another consideration is the coordinated effort needed to perform a cough and this could also lead to lower values. In addition, the small sample size and short duration of IMT might not translate into a change in cough ability and the majority of participants were non-ambulant. This warrants further investigation with clinical trials such as RCT.

5.11.4 Functional ability (level of ambulation and upper limb function)

Most participants were diagnosed with either DMD or SMA (n=6) and presented with decreased general function, with associated complications, as expected from patients with NMD in this age range. Half of the participants in this study were adolescents and had been non-ambulant for several years, as evident from the Vignos scale, with the majority (n=6) scoring nine out of ten. The Brooke and Vignos scores in this study correlated well with another study among children and adults (n=179) with a variety of muscular dystrophies (DMD, Becker muscular dystrophy (BMD), Limb-girdle muscular dystrophy (LGMD), facio-scapulo-humeral muscular dystrophy (FSHD)); Brooke and Vignos scores for the total sample were mean ($\pm$ SD) of 2.7 ($\pm$ 1.7) and 5.2 ($\pm$ 3.4) respectively (Lue et al., 2009).

For specific conditions, the mean ($\pm$ SD) Brooke scores were 3.2($\pm$ 1.9) for DMD, 1.9($\pm$ 1.5) for BMD, 2.3 ($\pm$ 0.8) for FSHD and 2.3($\pm$ 1.3) for LGMD; while Vignos was reported as 7.1($\pm$ 3.1) for DMD, 3.5($\pm$ 2.7) for BMD, 2.2($\pm$ 1.3) for FSHD and 3.9 ($\pm$ 2.7) for LGMD. Although general exercise programmes (skeletal training) in NMD might have physiological advantages such as improved muscle strength, evidence supporting translation into functional improvement remains limited (Eagle, 2002; Voet et al., 2019; Wenninger et al., 2019).

At baseline participants presented with moderate upper limb function (median 3/6) on the Brooke scale, but good combined upper limb function and coordination (mean and median MFM score of 26/30). This Brooke score is similar to a sample of boys with DMD who presented with a mean ($\pm$ SD) score of 4.2 ($\pm$ 1.2)(Meier et al., 2017).The high upper limb function and coordination score were unexpected, as upper limb weakness in DMD already starts when patients are still ambulant (Mazzone et al., 2012; Ricotti et al., 2019). In addition, progressive weakness and loss of upper limb function in DMD usually present in a proximal to the distal manner and a few years after the loss of ambulation, function against gravity is limited to the forearms and hands (Mazzone et al., 2012). The Brooke scale is acceptable for grading arm function in DMD (Janssen et al., 2016), but might not be as specific for other slowly progressing muscular dystrophies (Lue et al., 2009).

Most of the participants in this study presented with a Brooke scale of three at baseline (n=6), which indicates a transition in upper limb function with loss of the ability to reach overhead. A Brooke score of two or three indicates a level where pulmonary functional decline becomes apparent, especially once ambulation is lost (Mayer et al., 2017; Birnkrant et al., 2018), which was evident from these results. A significant correlation has previously been shown between upper limb function, measured using the Brooke scale, and both FEV₁ (p<0.001) and FVC % predicted (p<0.001) (Tangsrud et al., 2001). An association between upper limb activities and respiratory muscle function has been reported among adults with chronic obstructive pulmonary disease, indicating the synchrony between these muscle groups, as respiratory muscles also assist with postural control and thoracic stabilisation (Costa, Cancelliero, Ike, Laranjeira, Pantoni & Borghi-Silva, 2011). Although upper limb function on the Brooke scale did not show statistically significant improvement in this study, nor was there any association with change in spirometry or Pimax, there was a tendency towards a lower Brooke score (indicating improved function) post-intervention. This finding is contrary to the suggestion that upper limb function based on the Brooke scale, Egen classification and elbow flexion and grip strength is only responsive to change over an extended duration (one to two years) (Birnkrant et al., 2018), but this requires confirmation in larger studies.

The slight change in Brooke score post-intervention correlated well with the unexpected significant improvement in MFM ($p=0.03$), indicating improved upper limb function and coordination. Improvements in diaphragmatic strength (Pimax, S-index and PIF), cognitive awareness of posture, chest mobility and breathing patterns with IMT may have translated into better proximal stability (Costa et al., 2011; Mary et al., 2018; Corten & Morrow, 2020) and hence, improved upper limb function, but this warrants further research with RCT. Improved upper limb function and coordination might also be transferrable to activities of daily living (ADL), academic performance and a sense of achievement. However, the clinical relevance of a change of one point on the MFM score is unclear, especially considering the baseline scores were already high, and additional research is therefore needed.

There was no change in lower limb function (Vignos scale) following the intervention, which was not surprising, given the short duration of IMT (6 weeks) as well as the fact that most participants were already non-ambulant. In addition, progressive muscle weakness, fatigue, musculoskeletal deformities (including scoliosis), fractures, pain and frequent falls can add to decreased activity levels and affect the patient's HRQoL (Goemans & Buyse, 2014; van Ruiten et al., 2014; Janssen et al., 2016; Vry et al., 2016; Mary et al., 2018).

5.11.5 Health-related quality of life

Translating a patient's experience of their condition into a quantifiable outcome such as HRQoL (Bastiaansen et al., 2004) may assist caregivers and healthcare professionals to evaluate their clinical care strategies and guide decision making, therefore both child and proxy (caregiver and/or family) ratings add value (Eiser & Morse, 2001; Finder et al., 2004; Hull et al., 2012; Farrero et al., 2013). Due to the restrictive pulmonary conditions seen in NMD, patients often present with dyspnoea, reduced exercise tolerance, and chronic respiratory failure (Boentert et al., 2017) that can lead to decreased levels of activity and poor quality of life (Piper & Moran, 2006). In a vicious cycle, decreased function and a sedentary lifestyle further contributes to decreased ventilation and predisposes to respiratory complications (Schechter, 2007; Wang et al., 2007). Therapeutic interventions primarily targeting pulmonary function therefore ultimately aim to improve functional ability and HRQoL in patients with NMD (Eagle, 2002). According to the researchers, no published evidence of HRQoL (based on PedsQL) of children with NMD in SA is available.

Healthcare professionals might underestimate HRQoL in patients with NMD, especially those that are ventilator-dependent, but it has been shown that despite severe physical disability, children and adolescents with NMD tend to report an acceptable level of quality of life (Finder et al., 2004; Hull et al., 2012). Children view their HRQoL differently compared to their caregivers, as they might not always appreciate cost implications or change in physical parameters as a change in the quality of life (Eiser & Morse, 2001), for example in this pre-experimental, pilot study significant improvement in Pimax might not have much meaning to a child, but being able to sing louder in the choir is relevant to their ADL (Table 5.7). The cross-informant variance seen in parent/child intercorrelations supports assessing both the perspective of the child and parent/caregiver for HRQoL (Varni et al., 2002; Iannaccone et al., 2009; Hull et al., 2012), but age-appropriate self-report is strongly recommended (Hull et al., 2012; McDonald et al., 2013).

This study showed an improvement in the child reported PedsQL total scores, which although not statistically significant ($p=0.15$), did show a moderate effect size (0.52). The baseline PedsQL values for total and Physical domain scores were however lower than those reported among an ambulant cohort of boys with DMD (5-13 years) (Messina et al., 2016). The Physical domain mean values stayed the same pre-and post-intervention, which is expected as the duration of intervention was short, but participants did not view themselves as physically regressing during this time either, which may be clinically relevant. The change in the Psychosocial domain (social, emotional and school performance) was positive with a mean ($\pm$ SD) difference of 12.29 ($\pm$ 18.36). This did not reach statistical significance, however, the effect size was large (0.81). The lack of statistically significant improvement in PedsQL likely relates to the small sample size of this pre-experimental study, which was not sufficiently powered to detect this change and larger RCT are recommended. The findings could also relate to the short duration of the intervention (6 weeks), which may not have been sufficient to show meaningful changes in quality of life. There may also have been a misunderstanding of some of the concepts contained in the PedsQL, an area that requires further investigation. Mid- and long-term studies are therefore recommended to determine the impact of IMT on these patients' HRQoL, especially the Psychosocial domain, and to validate these instruments within the SA context.

Many studies tend to focus on physical and functional ability, but Eiser & Morse (2001) and Finkel et al. (2018) commented that in patients with neurological conditions, families might feel that emotional and social functioning is as important as physical or cognitive functioning. Although this pre-experimental, pilot study used both child and proxy versions (PedsQL) the researchers have their reservations regarding the validity and reliability of the proxy results.

Reasons include questionnaires from parents/caregivers not being returned within two weeks post-intervention, in some cases possibly being completed by different parents/caregivers pre and post-intervention, and alteration of the form and questions by one caregiver, rendering these results invalid.

Although this was not designed as a qualitative study, insights from the open-text feedback provided important individual perspectives from participants and their therapists, acceptability of IMT in this patient cohort and assisted with the planning of the RCT. All the children reported positive experiences with IMT, with perceived “better breathing” and other benefits such as improved voice projection and the ability to sing louder were also reported (Table 5.7). This subjective experience by participants is supported by a previous report, which showed that the use of other inspiratory augmentation techniques (such as glossopharyngeal breathing) was associated with improved voice projection (Toussaint et al., 2018).

5.11.6 Participant adherence and satisfaction

Although non-adherence have been reported with the implementation of IMT programmes (Eagle, 2002), in this pre-experimental, pilot study participants were very motivated throughout the six-week intervention period and adhered well to the intervention programme. A high level of agreement between the self-reported number of training sessions (training diaries) and electronically recorded (Powerbreathe[®]) training sessions were found. This could be attributed to the extremely high reported participant satisfaction with IMT (MDN: 9/10), participant motivation levels as well as the positive attitude of clinicians, parents and caregivers involved.

5.12 Limitations of study and recommendations for future research

5.12.1 Limitations

Although this study suggests possible advantages of IMT in patients with NMD, this was a pre-experimental, pilot study with small sample size, a variety of NMD with varying ages and included participants from only one province in SA, without a control group. The convenience sample selection may have introduced selection bias and the lack of a control group precludes conclusions being made as to the direct association between IMT and the reported outcomes. Therefore, external validity is limited and larger RCT are needed to determine the safety, efficacy and acceptability of IMT in children and adolescents with NMD in SA. It is also a possibility that the improvement in inspiratory muscle strength such as Pimax observed in this study could have been due to a learning effect, especially because the improvement occurred mostly in the first two weeks of intervention.

The potential impact of the learning effect could however not be determined based on this study design, and RCT is also warranted to elucidate this.

The qualitative analysis was limited because this study was not primarily designed as a qualitative study. An attempt was made to consider individual experience through open-text responses, as this was a pilot study and the researchers wanted to determine the practicality and acceptability of IMT in this patient cohort. Future qualitative studies are recommended to explore participants' perceptions of interventions such as IMT.

5.12.2 Recommendations for future research

Inspiratory muscle training may improve inspiratory muscle strength (Pimax, SNIP) in neurological conditions such as NMD, but the clinical effects are unknown and this warrants further clinical trials (McCool & Rosen, 2006; Hull et al., 2012; Pollock, Rafferty, Moxham & Kalra, 2013). Furthermore, owing to controversy in the literature, and potential safety concerns of IMT especially in patients with dystrophinopathies (Chapter 1) larger, longer-term RCT and qualitative studies are recommended to confirm the safety, acceptability (patient experience) and efficacy of IMT. Larger sample sizes are also needed to determine if any association exists between anthropometrics and pulmonary function in children with NMD in SA.

This pre-experimental, pilot study showed an unexpected improvement in upper limb function and coordination post-IMT intervention. This correlates with the notion that functional measurements are recommended to track changes over time and can even be used to predict upcoming changes, in order to be proactive when planning management strategies (Finder et al., 2004; Birnkrant et al., 2018; Finkel et al., 2018). There is currently limited research available regarding the correlation between upper limb function and IMT. Future studies should include functional measures and descriptors of disease progression, as was used in this study, as well as investigate the association between pulmonary and motor function as alluded to in other paediatric studies and the possible effect it might have on HRQoL (Mayer et al., 2017; Ricotti et al., 2019; Corten & Morrow, 2020).

As seen from this pre-experimental, pilot study, although not statistically significant, there was an improvement in self-reported HRQoL. Due to the small numbers and concerns about the validity of proxy questionnaires in this study, responses could not be analysed.

However, HRQoL is recommended as an outcome measure for future research to determine the effect of long term IMT. Obtaining the perspectives of both patients and their caregivers should be attempted in future studies and therefore the child and proxy PedsQL questionnaires were included in the RCT.

5.12.3 Lessons learned from the pre-experimental, pilot study

In preparation and planning for the multi-centre randomised cross-over trial (Chapter 6), the pre-experimental, pilot study provided valuable lessons and preliminary data.

To simplify the monitoring and data collection procedure, one of the clinicians at the school designed an electronic daily record sheet that could be pasted into the training diaries of participants. This adjustment decreased the burden of recording on the participants and/or parents/caregivers while providing information on progress, monitored levels of perceived exertion and training adherence as well. These record sheets were therefore implemented for the cross-over study also. The pre-experimental, pilot study provided the researcher with the opportunity to determine the time needed for assessment, the suitability of the objective outcome measures and IMT protocol in this particular patient cohort and SA research context and if the training was well tolerated. Minor changes to the data collection forms (recruitment and follow-up assessment) were made before the commencement of the cross-over trial. Participant and clinician feedback also provided valuable information about the suitability, acceptability and levels of exertion to consider when planning future clinical trials.

To determine if IMT can bring a true change (training effect) in inspiratory muscle strength instead of only a learning effect and be sufficient to counterbalance the natural decline of pulmonary function in patients with NMD, more mid and long-term multi-centre trials are needed. In addition, the benefits of IMT may only last for a short while once training is ceased; therefore follow-up and monitoring of patients over a longer period is recommended (Eagle, 2002; Rietberg et al., 2017). For these reasons, the cross-over study participants performed IMT for three months and after training ceased, they were followed up for another three months while monitoring their pulmonary function, inspiratory muscle strength and cough ability.

5.13 Conclusion

This was a pre-experimental, pilot study that showed short term IMT with a threshold tapered flow handheld device was safe, viable, acceptable, with good levels of participant adherence and associated with improved clinical outcomes among children and adolescents with NMD in SA. Even though the child-reported HRQoL did not improve significantly, the qualitative responses from participants suggest that the effects of IMT might translate into improved function and quality of life which could be assessed over a longer period of time.

The proposed objective outcome measures and IMT protocol were shown suitable for this SA patient cohort. Larger, longer-term randomised controlled trials are however recommended to determine the safety and efficacy of IMT in children with NMD and therefore the pilot study could proceed to a cross-over RCT.

Chapter 6: LET'S TRAIN: TAKE A DEEP BREATH!

Inspiratory muscle training cross-over randomised controlled trial

6.1 Introduction

Standard of medical practice is usually established based on clinical trial data, however well designed, adequately powered clinical trials in children with neuromuscular disease (NMD) are extremely limited (McCool & Rosen, 2006; Schechter, 2007; Wang et al., 2007; Auger et al., 2017). Both the systematic review (Chapter 3) and pre-experimental studies (Chapter 5) identified the need to establish the safety and efficacy of inspiratory muscle training (IMT) in children with NMD by implementing a sufficiently powered randomised controlled trial (RCT).

The pre-experimental, pilot study (Chapter 5: 5.13) suggested that IMT using an intensity of 30% Pimax was safe and feasible in children with NMD, and may positively impact inspiratory muscle strength. This chapter reports on the randomised controlled cross-over study designed to determine the effect of a three-month IMT programme, as an adjunct treatment strategy, on clinical outcomes and HRQoL in SA children (5-18 years) with NMD, presenting with respiratory muscle weakness.

The specific objectives are outlined in Chapter 1 (1.3) and the methodology was similar to the pre-experimental, pilot study in Chapter 5 (5.3).

6.2 Sample size

To account for drop-out, 27 participants (14 from Gauteng and 13 from Western Cape) were recruited over two years. A final sample of 23 was sufficiently powered to detect a mean decrease in the primary outcome measure of two fewer respiratory tract infections requiring antibiotics (SD:2) during the intervention period compared to no IMT (control), over three months (4.2.4.2).

6.3 Eligibility criteria

Inclusion and exclusion criteria were similar to those used for the pre-experimental, pilot study and are outlined in Chapter 4 (4.2.3). Despite the inclusion criteria allowing children from age five to participate, the lowest age that the Powerbreathe K3[®] device can be set for is seven. All 23 participants included in the cross-over trial were almost seven years or older.

6.4 Recruitment, allocation and follow-up

Recruitment was performed as outlined in Chapter 4 (4.2.5.2) with two primary sites namely Doctor George Mukhari Academic Hospital (DGMAH) in Gauteng and Red Cross War Memorial Children's Hospital (RCWMCH) in the Western Cape, over two years (2016-2018). Names of other institutions where patients were recruited were omitted for confidentiality but included schools for children with special needs and referrals from other parents that were already involved in the cross-over trial. Eligible children and their families were approached to participate (Appendix Cvii) informed consent and assent (if applicable) were obtained and participants were randomly allocated to Group 1 (ce) which received no training for the first three months (control period), followed by IMT for three months (experimental), or Group 2 (ec) where participants started with IMT (experimental) and the non-intervention control period followed thereafter (Figure 6.1) using a randomised opaque envelope system (Chapter 4: 4.4.2).

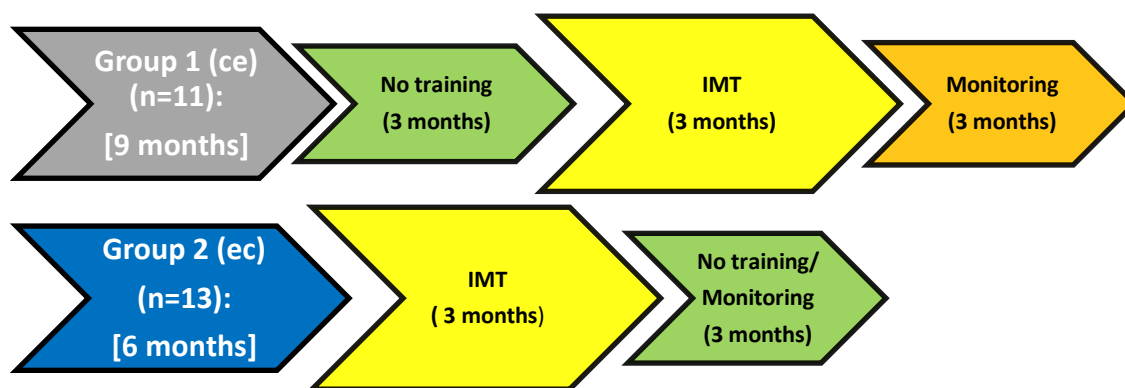


Figure 6.1: Group allocation for the cross-over randomised controlled trial (N=24).

The outcome measures (general and pulmonary function; health-related quality of life (HRQoL)) and IMT protocol used for the RCT was similar to that of the pre-experimental, pilot study (4.3 ;4.4.3) as it was found safe, viable and acceptable among children with NMD in SA. However, in order to further assess the safety and efficacy of IMT, participants trained for 12 weeks (3 months) during the RCT.

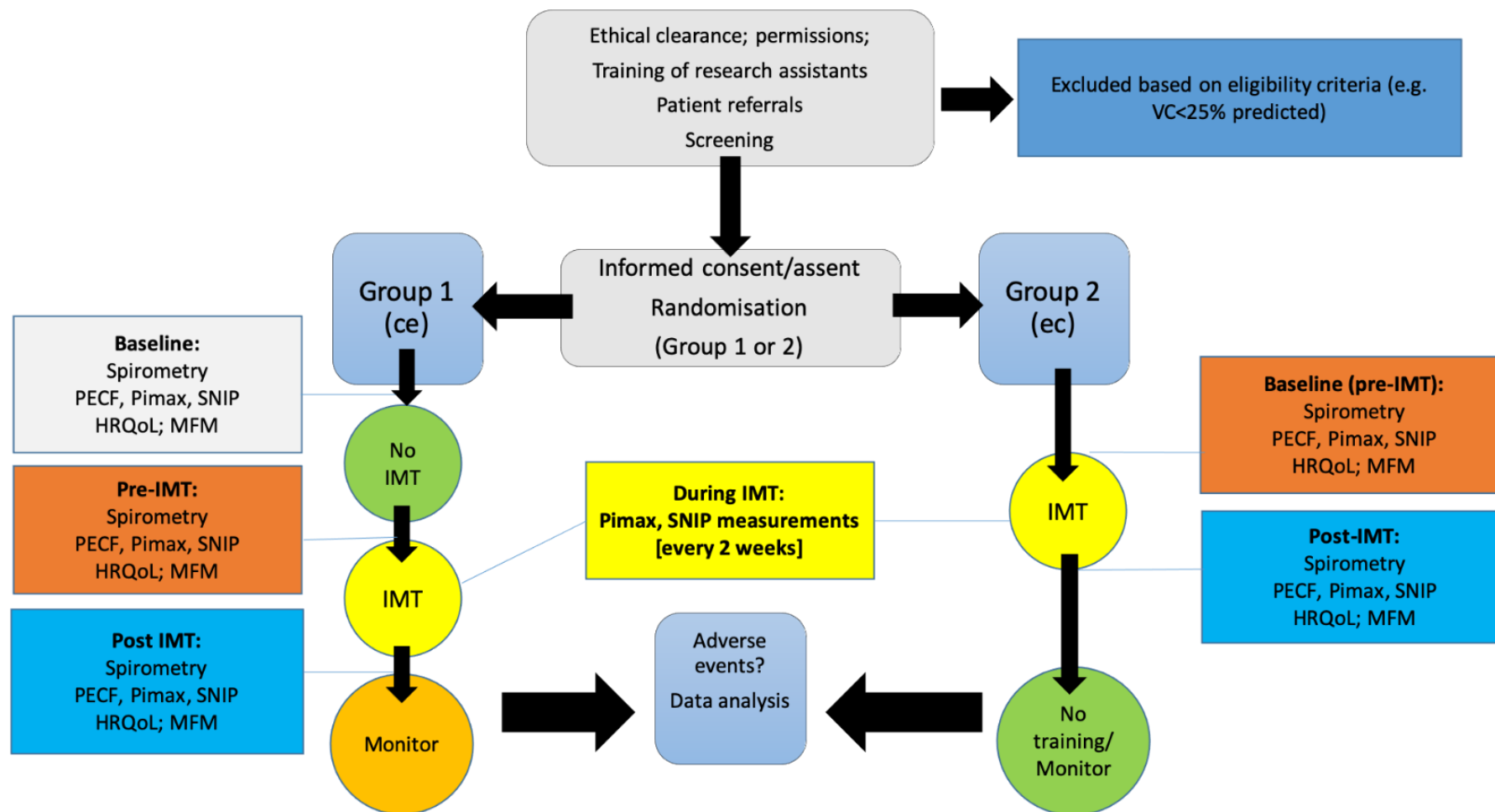


Figure 6.2: Summary of inspiratory muscle training cross-over randomised controlled trial methodology.

Baseline and follow-up assessments were performed (Figure 6.2) by the researcher (AH) and research assistants (LC, EL) either at the hospital (DGMAH; RCWMCH), school or at participants' homes in order to reduce the burden on families. If assessed at the hospital, participants were reimbursed for transport.

6.5 Data analysis

Descriptive statistics were expressed, for continuous variables, as mean $\pm$ standard deviation (SD) or median, interquartile ranges (IQR), and frequency distributions (%) where appropriate. To determine if both groups (ce; ec) were similar at recruitment, either a student t-test for independent samples or a Mann-Whitney U test was performed depending on normality. In Figures 6.3 to 6.4 the clinical outcome measurement time points are illustrated according to group allocation (Group 1 (ce) and Group 2 (ec)).

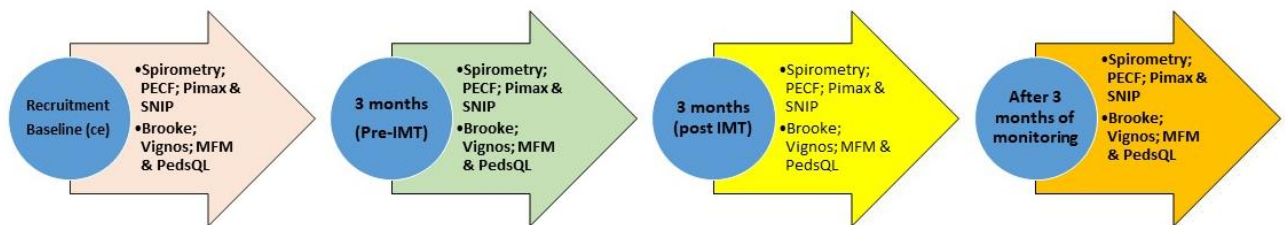


Figure 6. 3: Clinical assessments during the study period (Group 1: ce).

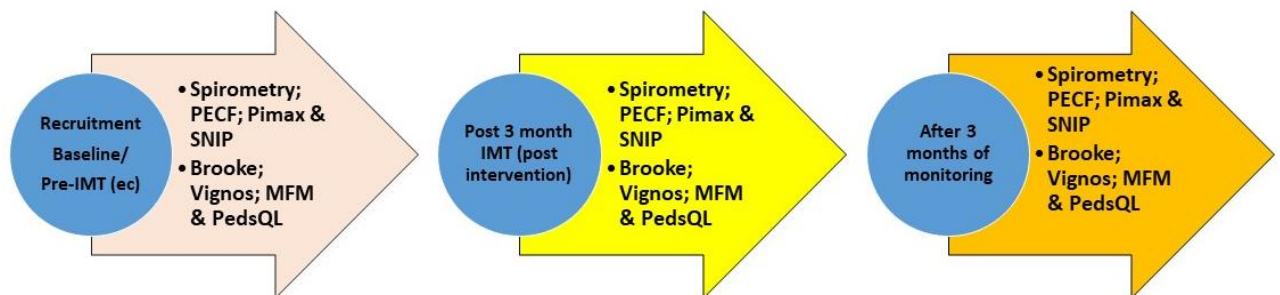


Figure 6.4: Clinical assessment during the study period (Group 2: ec).

Depending on the distribution of the outcome measure (e.g. Pimax, PedsQL), significant differences in continuous variables between IMT (experimental) and no IMT (control) periods (sub-groups) were tested using the student t-test for independent variables or the non-parametric Mann-Whitney U tests.

The dependent student t-test and non-parametric Wilcoxon matched pairs tests were used to test within group changes (comparing pre-and post IMT variables) and change over time (during the IMT period) was analysed using repeated measures analysis of variance (ANOVA). Associations between variables (e.g. pulmonary function and upper limb function) were calculated using either Chi-square (categorical variables), Pearson's correlation or Spearman's rank tests (continuous variables) depending on the data type and distribution (Chapter 4: 4.4.5).

6.6 Results

6.6.1 Bio-demographic description of participants

Participants were recruited during 2017 and 2018 from the two provinces (Gauteng (n=12) and Western Cape (n=11). Recruitment for this cross-over RCT was based on the CONSORT framework (Figure 6.5).

CONSORT Flow Diagram

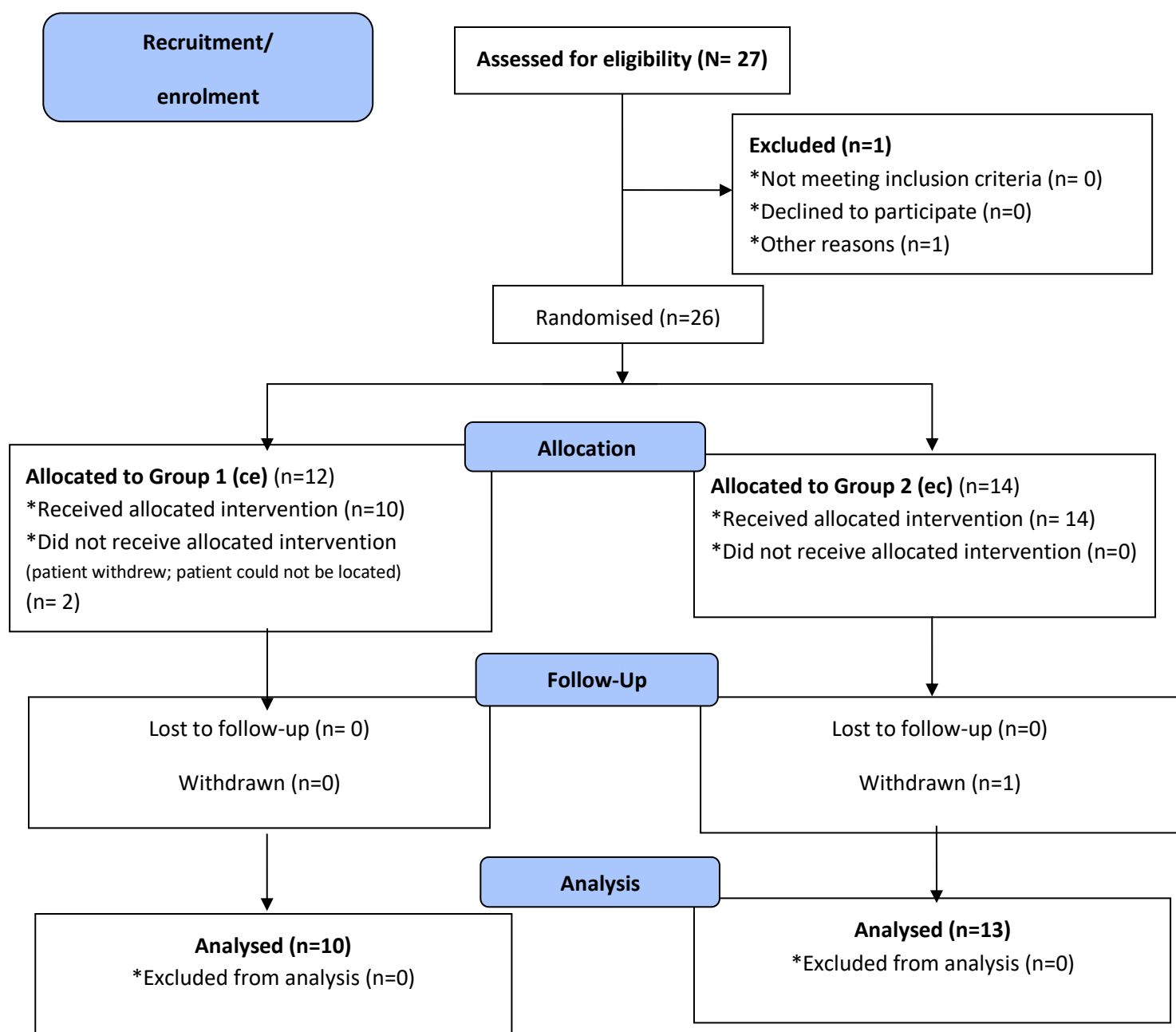


Figure 6.5: Patient recruitment and data collection process (CONSORT framework).

One eligible boy with Duchenne muscular dystrophy (DMD) was excluded from participation, before randomisation (4.2.3.2; Figure 6.5) as he could not perform a coordinated inspiratory effort against resistance, despite numerous demonstrations and explanations in his home language. Twelve children were randomly allocated to Group 1 (ce) which started with IMT post recruitment and 14 allocated to Group 2 (ec) which only started training after three months (Figure 6.2; Figure 6.5; Table 6.1). At recruitment, all 26 participants were clinically stable³⁹. One participant in Group 1 (ce) withdrew from the study at the start of the training period (IMT), due to an acute respiratory infection and fatigue and another patient that was recruited could not be found again for follow-up appointments despite numerous attempts. Another 15-year-old boy with DMD (Group 2: ec) withdrew after four weeks of intervention; he refused to continue with IMT because he did not like performing the exercises. There was no other loss to follow up in either group (ce; ec) (Figure 6.5). One participant did not train due to illness during the first two weeks of IMT nor the last four weeks of the intervention period because of exams, school holidays and thereafter he lost interest. This data were still included in the intention to treat analysis.

The final sample, therefore, consisted of 23 participants with a median (IQR) age of 12.33 (10.03-14.17) years, and most were males (n=20). The majority were non-ambulant (n=14), of which two could mobilise very short distances with support, but mostly used a wheelchair. Participants presented with overall good upper limb function (Table 6.1) and the majority had a confirmed diagnosis of DMD (n=13) and spinal muscular atrophy (SMA) (n=6). At recruitment, one participant with a tracheostomy received mechanical ventilation support during the day and three participants used non-invasive ventilatory support at night (Bi-level positive airway pressure (BiPAP)), whilst another participant commenced with nocturnal BiPAP during the course of the study (after IMT intervention). The remaining 18 participants did not receive any ventilatory support for the study period. All 23 participants were IMT naïve, having never used respiratory muscle training prior to recruitment.

³⁹ No use of antibiotics (for respiratory tract infection) within preceding month of intervention, resting arterial O₂ saturation measured with pulse oximetry of <90%. (M Chatwin et al., 2003).

Table 6. 1: Bio-demographic data and functional ability of participants (n=23).

Participant (allocation)	Sex (M/F)	Age (years)	NMD type	Weight for age (Z-scores)	BMI (Z-scores)	Mobility	Baseline (Brooke scale /6)	Baseline (Vignos scale /10)
1 (ce)	m	11.5	DMD	0.16	-0.76	A	1	3
2 (ec)	m	13.1	DMD	-1.92	-4.62	A	1	4
3 (ce)	m	13.3	DMD	-4.05	-10.27	NA	2	7
4 (ec)	m	15.9	DMD	-6.44	-15.45	NA	2	9
5 (ce)	m	15.9	DMD	-6.36	-16.53	NA	3	9
6 (ec)	m	8.7	DMD	0.65	-1.04	A	1	3
7 (ec)	m	12.4	CM	-1.45	-3.7	NA	4	9
8 (ec)	m	10.9	MD ⁴⁰	-0.31	-0.6	A	1	2
9 (ce)	m	12.9	MD	0.16	0.0	A	1	3
10 (ce)	m	8.3	DMD	0.23	-4.2	A	1	2
11 (ce)	m	11.1	DMD	0.58	-0.1	NA	2	9
12 (ec)	m	12.3	DMD	-3.74	-1.8	A	1	2
13 (ce)	f	14.3	SMA II	-4.82	-5.37	NA	3	9
14 (ce)	m	11.1	DMD	1.44	0.56	NA	4	9
15 (ec)	m	10.1	DMD	0.70	-1.13	NA	1	8
16 (ec)	m	8.8	DMD	-0.73	-6.57	A	1	2
17 (ec)	f	14.3	SMA III	-3.90	-5.66	NA	2	9
18 (ec)	m	13.3	SMA III	-0.49	-1.37	NA	3	9
19 (ce)	f	6.7	SMA II	0.28	-6.24	NA	3	9
20 (ce)	m	6.1	DMD	-0.35	0.76	A	1	2
21 (ec)	m	14.2	SMA II	-4.61	-12.88	NA	6	9
22 (ec)	m	10.0	SMA II	-1.34	-7.62	NA	2	9
23 (ec)	m	16.4	CM	-4.50	-6.33	NA	3	9

A=Ambulant; BMI=body mass index; ce=control-experimental; CM=congenital myopathy; DMD=Duchenne muscular dystrophy; ec=experimental-control; f=female; m=male; MD=muscular dystrophy; NA=Non-ambulant; NMD=neuromuscular disease/disorder;⁴¹ SMA=spinal muscular atrophy.

Seven participants reported co-morbidities such as gastro-oesophageal reflux (n=1), cardiac pathology (n=2) and other associated conditions such as learning disorders (e.g. autism spectrum disorder and/or attention deficit hyperactivity disorder (ADHD)) (n=4). A cardiologist confirmed that it would be safe for the two participants presenting with cardiac pathology to continue with IMT as they were not presenting with cardiac failure at the time. Despite associated behavioural and cognitive conditions in some participants, all could follow instructions and perform IMT adequately. In addition, eight participants presented with spinal deformities (primarily scoliosis), however only two had a recently documented Cobb angle. Seven participants reported undergoing one surgical procedure and two participants had two previous surgical procedures for scoliosis correction (spinal stabilisation) (n=3), tendon Achilles releases (n=2), percutaneous endoscopic gastrostomy (PEG) tube insertion (n=1), and one participant each underwent a muscle biopsy and tracheostomy. Other surgical interventions were minor and not related to NMD.

⁴⁰ Could not be confirmed as DMD

⁴¹ After the preliminary study (Chapter 5) it was decided to classify mobility as either ambulant or non-ambulant

Besides vitamins and supplements such as calcium and vitamin D, at baseline ten patients were taking gluco-corticoid steroids (mostly prednisone) daily as part of their chronic medication regime, five were taking medications to support cardiac function (e.g. Enalapril) and six did not use any chronic medication at the time of recruitment. Two participants started taking corticosteroids during the intervention (IMT) period.

Baseline bio-demographic data including weight (absolute values), weight for age (WFA) and body mass index (BMI) (absolute and Z-scores) were not normally distributed, and are therefore presented as median (IQR) values. Although normally distributed, age was also presented as median (IQR), providing the opportunity to compare results to the pre-experimental, pilot and other smaller studies (Table 6.2).

Bio-demographic data of participants (N=23) at baseline assessment (recruitment) for recruitment sites (Gauteng/DGMAH or Western Cape/RCWMCH) and allocated groups (Group 1 (ce); Group 2 (ec)) were well matched for variables such as sex, age, weight and BMI. Although there were significant differences between Gauteng and Western Cape recruitment sites in terms of participants' NMD type (diagnoses) ($p=0.04$) and pulmonary function variables of vital capacity (VC), peak expiratory cough flow (PECF) and inspiratory muscle strength (Pimax) ($p=0.03$), there were no differences in these variables between participant allocation groups (ec and ce) (Table 6.2).

Table 6.2: Bio-demographic and pulmonary function baseline data at recruitment based on recruitment site and group allocation (n=23).

Variable	All participants (N=23)	DGMAH (Gauteng) (n=12)	RCWMCH (Western Cape) (n=11)	Study site (p-value)	Group 1 (ce) (n=10)	Group 2 (ec) (n=13)	Allocation (p-value)
Bio-demographic data							
Age (years)#	12.33 (10.03-14.17)	12.38 (11.00-13.17)	11.08 (8.75-14.30)	0.79	11.29 (8.25-13.25)	12.42 (10.08-14.17)	0.48
Sex (male; female)	20 3	12 0	8 3	0.19*	8 2	12 1	0.81*
Type of NMD							
DMD	13	9	4	0.04	7	6	0.44
SMA	6	0	6		2	4	
CM	2	1	1		0	2	
MD	2	2	0		1	1	
Weight (absolute value) (kg)	30.00 (26.00-37.1)	32.00 (27.38-36.63)	27.50 (25.00-37.10)	0.57	27.50 (25.00-41.00)	31.00 (26.00-33.75)	0.93
WFA (Z-score)#	-0.73 (-4.05 to 0.23)	-0.88 (-3.89 to 0.19)	-0.73 (-4.50 to 0.28)	0.96	0.16 (-4.05 to 0.28)	-1.45 (-3.90 to -0.49)	0.28
BMI (kg/m²) (absolute value)	12.70 (10.79-16.03)	13.80 (11.03-16.04)	12.06 (10.79-15.99)	0.74	14.04 (10.79-17.07)	12.70 (10.96-14.86)	0.41
BMI (Z-score)#	-4.20 (-6.57 to -0.76)	-2.78 (-7.45 to -0.67)	-5.67 (-6.57 to -1.13)	0.65	-2.48 (-6.24 to 0.04)	-4.62 (-6.57 to -1.37)	0.26

Pulmonary function							
VC (L) (absolute value) (n=19)	1.38 (±0.37)	1.52 (±0.33) (n=12)	1.15 (±0.32) (n=7)	0.03	1.53 (±0.26)	1.28 (±0.41)	0.16
FVC (L) (absolute value)	1.59 (±0.53)	1.76 (±0.50)	1.41 (±0.52)	0.11	1.65 (±0.48)	1.54 (±0.58)	0.63
FVC Z-score	-3.47 (±2.40)	-3.39 (±1.49)	-3.56 (±3.19)	0.87	-3.11 (±1.72)	-3.75 (±2.85)	0.54
FEV₁ (L/s) (absolute value)	1.38 (±0.40)	1.50 (±0.33)	1.26 (±0.44)	0.14	1.44 (±0.33)	1.34 (±0.45)	0.57
FEV₁ Z-score	-3.34 (±1.55)	-3.10 (±1.21)	-3.59 (±1.88)	0.46	-2.77 (±1.49)	-3.78 (±1.50)	0.12
PEF (L/min)	189.13 (±72.80)	214 (±74.65)	162 (±63.07)	0.09	197.10 (±51.00)	183.00 (±87.59)	0.66
PECF (L/min) (n=22)	198.86 (±98.83)	240 (±100.81)	149.50 (±73.50)(n=10)	0.03	195.56 (±106.55)	201.15 (±97.51)	0.90
Pimax (cmH₂O) (absolute value)	38.13 (±22.65)	47.83 (±25.62)	27.55 (±13.06)	0.03	41.90 (±21.43)	35.23 (±23.98)	0.50
Pimax predicted value (%)	56.47 (±31.93)	69.60 (±36.29)	42.15 (±19.00)	0.04	61.58 (±27.16)	52.55 (±35.74)	0.51
SNIP (cmH₂O) (absolute value)	41.87 (±21.43)	49.00 (±23.64)	34.09 (±16.37)	0.10	45.10 (±22.06)	39.38 (±1.48)	0.54

Bio-demographic data values are indicated as median (IQR); Pulmonary function values are expressed as mean (±SD); * Yates χ^2 p-value.

BMI=body mass index; ce: control-experimental; CM=congenital myopathy; DGMAH=Dr George Mukhari Academic Hospital; DMD=Duchenne muscular dystrophy; ec=experimental-control; FEV₁=forced expiratory volume in one second; FVC=forced vital capacity; MD=muscular dystrophy; NMD=neuromuscular disease/disorder; PECF=peak expiratory cough flow; PEF=peak expiratory flow; PIF=peak inspiratory flow; Pimax=maximum inspiratory mouth pressure; RCWMCH=Red Cross War Memorial Children's Hospital; S-index=strength index; SNIP=sniff nasal inspiratory; VC=vital capacity; WFA=weight-for-age.

Participants' weight varied greatly with a median (IQR) weight of 30.00 (26.00-37.10) kg and a WFA Z-score of -0.73 (-4.05 to 0.23). Body mass index absolute median (IQR) values were 12.70 (10.79-16.03) and Z-score of -4.20 (-6.57 to -0.76). Ten participants were therefore within the normal BMI range while 13 were severely underweight (lower than three standard deviations below the mean) (Table 6.2).

6.6.2 Adverse events, hospitalisations, respiratory tract infections, change in medications and safety measures

6.6.2.1 Adverse events

No serious adverse events related to IMT during the three month intervention period were reported. At the tenth week of intervention, one participant from Gauteng reported slight discomfort on the left side of the thorax whilst training and throughout the day, for two days. The participant was monitored, but these symptoms did not re-occur. Another participant from Gauteng complained of chest and abdominal pain for a few days prior to surgery for an inguinal hernia. Post-operatively these symptoms did not re-occur and they were considered unrelated to the IMT.

6.6.2.2 Hospitalisations and respiratory infections

Less than a third of participants (7/23, 30.4%) had a respiratory tract infection during the study, while three participants (3/23, 13%) were hospitalised one or more times. Seven respiratory tract infections (RTI), requiring antibiotics and/or cough augmentation, occurred during the three month IMT period and two during the non-training period. Two participants who developed respiratory tract infection (RTI) during the non-training period also reported RTI during the IMT period for which they were hospitalised. Three of the seven participants who reported RTI during the training period were managed at home, while four were admitted to the hospital. The majority (6/7) of participants who developed a RTI during the training period were performing IMT during the high risk season for respiratory infections, which is in autumn and winter (April to September in SA).

Six hospitalisations for respiratory related conditions occurred during the entire study period (involving three participants), five during the intervention period and one during the non-training period. All three participants that were hospitalised throughout the study performed IMT during the autumn and winter season (April to September) when the risk for inspiratory infections are higher. One participant was admitted during both the training and non-training period, while two participants were admitted to the hospital twice during the three-month IMT period. The admission to the hospital during the non-training period (post-intervention) also occurred during winter time (July to September).

Based on the Mann-Whitney U test, there were no differences between the number of hospitalisations or RTI in the intervention (IMT) compared to control (non-training) periods of the study ($p=0.60$ and 0.21 respectively) (Tables 6.3 to 6.5).

Table 6.3: Respiratory tract infections and hospitalisations during training and non-training periods (n=23).

	Training period (IMT) (median (IQR))	Non-training period (median (IQR))	p-value*
Respiratory tract infections[#]	0.00 (0.00-1.00)	0.00 (0.00-0.00)	0.21
Hospitalisations (days) [#]	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.60

[#] Values were not normally distributed (expressed as Median (IQR)); *Mann-Whitney U

The prevalence of respiratory infections and hospitalisations during the non-training and training periods, based on recruitment site and group allocation are outlined in Tables 6.4 and 6.5 respectively.

Table 6.4: Respiratory tract infections and hospitalisations during the non-training/control period only, per recruitment site and group allocations (n=23).

Variable	All participants (n=23)	DGMAH (Gauteng) (n=12)	RCWMCH (Western Cape) (n=11)	Study cite (p-value*)	Group 1 (ce) (n=10)	Group 2 (ec) (n=13)	Allocation (p-value*)
Respiratory tract infections [#]	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.49	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.93
Hospitalisations [#]	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.74	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.69

[#] Values were not normally distributed (expressed as Median (IQR)); *Mann-Whitney U

Table 6.5: Respiratory tract infections and hospitalisations during the training period only, per recruitment site and group allocations (n=23).

Variable	All participants (n=23)	DGMAH (Gauteng) (n=12)	RCWMCH (Western Cape) (n=11)	Study site (p-value*)	Group 1 (ce) (n=10)	Group 2 (ec) (n=13)	Allocation (p-value*)
Respiratory tract infections #	0.00 (0.00-1.00)	0.00 (0.00-1.00)	0.00 (0.00-1.00)	0.83	0.00 (0.00-1.00)	0.00 (0.00-0.00)	0.52
Hospitalisations #	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-1.00)	0.29	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.65

Values were not normally distributed (expressed as Median (IQR)); *Mann-Whitney U

6.6.2.3 Change in medications

During the intervention period, ten participants reported a change in medications: two started with gluco-corticosteroid therapy, six received antibiotics for sinusitis, respiratory tract infections (upper and/or lower) and flu symptoms; one received paracetamol post inguinal surgery and one received medication to treat acute gastro-enteritis. During the non-training period, two participants changed medications: one received antibiotics for a respiratory tract infection whilst another participant started with Ritalin (prescribed for ADHD) to improve his concentration and school performance.

6.6.2.4 OMNI scores (level of perceived exertion)

Similar to the pre-experimental, pilot study the OMNI score was used to monitor the participants' level of perceived exertion during IMT. After every two weeks of training, participants were asked how tired they felt on average (based on a 10-point scale) while performing IMT over the previous two weeks (4.3.6). On average, over the first two weeks of the IMT period, the majority of participants reported a relatively low OMNI score with 12/19 (63.16%) reporting a score of between two and four out of 10, indicating a low level of perceived exertion. Three participants reported a score of 0/10, as they did not experience fatigue at all over the first two weeks of training and one participant (Group 2 (ec)) did not train for the first two weeks due to illness. After six weeks of training, the median (IQR) of 3.5 (2.00-5.00) was similar to the findings of the pre-experimental, pilot study after six weeks of IMT (5.10.3). Thereafter, the OMNI scores changed significantly between week six and eight weeks of training with the IMT device ($p=0.02$), indicating decreasing levels of perceived fatigue (Table 6.6).

OMNI scores could not be captured for all participants and ranged from 16-19 participant values.

Table 6.6: OMNI scores over the intervention period (n=16-19).

Number of weeks (timeline)(n)	OMNI score (/10) (MDN (IQR))	Minimum & maximum OMNI scores (/10)	Wilcoxon matched pairs test (p-value[#])
After two weeks of IMT (n=19)	3 (2-4)	0; 8	OMNI not measured at baseline/pre-intervention
Between week 2 and 4 of IMT (n=18)	4 (2-6)	0; 8	0.97
Between week 4 and 6 of IMT (n=18)	3.5 (2-5)	0; 10*	0.37
Between week 6 and 8 of IMT (n=18)	3 (1-4)	0; 9	0.02
Between week 8 and 10 of IMT (n=16)	2 (0.00-5.50)	0; 9	0.67
Between week 10 and 12 of IMT (n=16)	3 (0-5)	0; 8	0.67

Values are indicated as Median (IQR); * 0=Not tired at all; 10=Very, very tired; # p-values indicate a difference between current and previous score.

As can be seen from Table 6.6 there was a slight decrease in the average OMNI score towards the end of the IMT period, as the majority (13/16) reported a value between zero to five. Five participants expressed that they did not feel tired at all over the last two weeks of training. Only one participant reported feeling extremely tired (score 10/10) during the three month training period. There was no statistically significant difference between the median OMNI score at two weeks of intervention (0-2 weeks) compared to the last two weeks of IMT (10-12 weeks) (Wilcoxon $p=0.32$).

The difference in OMNI score (Δ OMNI) at the end of the intervention (post three months) and after the first two weeks of intervention indicated a decrease in perceived level of exertion (median (IQR) of -1.00 (-2.00 to 0.00)).

6.6.3 Pulmonary function

Similar to baseline recruitment (Table 6.2), participants were also well matched for pulmonary function regarding group allocation (Group 1 (ce) or 2 (ec)) prior to IMT, however pre-intervention VC, PEF, Pimax and SNIP were significantly higher in participants from Gauteng (DGMAH) as compared to the Western Cape (RCWMCH) (Appendix Ei).

There was no difference in the change (Δ) of any of the following pulmonary function measures for group allocation (Group 1 (ce) vs Group 2 (ec)) based on the t-test for independent variables: Δ VC ($p=0.26$), Δ FVC ($p=0.42$), Δ FEV₁ ($p=0.48$), Δ PECF ($p=0.60$), Δ Pimax ($p=0.88$) and Δ Total PedsQL for self-reported/child values ($p=0.75$) or proxy ($p=0.99$). Conversely, Δ peak expiratory flow (PEF) and Δ SNIP during the training period (IMT) were influenced by group allocation ($p=0.03$; $p=0.003$) and this should be considered when interpreting the results.

Spirometry was performed as outlined in Chapter 4 (4.3.3.1) and because the pulmonary function can be influenced by age and growth (Mayer et al., 2017), FVC and FEV₁ values are compared to normative data (Z-scores).

6.6.3.1 Pulmonary function changes between the training (IMT) and non-training period

Pulmonary function values (spirometry, inspiratory muscle strength and PECF) for the intervention/training period (IMT) and non-intervention/non-training period and differences between these groups are summarised in Table 6.7

Table 6.7: Pulmonary function during training and non-training periods (n=23).

Variable	IMT/intervention period (n=23)			No training (control) period (n=23)			Between-group difference in the change from baseline to 3 months.	Between groups (p-value)
	<i>Baseline (pre-IMT)</i>	<i>3 months (post-IMT)</i>	<i>Difference</i>	<i>Baseline</i>	<i>3 months (post non-training)</i>	<i>Difference</i>		
VC (L) (n=19)	1.42 (±0.40)	1.38 (±0.38)	-0.04 (±0.32)	1.41 (±0.34)	1.50 (±0.45)	0.09 (±0.27)	-0.12 (±0.44)	0.20
FVC (L)	1.55 (±0.46)	1.50 (±0.43)	-0.04 (±0.31)	1.59 (±0.46)	1.60 (1.28-1.69)	0.02 (±0.41)	-0.07 (±0.63)	0.53
FEV₁ (L/s)	1.34 (±0.42)	1.37 (±0.37)	0.04 (-0.12 to 0.20)	1.43 (±0.36)	1.37 (±0.38)	-0.05 (-0.11 to 0.02)	0.06 (-0.13 to 0.21)	0.27
PEF (L)	189.09 (±78.50)	188.26 (±64.71)	-0.83 (±51.49)	200.09 (±63.24)	195.26 (±67.00)	-4.83 (±34.36)	4.00 (±74.07)	0.76
Inspiratory muscle strength (Pimax) (cmH₂O)	40.57 (±24.56)	55.13 (±28.17)	14.57 (±15.67)	46.61 (±27.05)	49.65 (±24.66)	3.04 (±11.93)	11.52 (±23.62)	0.01
Inspiratory muscle strength (SNIP) (cmH₂O)	46.00 (21.00-70.00)	53.00 (36.00-67.00)	9.00 (-2.00 to 21.00)	47.00 (38.00-66.00)	54.00 (33.00-75.00)	4.00 (-3.00 to 15.00) [#]	3.00 (8.00 to 15.00)	0.45
Inspiratory muscle strength (S-index) (cmH₂O)	35.88 (±14.19)	49.33 (±14.32)	10.83 (±9.02)	NA	NA	NA	NA	-
PIF (L/s)	1.90 (±0.79)	2.65 (±0.88)	0.61 (±0.47)	NA	NA	NA	NA	-
Inspiratory volume (L)	0.78 (±0.22)	0.93 (±0.27)	0.11 (±0.29)	NA	NA	NA	NA	-
PECF (L/min)	200.87 (±94.18)	238.18 (±96.12)	32.27 (±36.60)	220.00 (±96.08)	204.57 (±98.53)	-16.59 (±48.29)	46.74 (±67.36)	0.0005

Values are mean (±SD) unless otherwise stated;[#] Median (IQR) FEV₁=forced expiratory volume in one second; FVC=forced vital capacity; PECF=peak expiratory cough flow; PEF=peak expiratory flow; PIF=peak inspiratory flow; Pimax=maximum inspiratory mouth pressure; VC=vital capacity; S-index=strength index; SNIP=sneiff nasal inspiratory pressure.

Participants' inspiratory muscle strength (Pimax) improved significantly during the IMT period (14.57 ($\pm$ 15.67)cmH₂O) as compared to the non-training period (3.04 ($\pm$ 11.93)cmH₂O) ($p=0.01$) (Table 6. 7). The mean ($\pm$ SD) difference in cough ability (PECF) during the training period was 32.27 ($\pm$ 36.60)L/min, while the mean PECF difference during the non-training period indicated a regression (-16.59 ($\pm$ 48.29)L/min) (independent student t-test $p=0.0005$). The mean ($\pm$ SD) differences between the intervention and control within-group changes in Pimax and PECF values were 11.52 ($\pm$ 23.62)cmH₂O and 46.74 ($\pm$ 67.36)L/min respectively.

All participants ($n=23$) were followed up monthly for a duration of three months after the end of the intervention period. There was no evidence of a change in measures of inspiratory muscle strength (Pimax, SNIP) and cough ability (PECF) following the intervention, with improvements maintained at three month follow-up. The change from baseline recruitment, pre-post IMT and post-monitoring for all pulmonary function values is summarised in Appendix Ei.

6.6.3.2 Pulmonary function changes within groups during intervention **Spontaneous and forced spirometry**

Spirometry values pre-intervention, post-intervention and after three months of monitoring are depicted in Table 6.8.

Table 6.8: Spirometry values pre-post intervention (IMT) and post monitoring ($n=23$).

Variable	Baseline (Pre-intervention)	Post-intervention	p-value (Pre-post intervention)	Post-monitoring	p-value (Post-intervention to monitoring)
VC (L)	1.42 ($\pm$ 0.40) ($n=19$)	1.38 ($\pm$ 0.38) ($n=19$)	0.63	1.44 ($\pm$ 0.44) ($n=20$)	0.19
FVC (L)	1.55 ($\pm$ 0.46)	1.50 ($\pm$ 0.43)	0.49	1.57 (1.32-1.80) [#]	0.14*
FEV₁ (L)	1.34 ($\pm$ 0.42)	1.37 ($\pm$ 0.37)	0.44	1.40 ($\pm$ 0.37)	0.61
FEV₁/FVC (%)	90.18 [#] (77.50-94.58)	95.90 [#] (90.16-97.69)	0.12*	93.94 [#] (81.99-98.31)	0.45*
PEF (L/min)	189.09 ($\pm$ 78.50)	188.26 ($\pm$ 64.71)	0.94	192.09 ($\pm$ 60.05)	0.61

Values are indicated as mean ($\pm$ SD) and dependent t-test unless otherwise stated: [#] Median (IQR), *Wilcoxon

FEV₁=forced expiratory volume in one second; FVC=forced vital capacity; PEF=peak expiratory flow; VC=vital capacity

There was no evidence of a change in any of the spirometry measures at any timepoint from baseline to three months post-intervention follow-up (Table 6.8).

Inspiratory muscle strength (Pimax and SNIP)

Inspiratory pressure at the mouth (Pimax) and sniff nasal inspiratory pressure (SNIP) were measured pre-post intervention and post-monitoring (three months after IMT) using the MicroRPM (4.3.3.2).

There were significant differences in both Pimax and SNIP from pre- to post IMT (3 months), based on the dependent t-test ($p=0.0002$; $p=0.01$) (Table 6.9).

Table 6.9: Inspiratory muscle strength values (Pimax; SNIP) pre-post intervention and post monitoring (n=23).

<i>Variable</i>	<i>Baseline (Pre- intervention)</i>	<i>Post-intervention</i>	<i>p-value (Pre-post intervention)</i>	<i>Post-monitoring</i>	<i>p-value (Post intervention to monitoring)</i>
Pimax (cmH₂O)	40.57 (±24.56)	55.13 (±28.17)	0.0002	55.26 (±23.91)	0.95
SNIP (cmH₂O)	47.09 (±24.49)	55.65 (±23.47)	0.01	51.00 (±19.72)	0.14

Pimax=maximum inspiratory mouth pressure; SNIP=sniff nasal inspiratory pressure.

In addition to the pre-post intervention improvement (Table 6.9) and similar to the pre-experimental study, the RCT cross-over also showed a statistically significant within-group change in Pimax over the intervention period (ANOVA $p=0.00006$) with post-hoc t-tests for dependent variables showing significant increases from baseline, after six weeks of IMT ($p=0.004$) (Figure 6.6). The Pimax measured at eight and 10 weeks were also higher than baseline measures ($p=0.002$). The improved Pimax post-training (both absolute and predicted) values were maintained throughout the three months monitoring period when IMT was not performed ($p=0.95$; $p=0.86$) (Table 6.9).

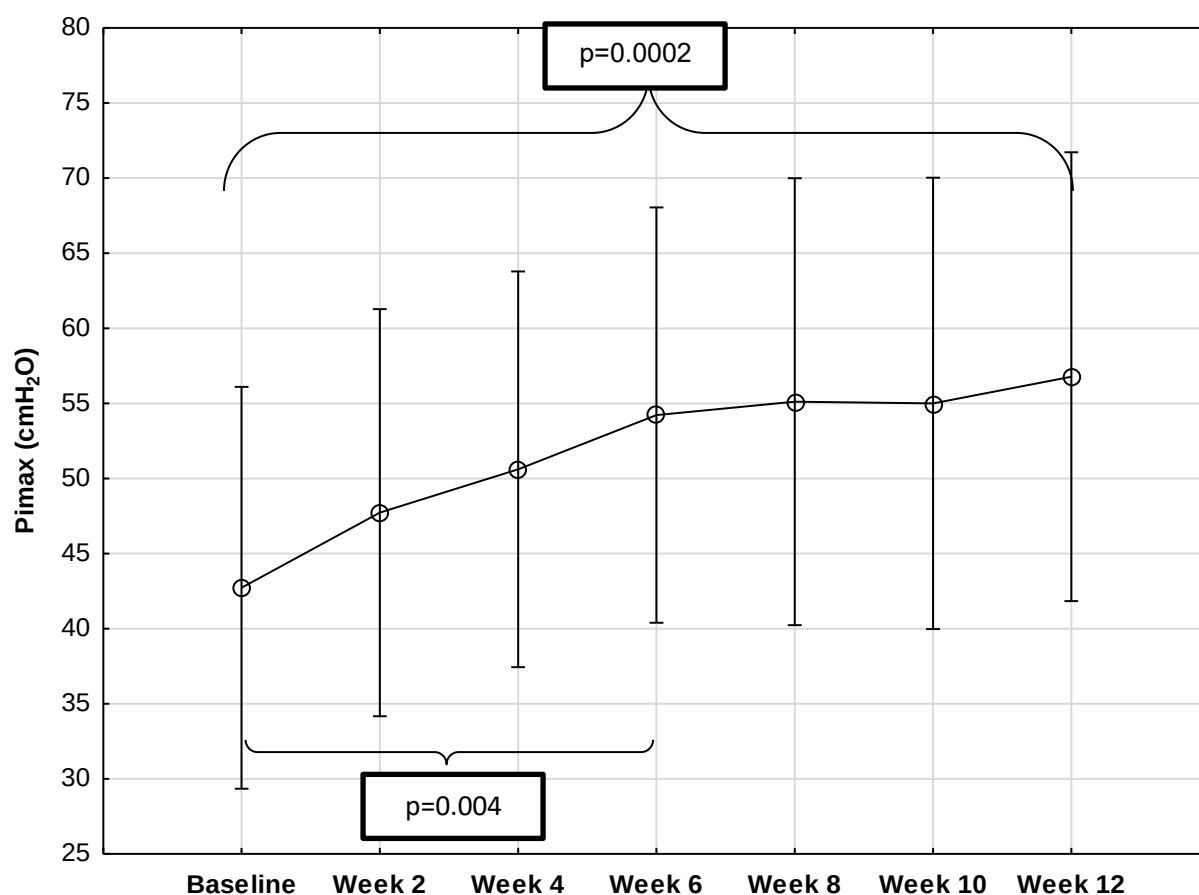


Figure 6.6: Change in inspiratory muscle strength (mean Pimax) over the intervention period (ANOVA $p=0.00006$). The vertical bars denote 0.95 confidence intervals. Significant *post-hoc* bivariate dependent tests between measurement points are indicated.

There was no evidence of a difference in the change in Pimax during the intervention between participants with and without spinal deformities (Current effect ANOVA: $F(6,96) = 0.42$; $p=0.87$); those with different types of NMD (diagnoses) (Current effect ANOVA: $F(24, 78) = 0.52$; $p=0.97$) or between independently ambulant and non-ambulant participants (Current effect ANOVA: $F(6, 96) = 2.00$; $p=0.07$).

SNIP values changed significantly over the intervention period (ANOVA $p=0.02$), with post-hoc dependent t-tests indicating significant improvements between baseline and both week six ($p=0.03$) and week 12 ($p=0.01$) (Figure 6.7; Table 6.9). Improvements in SNIP were maintained for three-months follow-up after cessation of IMT ($p=0.14$).

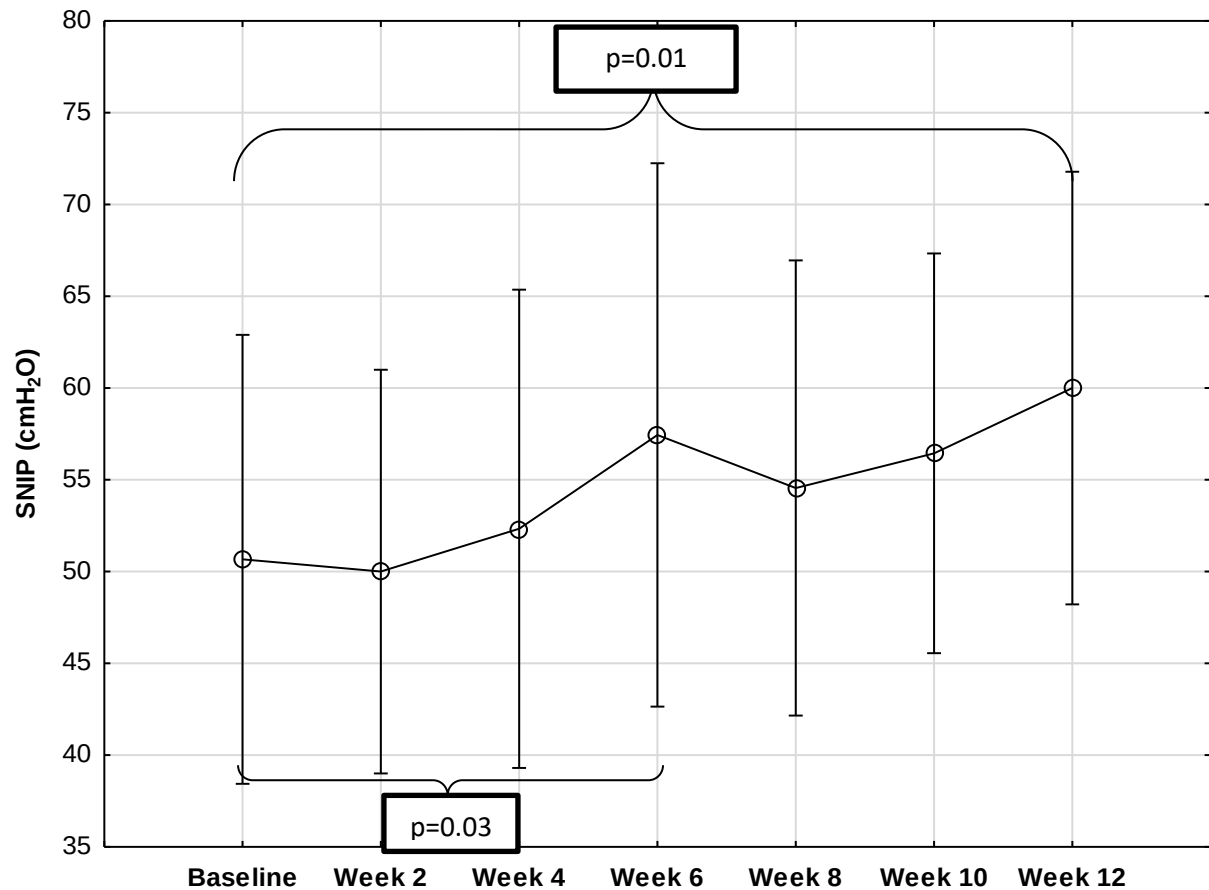


Figure 6.7: Change in inspiratory muscle strength (mean SNIP) over the intervention period (ANOVA $p=0.02$). The vertical bars denote 0.95 confidence intervals. Significant *post-hoc* bivariate dependent tests between measurement points are indicated.

Strength-index, peak inspiratory flow and volume

Strength-index, peak inspiratory flow and volume were measured with the Powerbreathe K3[®] device during the intervention (IMT) period only. These measures were not documented for all participants, as they were not listed as pre-specified outcome measures in the study protocol. However, the results obtained are thought to be of sufficient interest to report here.

All the values for strength-index (S-index), peak inspiratory flow (PIF) and volume from baseline (pre-intervention) to three months post-training are outlined in Table 6.10. The dependent t-test or Wilcoxon test p-values between baseline and two, four, six, eight, ten and 12 weeks (3 months) are also indicated.

Table 6.10: Pulmonary function measured by Powerbreathe K3 ® during training period (n=19).

Variable	Baseline (pre-intervention) (n)	Week 2 (n) (p-value)	Week 4 (n) (p-value)	Week 6 (n) (p-value)	Week 8 (n) (p-value)	Week 10 (n) (p- value)	Week 12 (3 month) (post-intervention) (n) (p-value)
S-index (cmH₂O)	35.88 (±14.19) (n=16)	40.20 (±17.04) (n=15) (0.02)	40.18 (±16.52) (n=17) (0.03)	40.68 (±16.76) (n=19) (0.0003)	45.00 (±17.16) (n=17) (0.003)	42.72 (±16.40) (n=18) (0.0001)	49.33 (±14.32) (n=12) (0.002)
PIF (L/s)	1.90 (±0.79) (n=16)	2.14 (±0.96) (n=16) (0.02)	2.18 (±1.00) (n=17) (0.01)	2.24 (±1.07) (n=19) (0.002)	2.44 (±1.01) (n=17) (0.0006)	2.3 (±0.97) (n=18) (0.00005)	2.65 (±0.88) (n=12) (p=0.0009)
Volume (L)	0.78 (±0.22) (n=16)	0.77 (±0.23) (n=16) (1.00)	0.84 (±0.23) (n=17) (0.39)	0.80 (0.70-0.90) [#] (n=19) (0.13)*	0.82 (±0.25) (n=17) (0.44)	0.80 (0.70-1.00) [#] (n=18) (0.14)*	0.93 (±0.27) (n=12) (0.22)

Values are mean (±SD) unless otherwise indicated; # Median (IQR); p-values (between baseline and measurement point), either dependent t-test or *Wilcoxon rank test

PIF=peak inspiratory flow; S-index=strength index

There were statistically significant changes in S-index over the intervention period (ANOVA p=0.009) with post-hoc dependent t-tests indicating significant improvements between baseline and every two weeks measurement point over the intervention period as well as between pre-intervention and 10 weeks (p=0.0001), and pre- to post-intervention (3 months) (p=0.002) (Table 6.10; Figure 6.8).

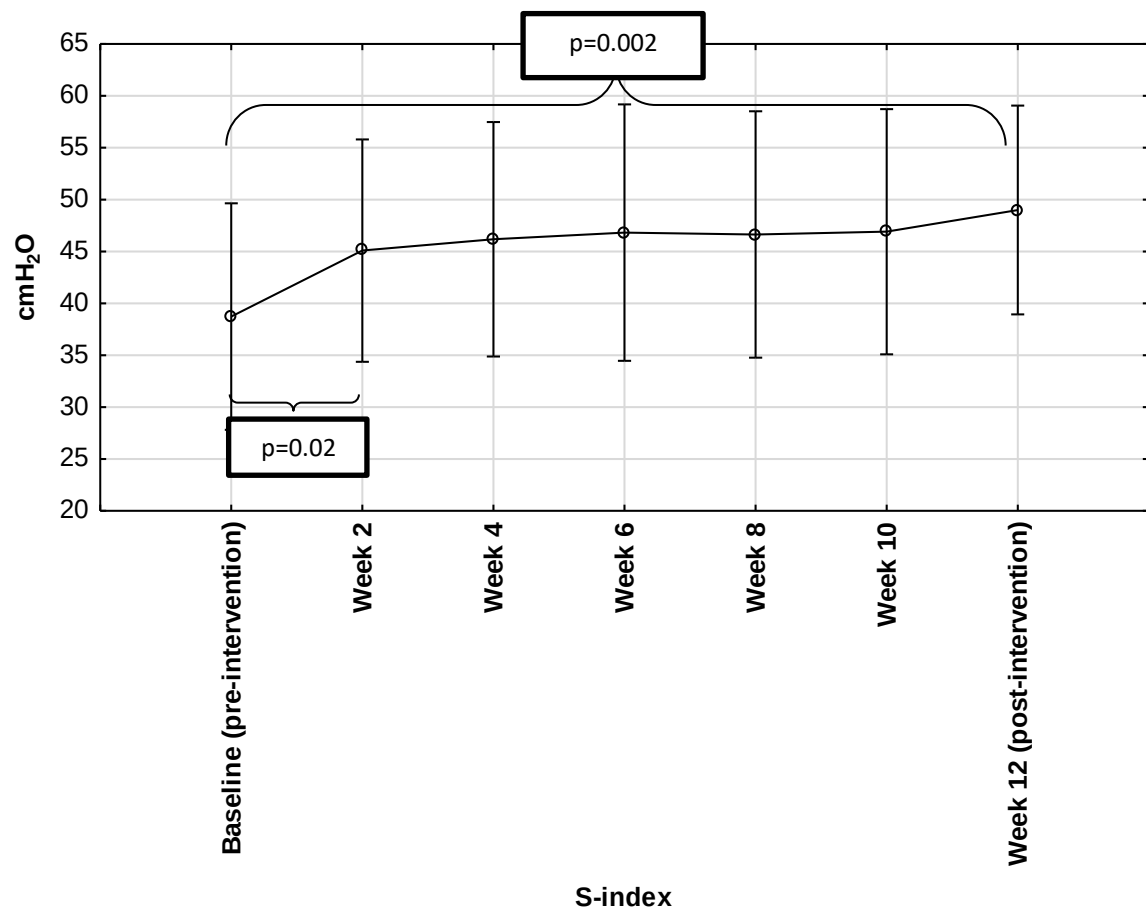


Figure 6. 8: Change in inspiratory muscle strength (mean strength index) throughout intervention (ANOVA $p=0.009$). The vertical bars denote 0.95 confidence intervals. Significant *post-hoc* bivariate dependent tests between major measurement points are indicated.

There were similar changes in peak inspiratory flow (PIF) during the intervention period (ANOVA $p=0.0004$), with posthoc identified improvements from baseline to two weeks ($p=0.02$); six weeks ($p=0.002$); week 10 ($p=0.00005$) and week 12 ($p=0.0009$) (Table 6.10; Figure 6.9).

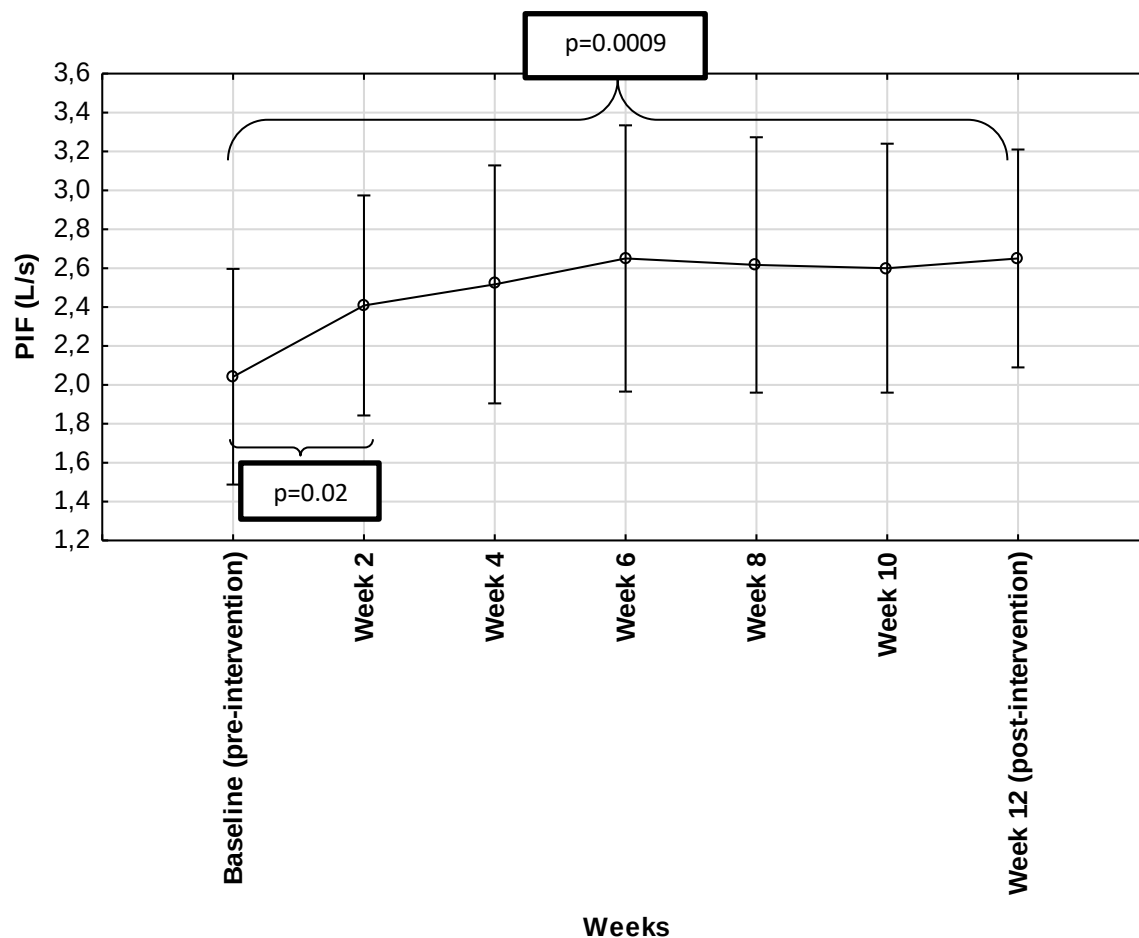


Figure 6. 9: Change in mean peak inspiratory flow (PIF) throughout intervention (ANOVA $p=0.0004$). The vertical bars denote 0.95 confidence intervals. Significant *post-hoc* bivariate dependent tests between major measurement points are indicated.

Volume measured on the Powerbreathe device[®] showed no statistically significant change over the intervention period (ANOVA $p=0.57$) with no evidence of change on post-hoc dependent t-tests and Wilcoxon paired test between baseline and any measurement point (Table 6.10).

Cough ability (PECF)

Participants' cough ability was measured with a Wright peak flow meter at three month intervals, which accounted for a total of three or four measurements, depending on group allocation (Group 1 or 2). The PECF values at baseline/pre-intervention, post-intervention and post-monitoring are presented in Table 6.11.

Table 6.11: Pre-post intervention and post-monitoring variables for cough ability (PECF) (N=22-23).

<i>Variable</i>	<i>Baseline (Pre- intervention)</i>	<i>Post- intervention</i>	<i>p-value (Pre-post intervention)</i>	<i>Post- monitoring</i>	<i>p-value (Post intervention & monitoring)</i>
PECF (L/min)	200.87 (±94.18) (n=23)	238.18 (±96.12) (n=22)	0.0005	213.70 (±110.55) (n=23)	0.17

PECF=peak expiratory cough flow

There was a statistically significant change pre-post intervention ($p=0.0005$) as well as over the period from pre-intervention until the last PECF measurement (three months after IMT was ceased) (ANOVA $p=0.02$) (Table 6.11.; Figure 6.10). The PECF at the end of three months of no training did not show a significant change ($p=0.17$) (Table 6.11).

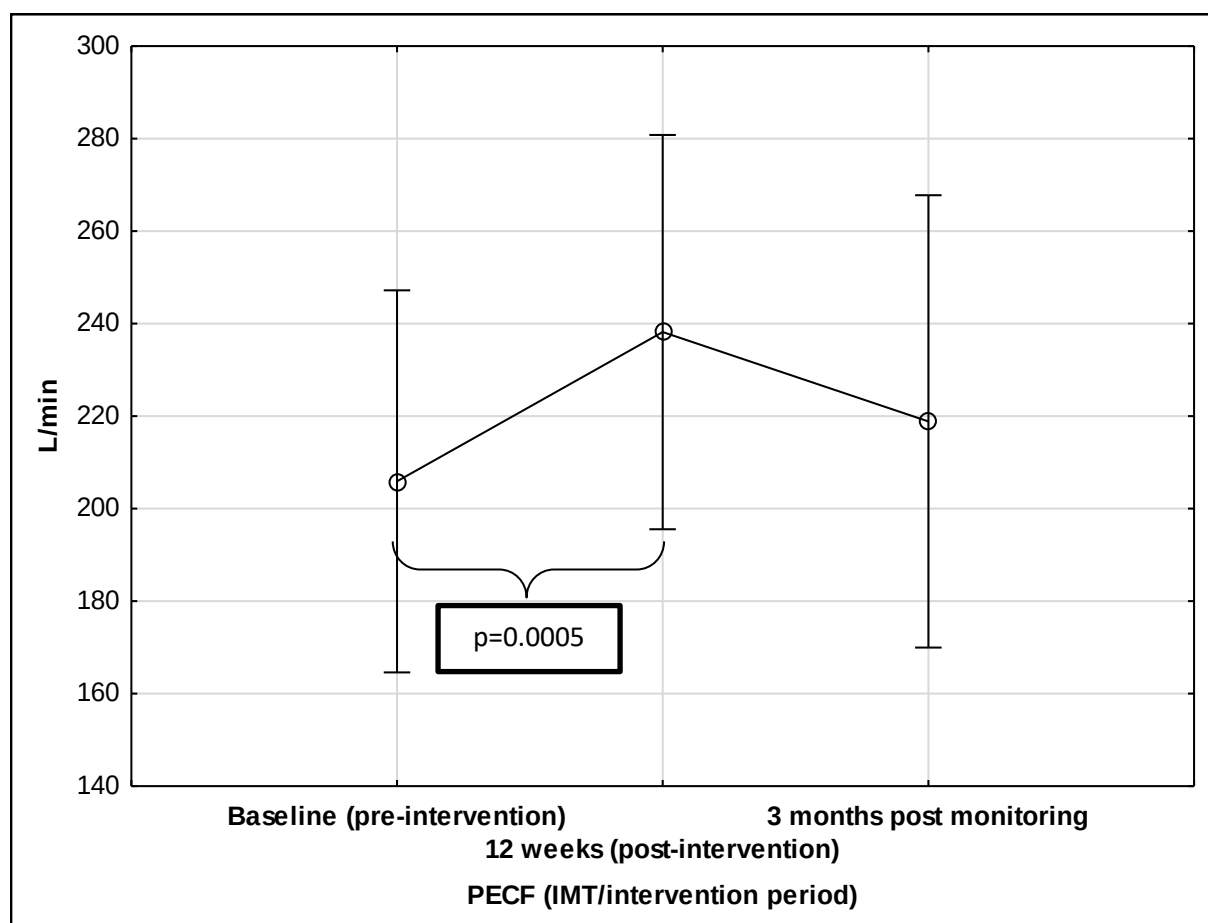


Figure 6.10: Change in cough ability (mean PECF) throughout intervention (ANOVA $p=0.02$). The vertical bars denote 0.95 confidence intervals. Significant *post-hoc* bivariate dependent tests between measurement points are indicated.

Although not a pre-specified objective of the study, there was no evidence of a difference in the change in PECF from baseline to three months post intervention on sub-group analysis between participants with and without spinal deformities (current effect ANOVA: $F(1, 20) = 0.29$, $p=0.59$), among participants with different diagnostic categories (type of NMD) (current effect ANOVA: $F(4, 17) = 0.42$, $p=0.79$) or level of ambulation (ambulant and non-ambulant) (current effect ANOVA: $F(1, 20) = 0.08$; $p=0.78$).

Additional data related to participants' pulmonary function are provided in Appendix Ei.

6.6.4 Functional ability (level of ambulation and upper limb function)

At recruitment (first baseline assessment for all) the Brooke, Vignos and Motor Function Measure (MFM) scores were not normally distributed.

6.6.4.1 Brooke, Vignos scale and motor function measure (MFM)

Most participants were already non-ambulant and using a wheelchair (manual, electric or both) (Meier et al., 2017)(6.6.1) as reflected in the median (IQR) baseline recruitment Vignos score of 9 (3-9). Upper limb function was more preserved with baseline median (IQR) Brooke score of 2 (1-3), indicating the ability to raise the arms above their head only when flexing their elbows. At baseline participants presented with a high median (IQR) upper limb function and coordination (MFM) score of 27 (16-29) out of 30. There was no evidence of a change in Brooke, Vignos or MFM scores during either the training or non-training period (Table 6.12). These changes were also not influenced by order or group allocation based on Mann-Whitney U tests performed.

Table 6.12: Change in Brooke, Vignos and MFM during training and non-training periods (n=23).

Variable	Training (IMT) period	Non-training period	Mann Whitney U p-value
Δ Brooke (/6) (n=15)	0 (0.00 to 0.00)	0 (0.00 to 0.00)	0.25
Δ Vignos (/10) (n=15)	0 (0.00 to 0.00)	0 (0.00 to 0.00)	0.16
Δ MFM (/30) (n=23)	0 (-1.00 to 1.00)	0 (0.00 to 1.00)	0.06

MFM=Motor Function Measure

Pre-intervention, post-intervention and post-monitoring Vignos, Brooke and MFM scores remained similar. The Brooke ($p=0.11$), Vignos ($p=0.11$) and MFM ($p=0.64$) scores did not show any statistically significant change over the three month IMT intervention period, nor was there evidence of change over the three month post-monitoring period, based on the Wilcoxon matched pair test for changes within groups (Table 6.13).

Table 6.13: Functional ability (ambulation) and upper limb function and coordination.

Variable	Baseline (pre-intervention) (n=15; 23)	Post intervention (n=23)	Wilcoxon p-value (Pre-post intervention)	Post monitoring (n=23)	Wilcoxon p- value (Post IMT vs monitoring)
Brooke (/6)	2 (1-3)	2 (1-3)	0.11	2 (1-3)	0.42
Vignos (/10)	9 (2-9)	9 (3-9)	0.11	9 (3-9)	0.69
MFM (/30)	27 (16-29)	27 (16-30)	0.64	27 (18-30)	0.24

MDN (IQR), unless otherwise indicated. MFM=Motor Function Measure

6.6.5 Associations/correlations

6.6.5.1 Associations between participants' pulmonary function and functional ability

There was a very weak, positive and non-significant correlation between Δ PECF and the pre-intervention Brooke, Vignos and MFM scores (Spearman's rank=0.03; $p=0.90$; $r_s=0.19$; $p=0.49$; $r_s=0.10$; $p=0.65$). A negative, moderate and significant relationship was found between Δ Pimax and pre-intervention Brooke and Vignos scores (Spearman's rank=-0.56; $p=0.03$; $r_s=-0.58$; $p=0.02$), and a very weak, positive and non-significant correlation between Δ Pimax and pre-intervention MFM values (Spearman's rank=0.23; $p=0.29$).

6.6.5.2 Associations between participants' pulmonary function measures

A moderately positive and significant correlation was found between the change in Δ PECF and Δ PEF during the intervention period (Pearson's $r=0.44$; $p=0.04$).

There were no significant correlations between spirometry measures such as VC, FVC, FEV₁, PEF (pre-intervention) and Δ Pimax or Δ PECF during the intervention (IMT) period and associations were very weak (Pimax: Pearson's $r=0.24$, $p=0.33$; $r=0.37$, $p=0.08$; $r=0.36$, $p=0.09$; $r=0.35$, $p=0.10$); PECF: Pearson's $r=-0.15$, $p=0.53$; $r=-0.20$, $p=0.38$; $r=-0.17$, $p=0.45$; $r=-0.14$, $p=0.54$). There were moderately positive and significant correlations between the pre-intervention and post-intervention (3 month) PECF and Pimax values (respectively Pearson's $r=0.64$ and $r=0.65$; $p=0.01$ for both) as well as SNIP and PECF values (Baseline: Pearson's $r=0.55$; $p=0.007$; post-intervention: Pearson's $r=0.48$; $p=0.02$).

6.6.6 Health-related quality of life (PedsQL)

Similar to the pre-experimental study, HRQoL was measured using the Pediatric Quality of Life Inventory (PedsQL) (5.10.6). Results are presented as self-reported and proxy total PedsQL score (%) as well as the physical and psychological (social, emotional and school performance) domains. Group allocation did not influence the change in child/self-reported PedsQL or proxy PedsQL (Δ PedsQL) for either the total scores, Physical or Psychosocial domains.

There was no evidence of a difference in the change of PedsQL scores between the training and non-training periods for proxy PedsQL total score, Physical and Psychosocial domains as well as the child reported PedsQL total and Psychosocial domain. The change in the self-reported child PedsQL Physical domain score however showed a significant difference ($p=0.003$) between the training and non-training period (Table 6.14).

Table 6.14: Health-related quality of life measurements: total scores, subdomains for child and proxy (training vs non-training).

Variable	Training (IMT) period	Non-training period	p-value
Δ Child PedsQL (total) % n=22	5.93 (±16.74)	4.64 (±8.98)	0.75
Δ Child PedsQL Physical domain (%) n=21; 22	13.98 (±16.54)	-1.26 (±14.40)	0.003
Δ Child PedsQL Psychosocial domain (%) n=21; 22	7.30 (0.00-16.30)	5.00 (1.67-13.33)	0.99
Δ Proxy PedsQL (total) % n=18; 21	-0.35 (±14.85)	-1.31 (±9.45)	0.07
Δ Proxy PedsQL Physical domain (%) n=17; 20	-5.96 (±22.33)	-2.95 (±17.68)	0.35
Δ Proxy PedsQL Psychosocial domain (%) n=17; 20	0.00 (-5.00 to 8.33)	1.67 (-5.00 to 3.33)	0.92

Values indicated as mean (±SD) or median (IQR). PedsQL=Pediatric Quality of Life Inventory

The within group changes from pre to post-intervention and post monitoring are outlined in Table 6.15. Although there was no statistically significant difference between child/self-reported and proxy PedsQL mean values prior to intervention ($p=0.18$), a significant difference between the child reported and proxy values post-intervention (after three months of IMT) was found ($p=0.01$).

Table 6.15: Health-related quality of life measurements: total scores, subdomains for child and proxy (intervention period).

Variable	Baseline (pre- intervention)	Post- intervention	p-value (pre-post intervention)	Post monitoring	p-value (post-intervention to post- monitoring)
Child PedsQL (total) (%) n=22;23	64.83 (±17.06)	69.86 (±16.53)	0.11	68.33 (±15.57)	0.51
Child PedsQL Physical domain (%) n=21-23	47.75 (±23.04)	59.56 (±19.06)	0.002	55.81 (±20.99)	0.40
Child PedsQL Psychosocial domain (%) n=21-23	75.00 (63.33-86.67)*	83.33 (56.67-88.33)*	0.22 [#]	76.67 (60.00-88.33)*	0.88 [#]
Proxy PedsQL (total) (%) n=20; 21; 23	58.24 (±14.80)	58.86 (±12.33)	0.91	56.53 (±9.23)	0.50
Proxy PedsQL Physical domain (%) n=19; 20; 21	54.81 (±25.18)	49.70 (±23.64)	0.16	52.21 (±22.19)	0.73
Proxy PedsQL Psychosocial domain (%) n=21; 23	59.66 (±14.21)	61.43 (±14.33)	0.87	53.33* (48.33-65.00)	0.06

Values are expressed as mean (±SD); unless otherwise indicated; *MDN (IQR); [#]Wilcoxon matched pair test. PedsQL=Pediatric Quality of Life Inventory

Although there was an improvement in the self-reported HRQoL There was no evidence of change in the self-reported HRQoL from baseline to post-intervention, based on the total PedsQL scale (%) (p=0.51). There was however a statistically significant improvement in the mean (±SD) self-reported PedsQL Physical domain (p=0.002) (Table 6.15) and a change over time from baseline to post monitoring (ANOVA p=0.007). By contrast, there was no evidence of change in the proxy PedsQL Physical domain (p=0.16), after the intervention.

6.6.7 Home programme of participants

Participants were asked which activities they performed as part of their home programme on a daily or weekly basis, for maintaining range of motion (ROM) and/or strength as well as airway clearance techniques (ACT) and/or respiratory muscle training.

Most participants (n=12) performed ROM exercises especially of the lower limbs, with most indicating (n=7) a frequency of once a week while two participants performed these exercises daily.

Twelve participants indicated the use of passive stretches, of both the upper and lower limbs, performed once a week (n=6) or daily (n=3). The majority (n=13) also performed strengthening exercises of both the upper and lower limbs (n=8), at a frequency of once a week (n=7), while two participants performed strengthening exercises daily. Regarding respiratory management, seven participants indicated that they used ACT such as incentive spirometry, deep breathing exercises (DBE), autogenic drainage (AD) and cough augmentation. Those that reported the use of incentive spirometry (n=3), implemented it once a week, while those that indicated the use of cough assistance (n=4) reported its implementation mostly when the child had difficulty with clearing secretions or had a respiratory infection. Two participants used DBE, AD and cough augmentation (manually assisted cough) as preventative, daily treatment strategies. These same two participants reported using both independent and assisted breath-stacking (lung volume recruitment techniques) as part of maintenance care, but the frequency per week was not specified. None of the participants mentioned the use of glossopharyngeal breathing techniques (GPB).

Three participants had access to mechanical cough augmentation (MI-E), but only two reported making use of MI-E when needed, for instance when they presented with an acute respiratory infection or had difficulty with secretion clearance. One participant mentioned that he preferred the use of manually assisted cough augmentation, rather than MI-E. The children with access to mechanical cough assist devices did not use them for lung volume recruitment or as part of maintenance care.

Under additional comments related to their home programme, seven respondents reported participating in swimming/hydrotherapy regularly (at least once a week), and although one participant had access to a respiratory training device (Luft), they had never used it before. Other components mentioned under the home programme included nebulisation and suctioning when needed, incorporating breathing exercises whilst swimming, abdominal exercises, using a standing frame and playing soccer.

6.6.8 Adherence with the inspiratory muscle training programme and feedback from participants and parents/caregivers and physiotherapists

6.6.8.1 Participant adherence

Overall adherence with the IMT programme was very good and the number of training sessions recorded on the Powerbreathe® devices were normally distributed, but the training diaries were not.

The number of training sessions recorded on the device and in the training diaries was not influenced by group allocation based on the Mann-Whitney U by group ($p=0.26$; $p=0.06$).

The total number of training sessions for participants over the three-month IMT period, as noted in the training diaries by the parents/caregivers or physiotherapists at the school, ranged from 19 to 170, with a median (IQR) of 95 (64-159). A total of 120-168 training sessions were targeted, depending whether interventions were performed at home or at school and therefore adherence ranged from 56.5% to 79%. The number of training sessions recorded on the Powerbreathe[®] device (dependent on the quality of breaths) ranged from 10 to 169, with a mean ($\pm$ SD) of 96.65 ($\pm$ 48.45). The majority of participants (19/23) had the same number of training sessions noted in their training diary as recorded on the Powerbreathe[®] device which was confirmed with the non-significant difference between the self-reported recordings and the device records, based on the Mann-Whitney U ($p=0.43$). There was a very weak to weak, non-significant correlation between the number of training sessions recorded on either the Powerbreathe[®] device or self-reported (training diaries) for inspiratory muscle strength measures of Pimax (Pearson's $r=-0.07$; $p=0.74$; Spearman's rank= -0.30 ; $p=0.17$) and SNIP (Pearson's $r=-0.09$; $p=0.69$; Spearman's rank= -0.14 ; $p=0.52$). Unlike inspiratory muscle strength values, cough ability (PECF) showed a moderate, positive and significant correlation with the number of training sessions recorded on the Powerbreathe[®] devices (Pearson's $r=0.47$; $p=0.03$) and self-reported adherence (training diaries) was non-significant (Spearman's rank= 0.49 ; $p=0.02$).

6.6.8.2 Participant satisfaction and feedback

Overall participant satisfaction with the IMT programme on a 10-point visual analogue scale (VAS) was high, with a median (IQR) of 8(5-10) reported by participants. When participants and parents/caregivers were asked if they would like to continue with IMT after the study ceased, the majority of participants ($n=18$) and parents/caregivers ($n=20$) indicated that they would.

Regarding their experience of IMT, open-ended comments made by the participants, parents/caregivers or physiotherapists involved in the study are depicted in Table 6.16.

Table 6.16: Open-text responses from participants and parents/caregivers/physiotherapists about inspiratory muscle training (n=23).

Participant number	What did the participants have to say about IMT?	What did the parents/caregivers/physiotherapists have to say about IMT
1	It is fun, keeps me stronger and improves my breathing.	His mother and sister commented that his walking and soccer playing have improved. The mother reported that in her opinion IMT assists him in staying as independent as possible and stronger.
2	IMT helps with my breathing muscles, makes them stronger.	Decreased chest-related problems, decreased wheezing and chest tightness.
3	Very happy with the training device, it is really helping me a lot.	He had his annual follow-up appointment for lung function tests and the dr was very impressed with the results (copy of results can be made available on request). Yes, would like him to continue with the device (prevention is better than cure), we rather prevent than deal with the worse (sic).
4	Did not elaborate/did not want to comment	Decrease in bad breath (halitosis) and an increase in his overall strength.
5	At times I am satisfied with performing training, other times not.	The caregiver was satisfied overall, it was good as it improved his cough (secretion clearance) and now the cough is gone (patient did not present with a chronic cough anymore)! It even improved his mood.
6	It was nice, helps me with breathing and I feel better.	Increases his boy's confidence, energy levels (more playful), improved his walking (gait), breathing, health and he is happier. He still presents with a dry cough (possibly due to sinus). It is worth it, to maintain function.
7	Unsure if it made any difference (post-IMT); but after three months of monitoring (no-training) he reported: IMT helped me and my lungs because I am less tired than before.	According to the father, he could not see any difference, but the clinicians noticed increased oral control, as well as improved posture and breathing pattern.
8	Values on the device increased and my lungs now feel stronger, my breathing muscles are better	Clinicians reported (as the parents were unavailable). Improved breathing, motivation and quality of life. He also presents with an increased responsibility for his own health. Also, there seems to be transfer of training to activities of daily living.
9	Good, as it helps my lungs, helps me to take bigger breaths.	Clinicians (as the parents were unavailable): Improved posture and breathing, IMT worked very well.
10	I do not really like doing the training, I feel tired, don't feel up to it and do not really think that it is making any difference. [Patient lost his ambulation during the intervention time, struggled emotionally, was demotivated].	Improved lung function and maintenance of his general function. If it can keep him better for longer- I am game!
11	Parents commented that he was the one asking about the device (when they were training), so in their experience, he liked using IMT. On the day, he did not want to say much as he was upset about being taken out of	Parents reported that he experienced a decreased frequency of headaches in the mornings and slept better. At hydrotherapy sessions, they also realised he could hold his breath better and for longer periods. The cardiologist was also impressed

	school and doing home schooling (participant also presents with Asperger).	with the training, as he seemed to present with improved cardiac function (most likely due to decreased strain on the heart because the patient gets more oxygen into the body due to better/improved breathing). Parents do not think that IMT causes any regression, but rather overall improvement and long-term advantage.
12	Helps me, as it makes my lungs stronger and I can take deeper breaths.	No additional comment
13	Makes it easier to cough, fewer chest infections.	No additional comment
14	Body is tired and needs a break [No motivation/reason provided].	Very satisfied with the training (did not elaborate)
15	No comment	No comment
16	IMT is nice to do!	No additional comment
17	No comment	Observed an improvement in her breathing.
18	No comment	Observed an improvement in his breathing.
19	It did help me and my chest feels stronger (sic).	To try and get more into a routine and try training [participant completed very few IMT sessions over the 12 weeks.
20	Helps me breathe better.	IMT made his breathing and cough stronger and he is managing his allergies better.
21	Helped me improve the strength of my cough.	Observed an improvement in the power of his cough (cough ability) and he needed less suctioning. During the intervention period (IMT) for eight days at school, he did not require daily suctioning.
22	Help make me stronger so I can cough up my secretions. [After approximately 60 IMT sessions, he reported improvement in cough and being able to clear secretions].	It really helped him keep his chest clear and he is stronger and can cough up his secretions. Many comments were noted from him/his physio at the school and his mom (in the training diary) about how this study helped him. [Diary: After about 15 training sessions: He had phlegm over the weekend. Felt that his cough was stronger and that he managed to expectorate without assistive cough! Productive, but able to expectorate independently].
23	Would like to try and train more with the machine.	Would like him to get more of a chance to train as he couldn't do much due to sickness and school commitments.

Additional comments that were made by participants and/or caregivers included that at baseline the patient needed assistance with mouth closure to perform tests or training, but after the intervention, he was able to perform these activities independently. Also at the end of the monitoring period, post-intervention the caregiver reported that IMT assisted him with his breathing, improved his muscle strength (blowing) and his cough subsided. A disadvantage of the training device mentioned by one of the parents was that at times the device will be on the “automatic” setting, instead of “manual” when switched on, and this might influence the monitoring of training results, as the parents were not always aware on how to correct/change the setting.

6.7 Discussion

In patients with NMD, respiratory muscle weakness causes an imbalance between the load of the respiratory system and respiratory capacity leading to hypoventilation and poor cough, which causes morbidity and mortality at different phases during the course of the disease (McCool & Rosen, 2006; Nicot et al., 2006; Panitch, 2017; Benditt & Boitano, 2013; Boentert et al., 2017; Chiang et al., 2018; Finkel et al., 2018; Morrow et al., 2019) (Chapters 1 and 3).

Until curative treatment is available for patients living with NMD, the focus of treatment strategies are to slow down the regression of musculoskeletal and cardiopulmonary function as well as improve HRQoL (Gozal, 2000; Avendaño & Güell, 2003; Yang & Finkel, 2010; Wenninger et al., 2019). This chapter describes the first RCT of IMT in a SA cohort of children with NMD presenting with respiratory muscle weakness.

6.7.1 Participant characteristics

The sample size of 23 in this RCT is comparable to other international respiratory muscle training studies in children with NMD (DiMarco et al., 1985; Martin et al., 1986; Stern et al., 1989; Rodillo et al., 1989; Gozal & Thiriet, 1999; Koessler et al., 2001; Yeldan et al., 2008). At recruitment, all patients were clinically stable and did not show any signs of inspiratory muscle fatigue such as exertional dyspnea, orthopnea or paradoxical breathing (Wanke et al., 1994; Winkler et al., 2000; Topin et al., 2002) and only one patient received mandatory ventilation via a tracheostomy. Participants were generally well matched (age, sex, weight and BMI) between the primary recruitment sites and allocated groups (Group 1 and 2), although those from the Western Cape presented with lower pulmonary function values at recruitment and pre-intervention, compared to their counterparts from Gauteng (Tables 6.2 and 6.5). None of the participants had used IMT prior to recruitment.

The participant characteristics (age, sex, weight, presence of spinal deformity, type of NMD, functional ability, pulmonary function and HRQoL) in the cross-over RCT were similar to those described in the pre-experimental, pilot study (Chapter 5: 5.10.1) and to other international studies that included children with a variety of NMD (Dohna-Schwake et al., 2006; Jansen et al., 2013; LoMauro et al., 2014; Landfeldt et al., 2015; Marques et al., 2014; Nève et al., 2013; Meier et al., 2017; Torres-Castro et al., 2016). There was a significant association between the sex of the participants of this cross-over RCT and their diagnosis (type of NMD) ($p=0.04$) which was not surprising as most participants presented with DMD ($n=13$), which is the most common type of NMD reported in the paediatric population (Gozal & Thiriet, 1999; Winkler et al., 2000; Koessler et al., 2001; Bérard et al., 2005; Nicot et al., 2006) (Table 6.1). The NMD type did not significantly influence the change in inspiratory muscle strength (Pimax) or cough ability (PECF) in this cross-over RCT. Sixty percent ($n=14$) of participants were non-ambulant (based on their Vignos scores) at the time of recruitment, which was expected as most were already in the pre- or adolescent phase (older than 10 years) (Guglieri & Bushby, 2011; van Ruiten et al., 2014; Boentert et al., 2017; Meier et al., 2017; Birnkrant et al., 2018). Participants had relative preservation of their upper limb function and coordination, as indicated by the Brooke and MFM scores and similar to the profile of participants in the pre-experimental, pilot study (5.10.5). Pre-intervention scores (Vignos, Brooke and MFM scores) showed no statistically significant functional difference between participants based on the allocated groups (Group 1 and 2) (6.6.4.1).

Despite most participants being non-ambulant, overall cardiopulmonary function was fair, with the majority ($n=22$) non-ventilator dependent, as reported by other studies (Wanke et al., 1994; Topin et al., 2002; Yeldan et al., 2008; LoMauro et al., 2014). A small proportion ($n=4$) of participants used regular nocturnal non-invasive ventilation and only two presented with cardiac pathology, despite four using cardiac medication. Despite the majority of patients presenting with DMD, only ten reported using gluco-corticosteroids, particularly prednisone. This proportion of gluco-corticosteroid use was lower than those reported among other international DMD cohorts (Janssen et al., 2016; Kinane et al., 2018).

Regardless of the numerous advantages of glucocorticoid steroid treatment such as decreased regression of motor and pulmonary function, chronic use in clinical practice in different settings is highly variable and may be limited by significant adverse events such as obesity (Goemans & Buyse, 2014; van Ruiten et al., 2014; Landfeldt et al., 2015; Mayer et al., 2017).

Due to the early loss of ambulation, use of corticosteroids and a more sedentary lifestyle, children with NMD are at risk of overweight and obesity, however, with advancing age they may also be at risk of becoming underweight and present with malnutrition, particularly in the presence of decreased oral control and/or swallowing problems (Perrin et al., 2004; Hull et al., 2012; Goemans & Buyse, 2014; Birnkrant et al., 2018; Wadman et al., 2020). Thirteen participants in this cross-over RCT were classified as severely underweight based on BMI Z-scores, but a sub-analysis could not be performed due to the small sample size. The median BMI Z-score (-4.20) in this study was much lower than that reported by Nève et al. (2013) among 33 children with DMD of -0.1 (-4.8 to -6.3). The value of BMI measures might be limited in children with NMD (Wang et al., 2007), due to spinal deformities such as scoliosis and therefore classifications based on BMI might not be as valid and reliable in this cohort of patients.

The participants' home programmes mostly consisted of stretches and activities to maintain range of motion (of both the upper and lower limbs, with emphasis on the lower limbs) which corresponds to findings of the pre-experimental, pilot study (5.10.2) and aligns with clinical practice recommendations for patients (Guglieri & Bushby, 2011; Ho et al., 2015; Vry et al., 2016; Mercuri et al., 2018). Strengthening exercises were performed by more than half of the participants (13/23). This corresponds with a study among boys with DMD which recommended implementing assisted bicycle training at a young age, to ameliorate disuse atrophy (Jansen et al., 2013) and a Cochrane review on strength and aerobic exercise in patients with muscle diseases (Voet et al., 2019). Respiratory management techniques described as part of the home programme of the cross-over RCT participants correlate well with the findings of the SA survey study (Chapter 2: 2.6), with breathing exercises and manually assisted cough (MAC) being commonly prescribed as ACT. Similarly to the survey findings and despite clinical practice guidelines recommending these respiratory management strategies, a small number of participants (3/23; 13%) had access to and/or used MI-E or made use of lung volume recruitment techniques (2/23; 8.7%). The utilisation of these two techniques was however higher than the findings of the pre-experimental, pilot study and align with recommendations for patients with NMD (2.7.9). Similar to the pre-experimental study, no participants used alternative breathing techniques such as GPB.

What was of great concern was that three participants reported not using a home programme at all, either because they were not referred to physiotherapy or occupational therapy or the child refused to comply. Two participants reported not performing any breathing exercises at the time of the study.

6.7.2 Adverse events, hospitalisations and respiratory tract infections and safety measures

Similar to the pre-experimental, pilot study (5.10.3) and another IMT study among children and adults with NMD (DMD; SMA) (Winkler et al., 2000), no serious adverse events were reported related to IMT during this cross-over RCT, supporting previous suggestions that IMT is a safe adjunct to the management strategies of children with NMD.

Many children living with NMD will be hospitalised over their lifespan due to acute respiratory infections, caused by their underlying respiratory muscle weakness and the development of restrictive lung disease (Tzeng & Bach, 2000; Nicot et al., 2006; Panitch, 2006; Yang & Finkel, 2010; Finkel et al., 2018). It was therefore expected that participants would develop respiratory tract infections, some of whom would require hospitalisation, during the two-year data collection period. In this study, respiratory tract infections included, but were not limited to, bacterial and viral upper respiratory tract infections and lower respiratory tract infections such as bronchitis and pneumonia (Mayer et al., 2017; Boentert et al., 2017; Birnkrant et al., 2018).

Almost a third of participants (7/23) in this cross-over RCT experienced respiratory tract infections requiring antibiotics over the intervention (IMT) and non-training periods. There was no evidence of a difference in the number of respiratory tract infections or hospitalisations per participant between the training and non-training periods ($p=0.21$; $p=0.60$) (6.6.2). Although most of the nine respiratory infections reported throughout the study (7/9) occurred during the training period; this phenomenon might be explained by the fact that six of these participants were performing IMT during the high risk season for respiratory tract infections in SA (April to September) and might be more prone to contracting RTI during this time. These RTI were not severe, because only a minority of participants were hospitalised over the training and non-training period (3/23). The prevalence of respiratory infections is also dependent on co-morbidities, the child's age and seasonal changes; however larger sample sizes are needed to perform sub-analyses.

This cross-over RCT aimed primarily to describe the effect of IMT on respiratory infections and hospitalisations, as previously recommended (Aslan et al., 2013; Wenninger et al., 2019), but could not show a significant difference between the training and non-training periods as defined in the objectives (1.3.1). This study was unable to show that IMT is effective in reducing RTI/hospitalisations, possibly due to sample size and being underpowered. Larger, longer-term clinical trials and monitoring periods might be needed to determine the long-term effect of IMT in children and adolescents with NMD.

As a safety measure, the OMNI scale was used to monitor the participants' level of perceived exertion on a daily and every two weekly basis. After six weeks of IMT, the median (IQR) OMNI score of 3.5 (2-5) was similar to that of the pre-experimental study values (median 3.5 (1.5-6)) and correlated well with another pre-experimental IMT study among adult patients with Pompe disease (Wenninger et al., 2019). For this study, most participants presented with low and moderate OMNI scores ($<6/10$), and the median OMNI values over the three-month intervention period ranged from two to four, similar to values reported in a study on the use of assisted upper and lower limb cycling in boys with DMD (Jansen et al., 2013). Only once did one participant report feeling severely tired (OMNI 10/10), which could be explained by the presence of a mild RTI. Interestingly, in this study, there was a statistically significant decrease in median OMNI score from week six to week eight of IMT ($p=0.02$). Participants may have had to physiologically adapt to training and a minimum duration of six weeks of inspiratory threshold training might be needed to gain clinical benefit (Wanke et al., 1994; Gozal & Thiriet, 1999; Topin et al., 2002; Zupan, 2004; Takaso et al., 2010), contrary to the minimum of four weeks of IMT suggested by Woszezenki et al. (2017). On the other hand, because this was the only significant difference found during the course of intervention, it should be considered that this might have been merely due to chance. A slight decrease in the OMNI score was reported at three months (end of IMT intervention) as compared to the first two weeks of training, but this was not significant ($p=0.32$).

Reasons for the lack of significant change could include i) the baseline values reported (after two weeks of IMT) were already relatively low with the majority reporting between two and four out of 10 which indicates "a little tired" to "getting more tired"; ii) the OMNI scale might not be sensitive enough to detect small changes in perceived level of exertion, could be affected by respiratory complications or illness and iii) some children may have had difficulty understanding the abstract concept of exertion level (Pfeiffer et al., 2002) and the OMNI score might therefore not be the most suitable outcome measure in the SA context. The lack of fluctuation in perceived level of exertion throughout the IMT period could also be related to training intensity levels and adapting to the individual's inspiratory muscle strength reducing the risk of fatigue or overexertion. Alternatively the training load stimulus provided was not high enough in order for a perceptible change to be evident.

Although the clinical value of perceived exertion has been indicated in the literature (Gozal & Thiriet, 1999; Nicot et al., 2006; Chatwin & Simonds, 2009) and the OMNI scale is a validated tool to determine perceived exertion in NMD, the experience from this study was that the participants, especially the younger ones could not reliably express themselves.

The reliability and validity of the OMNI scale should therefore be determined for all age groups (particularly younger than 8 years), sex and ethnicities (Pfeiffer et al., 2002). This suggestion warrants further study and larger samples over a longer duration.

6.7.3 Pulmonary function

Patients that are still ambulant tend to have higher lung volumes and inspiratory muscle strength than their non-ambulant counterparts (Nicot et al., 2006). Most participants in this cross-over trial were already in their pulmonary function decline phase (10-18 years), non-ambulant and with PEF<80% predicted (Meier et al., 2017) as evident by their upper, lower limb function and pulmonary function tests (6.6.3; 6.6.4). Despite the recommendations of having a chest X-ray taken annually in children with NMD once they start using a wheelchair (Finder et al., 2004), most participants did not have X-rays to refer to for confirmation of pulmonary status. This is contrary to the recommendation of regular pulmonary assessment and monitoring, even in the absence of respiratory symptoms (Farrero et al., 2013; 2.7.9). Many patients might not realise that they have respiratory muscle weakness until they present with a poor cough and recurrent respiratory infections such as pneumonia (Gómez-Merino et al., 2002; Finder et al., 2004; Perrin et al., 2004). This cross-over study assessed lung volumes, flows and static inspiratory muscle strength measures as recommended in order to inform management planning strategies (Meier et al., 2017).

6.7.3.1 Spirometry

Similar to the pre-experimental, pilot study findings (5.10.4) as well as other studies (Martin et al., 1986; Rodillo et al., 1989; Winkler et al., 2000; Yeldan et al., 2008), no significant changes in spirometry (VC, FVC and FEV₁) were observed pre to post-intervention nor was there any evidence of a difference in the change in these parameters between the intervention and control periods. This might be explained by the fact that a few participants were still partially or completely ambulant during the intervention period and their spirometry, as well as Pimax values at baseline, were within normal ranges (Yeldan et al., 2008).

Spontaneous spirometry

This cross-over RCT did not find evidence of a difference in Δ VC between the training and non-training periods. The VC values at the end of three months of monitoring were comparable to baseline (pre-intervention), similar to the findings from other studies (Wanke et al., 1994; Aslan et al., 2013). This requires further investigation in longer-termed and larger sample size clinical trials.

Forced spirometry

Forced spirometry may become difficult to perform once children with NMD grow older and because these manoeuvres are effort-dependent and require coordination (Nicot et al., 2006; Mayer et al., 2015; Meier et al., 2017; Birnkrant et al., 2018). Although the majority of participants in this cross-over RCT were pre-adolescents/adolescents, presenting with restrictive respiratory lung disease and in the pulmonary decline phase (6.6.3; Farrero et al., 2013; Meier et al., 2017). All 23 participants could perform acceptable spirometry, similar to another study in boys with DMD (6-16 years) (Mayer et al., 2015). However, this study's participant spirometry performance was much higher than reported by Nicot et al. (2006) among children with DMD, SMA and congenital myopathy, as only 61% of their participants (n=25) were able to perform FVC manoeuvres.

Regression in spirometry, including PEF, is also associated with regression in cough ability (Mayer et al., 2015; Mayer et al., 2017) and can indicate when airway clearance techniques (ACT), especially cough augmentation might be required (Finder et al., 2004; Gauld & Boynton, 2005). Similar to spontaneous spirometry (Δ VC), there were no significant difference in Δ FVC, Δ FEV₁ or PEF between the training and non-training periods ($p=0.53$; $p=0.27$; $p=0.76$). Group allocation and geographical site also did not influence the change in the forced spirometry values. Whether IMT can slow down regression of pulmonary function such as FVC in children with NMD remains to be confirmed through longer, larger RCT as recommended by other authors (Stern et al., 1989; Wanke et al., 1994; Winkler et al., 2000).

6.7.3.2 Inspiratory muscle strength measures (Pimax and SNIP)

Inspiratory muscle strength (e.g. Pimax; SNIP) is thought to be a more sensitive measure of respiratory strength than lung volumes and flow such as VC and PEF and in addition can be assessed early during the course of the disorder (Lötters et al., 2002; ERS, 2002; Farrero et al., 2013; Nève et al., 2013; Boentert et al., 2017; Wenninger et al., 2020).

This cross-over RCT found a significant change in Pimax during the IMT period ($14.57 (\pm 15.67) \text{ cmH}_2\text{O}$) as compared to the non-training period ($3.04 (\pm 11.93) \text{ cmH}_2\text{O}$) ($p=0.01$). This is contrary to the findings by Martin et al. (1986), but similar to that of Gozal & Thiriet (1999) in 21 children with NMD (DMD and SMA III) which reported a similar difference between mean Δ Pimax in the IMT ($19.8 (\pm 3.8)$) versus the non-training group ($4.2 (\pm 3.6)$; $p=0.02$).

Reasons for variations in values of inspiratory muscle strength between different studies can be attributed to the equipment/devices used, characteristics of the participants, their level of motivation and the experience of the assessor (Verma et al., 2019; Wenninger et al., 2019). Similar to the pre-experimental, pilot study (5.10.4) the cross-over study also indicated a statistically significant improvement in Pimax pre-post intervention ($p=0.0002$), similar to an IMT study among 16 children and adults with NMD (Winkler et al., 2000). Unlike the pre-experimental study results, the cross-over study improvement in Pimax over the first two and four weeks of training was not statistically significant but did show improvement from six weeks onwards. This could indicate that the Pimax improvement observed in the cross-over study was a true reflection of intervention and not caused by a learning effect alone. The increased Pimax was maintained for three months after the participants stopped IMT ($p=0.95$) which is contrary to previous reports (Martin et al., 1986; Rodillo et al., 1989; Eagle, 2002), but aligned with maintained inspiratory muscle strength after training was ceased (Wanke et al., 1994; Wenninger et al., 2019).

The change in Pimax observed after three months of IMT was significantly correlated with pre-intervention Vignos and Brooke scales ($p=0.02$; $p=0.03$). The type of NMD (DMD, SMA, congenital muscular dystrophy (CMD)), as well as the presence of a spinal deformity, did not influence the Δ Pimax during the intervention period. This cross-over RCT also did not find any significant association between pre-intervention lung volumes (VC, FVC, FEV₁ and PEF) and the change in either Pimax or PEF during the IMT period, similar to a cohort of DMD boys (Martin et al., 1986). There was however a statistically significant correlation between the Pimax and PEF values pre-intervention and after three months of IMT, as expected considering that improving inspiratory strength should lead to greater inspiratory volumes and consequently better cough flows.

Alternative inspiratory muscle strength measures, such as SNIP, might need to be considered especially if oropharyngeal muscles are affected (Farrero et al., 2013; Nève et al., 2013 ; Boentert et al., 2017; Birnkrant et al., 2018; Finkel et al., 2018). Monitoring SNIP may assist in determining pulmonary regression, as it has been reported to be a strong predictor of VC in children, adolescents and adults with a variety of NMD. Furthermore, Pimax and SNIP values are strongly correlated (Stefanutti et al., 2000; Nicot et al., 2006), implying that the one could be used as a surrogate for the other to indicate inspiratory muscle strength. However, it has also been reported that the diaphragm activation pattern in patients with NMD during a sniff manoeuvre is unknown (Stefanutti et al., 2000).

The different patterns of muscle activation and type of effort between Pimax and SNIP suggest that these tests might represent different aspects of inspiratory muscle function, which needs to be considered when planning for future clinical trials. This may explain the finding in this cross-over RCT that despite the statistically significant difference in Pimax change between training and non-training periods, the between group difference for Δ SNIP was not significant.

The SNIP values did, however, show a statistically significant within group improvement over the three month intervention period ($p=0.01$), which differed from the findings in the pre-experimental study (Chapter 5: 5.10.4). A non-significant decline during the post-monitoring period ($p=0.14$) was also seen. Despite the improvement in SNIP values during IMT in the cross-over study, these values were still much lower than in children without NMD ($93 (\pm 23)\text{cmH}_2\text{O}$ (girls); $104(\pm 26)\text{cmH}_2\text{O}$ (boys)) and adults ($>60\text{cmH}_2\text{O}$ (females); $>70\text{cmH}_2\text{O}$ (males)) (Boentert et al., 2017). Inspiratory muscle strength (Pdi sniff) in 41 children with a variety of NMD previously showed significant correlation with cough ability ($r=0.70$; $p=0.001$) (Nicot et al., 2006), which was also seen in this study between SNIP and PEF at baseline and post-intervention. This confirms the relationship between inspiratory muscle strength (Pimax, SNIP) and cough ability (PECF). Furthermore, the findings might be explained by the longer training duration (three months instead of six weeks), as the adaptation of ventilatory muscles such as the diaphragm becomes greater with longer training periods (Wanke et al., 1994).

The SNIP values at baseline for participants in the Western Cape were much lower than that of their Gauteng counterparts for the cross-over study and the reasons for this are not clear, but could have occurred by chance. Geographical context should be considered when interpreting results and planning future clinical trials.

6.7.3.3 Strength index (S-index), peak inspiratory flow and volume

Similar to the pre-experimental, pilot study (5.10.4), participants in this cross-over RCT also presented with a statistically significant improvement in their inspiratory muscle strength index (S-index) as well as their ability to create airflow during inspiration (PIF) between the pre-and post-intervention ($p=0.002$; $p=0.0009$) (Table 6.10). This aligns with the improvements observed in Pimax and SNIP.

Like the pre-experimental study, there was a significant difference ($p=0.02$) between baseline measurement and the first two weeks of training for both S-index and PIF, which could be attributed to a learning effect. Unlike the experimental study, however, the difference was greater after six weeks of IMT ($p=0.002$; $p=0.0003$).

Improved respiratory muscle coordination when performing an inspiratory manoeuvre rather than respiratory muscle strength improvement has been offered as a possible explanation for these increases (ERS, 2002; Mayer et al., 2017). However, the variety of assessment tools used in this cross-over study (MicroRPM, Powerbreathe[®]) as well as the continued improvement after six weeks of intervention might indicate a true inspiratory muscle strength improvement (training effect), but warrants further investigation.

A change in lung volume would not have been expected over a short duration of IMT (6 weeks), however over 12 weeks/three months a change might have been evident, hence these values captured by the Powerbreathe[®] device were recorded and analysed. There was no evidence of change in inspiratory lung volumes during the intervention period ($p=0.57$). This could be explained by the common occurrence of restrictive lung disease among children and adolescents, especially once ambulation is lost and were similar to the spirometry findings.

6.7.3.4 Cough ability (PECF)

An effective cough is an important airway clearance mechanism (McCool & Rosen, 2006; Panitch, 2006; Finder, 2010), which may be affected by inspiratory muscle weakness and difficulty with glottis closure, evident in decreased PECF values with NMD progression (Nicot et al., 2006; Chatwin et al., 2018). Cough ability as an outcome measure can also provide an indication of difficulty with airway clearance and the need for ACT (Farrero et al., 2013; França et al., 2015; Auger et al., 2017) (Chapter 1: 1.1.1; 1.1.2 ; 1.1.3).

This cross-over study showed a significant difference ($p=0.0005$) between the mean ($\pm$ SD) difference in cough ability (PECF) during IMT ($32.27 (\pm 36.60)$ L/min) and the non-training period ($-16.59 (\pm 48.29)$ L/min). While the pre-experimental, pilot study did not find a significant change in PECF after six weeks of intervention, in the cross-over study there was a significant improvement from pre-to post-intervention as well as over the period from pre-intervention to three months post-monitoring. These findings further support the theory that improved inspiratory muscle strength translates into an improved cough ability (Chapter 1: 1.1.3; 1.1.4.1), but training periods of more than six weeks are most likely needed to see this effect. Furthermore, a moderately positive and significant correlation was found between the change in PECF and PEF during the intervention period, confirming the previously reported relationship between these two parameters in children with NMD in SA (Morrow et al., 2019). These associations can be of clinical value to plan management strategies such as the use of lung volume recruitment and cough augmentation.

Despite this association and the significant improvement of PEF, this cross-over RCT did not show a significant change in PEF due to IMT. Hence, although PEF may be a valuable indicator of cough ability (Meier et al., 2017), it might not always be a reliable and valid surrogate end-point (Auger et al., 2017).

The improved airway clearance ability (PECF) after implementing the three month IMT programme, could be explained by the increased ability to inhale better during the inspiratory phase of the cough because of improved inspiratory muscle strength (McCool & Rosen, 2006; Toussaint et al., 2009; (Chapter 1: 1.1.3; 1.1.4.1). Despite this improvement, and although the values were within normal ranges for children (Bianchi & Baiardi, 2008; Gogou et al., 2017), the mean ($\pm$ SD) PECF value post intervention was still below 270L/min, suggesting susceptibility to respiratory tract infections due to ineffective airway clearance and the need for cough assistance (Sejerson & Bushby, 2009; Hull et al., 2012; LoMauro et al., 2014; Boentert et al., 2017; Toussaint et al., 2018).

The presence of kyphoscoliosis in patients with neuromuscular weakness may exacerbate the effect that respiratory and bulbar weakness has on airway clearance and ventilation (Marques et al., 2014) (Panitch, 2017; Morrow et al., 2019) and further increase the risk of hospitalisations and negatively affect HRQoL because of impaired airway clearance and cough (Perrin et al., 2004; Finder et al., 2004). In this RCT about a third of participants (n=8) presented with a spinal deformity at baseline which could increase their risk for respiratory complications (McCool & Rosen, 2006; Marques et al., 2014), although the presence of a spinal deformity did not significantly influence the Δ Pimax or Δ PECF during IMT. This suggests that IMT could be equally beneficial in patients with spinal deformities, but this requires confirmation in larger studies.

Individual patients' who did not show improvement in Pimax or PECF values post intervention could be explained by relatively high baseline (pre-intervention) values (Dohna-Schwake et al., 2006), which should be considered when interpreting results and planning future clinical trials. Furthermore, the change in PECF during intervention was significantly correlated with the number of IMT sessions recorded on the Powerbreathe[®] device, which suggests that improved cough ability may be dose-dependent (Wanke et al., 1994; Winkler et al., 2000). Like Pimax and SNIP, PECF values remained constant from post-intervention to post-monitoring suggesting maintenance of the positive effects of IMT over the medium term.

6.7.4 Change in functional ability (level of ambulation and upper limb function) and health related quality of life and participant adherence and satisfaction.

6.7.4.1 Functional ability

Although the majority of participants in this cross-over RCT were already non-ambulant and presented with lower Pimax and PEF values during IMT than their ambulant counterparts, the level of ambulation did not have a significant difference on Δ Pimax and Δ PEF throughout the intervention. Once ambulation is lost, pulmonary function decline becomes more apparent and has been associated with a Brooke score of two or three; a Brooke score of five indicating that FVC% predicted has decreased to <50% (Mayer et al., 2017; Meier et al., 2017; Birnkrant et al., 2018). This confirms that participants in this cross-over RCT were already in their upper limb transition phase, based on their FVC values.

The relative preservation of upper limb function and/or coordination in this cross-over RCT was quite surprising due to the associated decline of upper limb function when children become non-ambulant (Mazzone et al., 2012; Janssen et al., 2016) and the low lung volumes found with spirometry. There was no evidence of change in the Brooke, Vignos and MFM scores during either the training (IMT) or non-training period of this cross-over RCT. Interestingly, the median (IQR) values for the level of ambulation, upper limb function and coordination remained similar even three months after IMT was ceased. Whether this tendency is an indication of decreased regression of functional ability due to improved inspiratory muscle strength, breathing and improved posture (Costa et al., 2011), remains a question to be answered through further research.

Although the pre-experimental, pilot study found a statistically significant difference in the upper limb function and coordination (MFM score) pre-post intervention (5.10.5), there was no evidence of change associated with either the intervention or control periods in the cross-over trial. This is contradictory to the findings of Jansen et al. (2013) who reported that MFM scores remained stable during assisted cycling intervention (upper and lower limbs) and declined during the non-training period in a cohort of boys with DMD. The difference in findings might be explained due to the reported study using the complete MFM tool (32 items) including three dimensions, whereas this cross-over IMT study only used 10 MFM items, but included six items from the distal motor function dimension (D3), as proximal muscles are usually affected before distal muscles in NMD. In addition, the study by Jansen et al. (2013) implemented training of upper and lower limbs, while this RCT focused on IMT, which might only have an indirect effect on upper limb function and coordination.

Inter-rater variability, time of day, type of NMD, co-morbidities and patient cooperation might have influenced the functional ability measurements (Brooke, Vignos and MFM) in this cross-over study. Upper limb scores and classifications might also not be sensitive enough to identify smaller changes and assessment periods of longer than three months might be required (Mazzone et al., 2012; Birnkrant et al., 2018). The observed improvements in inspiratory muscle strength (Pimax) and cough ability (PECF) with IMT may not translate into improved proximal (trunk) stability and activities of daily living. Once more, the intervention period of three months may have been too short to detect these changes and warrants further research in larger samples and longer-term intervention studies.

The Δ PECF during intervention was not significantly influenced by the participants' functional ability (Brooke, Vignos and MFM) before IMT, but Δ Pimax was influenced by pre-intervention Brooke and Vignos scores. In conditions that are more rapidly progressing such as SMA, pulmonary intervention might be needed earlier in the disease as compared to NMD types that progress at a slower rate (Farrero et al., 2013). On the other hand, statistically significant differences in mean Brooke and Vignos scale scores between patients with different types of NMD have been reported (Lue et al., 2009), which was not the case in this cross-over RCT, as type of NMD did not have a significant effect on the change of Pimax during the intervention period.

6.7.4.2 Health-related quality of life (PedsQL)

Children with NMD and their parents/caregivers tend to report a lower HRQoL as compared to their peers without NMD (Iannaccone et al., 2009). This study recorded both self-reported/child and proxy PedsQL measures, as previously recommended (Finder et al., 2004; Messina et al., 2016; Finkel et al., 2018). There was no statistically significant difference in the child and proxy PedsQL total or subdomain scores between training and non-training periods in this cross-over RCT, except for the child reported Physical domain, which showed within-group change from pre-post intervention as well as a change over time from baseline to post monitoring. This supports a previous report of the Physical functioning scale showing a greater ability to discriminate change in function than Psychological and Social functioning scales (Psychosocial domains) (Varni et al., 1999).

There was a significant difference between the self-reported/child and proxy PedsQL total values post-intervention (3 months), supporting a previous study by Gold et al. (2009) in which children with NMD reported less fatigue, greater school function and general HRQoL than their caregivers/parents, highlighting the variation in HRQoL perception between children and their caregivers.

This difference in perception, also reported by others (Eiser & Morse, 2001; Varni et al., 2002; Bastiaansen et al., 2004; Iannaccone et al., 2009), was confirmed with the RCT findings that despite a significant improvement in the mean self-reported/child PedsQL Physical domain pre-post intervention, the same change was not observed for the proxy PedsQL Physical domain.

Based on the natural progression of NMD and the subsequent loss of upper and lower limb function, it was interesting that the self-reported PedsQL Physical domain showed such improvement pre-post IMT and over the three month intervention period, despite no evidence of improvement in the more objective functional level scales (Vignos, Brooke and MFM). This was contrary to what was reported by Messina et al. (2016) among an ambulant cohort of boys with DMD (5-13 years), which found a significant decrease in self-reported total PedsQL and Physical domain score over three months and a significant correlation between baseline HRQoL and functional status such as 6MWT and the North Star Ambulatory Assessment. The implementation of IMT might positively affect participants' actual or perceived ability to perform activities of daily living (ADL) and participate in physical activities, although it was suggested that PedsQL might not be sensitive enough to reflect the physical changes that occur in ambulant children due to the progressive nature of NMD (Messina et al., 2016). Although the absolute values were within a similar range, there were differences between the pre-experimental study and cross-over RCT in the change in PedsQL measures. Change in the total child PedsQL score and Psychosocial domain of the cross-over study was smaller than that of the pre-experimental study, but the Physical domain difference in the cross-over study was much larger. These discrepancies may be explained by the larger sample size of the cross-over study as well as the longer duration of IMT intervention.

This study suggests the use of IMT may positively influence HRQoL (Physical and/or Psychosocial domain) in children with NMD, but this requires confirmation with further research.

6.7.4.3 Participant adherence and satisfaction

The importance of children's adherence with an IMT programme has been highlighted (Wanke et al., 1994; Eagle, 2002; Topin et al., 2002) as a potential factor influencing clinical outcomes. Good participant adherence was seen in both the pre-experimental, pilot (Chapter 5: 5.10.7) and cross-over studies (6.6.8) and most participants were very motivated throughout the intervention (IMT) periods. This was also evident from the high level of agreement between the self-reported number of training sessions (training diaries) and electronically recorded (Powerbreathe[®]) training sessions.

This could also be attributed to the high reported level of participant satisfaction with IMT (MDN: 8/10) as well as the generally positive attitude of the parents/caregivers and physiotherapists involved.

The finding of overall good participant adherence in this cross-over RCT is similar to other studies conducted among children with NMD (Wanke et al., 1994; Yeldan et al., 2008; Jansen et al., 2013) and adults with late-onset Pompe disease (Wenninger et al., 2019). The majority of participants (18/23; 78.30%) reported that they would like to continue with IMT as part of their respiratory management strategy after the study was completed and 86.96% (20/23) of parents/caregivers supported the continuation of IMT. A clear advantage of IMT is that it can feasibly be performed as part of a home programme (Wanke et al., 1994).

The number of IMT sessions completed, duration and training intensity has been reported to be associated with improvements in inspiratory muscle strength (Pimax, 12sMVV) (Wanke et al., 1994; Winkler et al., 2000; Topin et al., 2002; Yeldan et al., 2008). Conversely, this cross-over study found no significant association between the number of training sessions (self-reported and recorded on the Powerbreathe[®] device) for inspiratory muscle strength (Δ Pimax, Δ SNIP), and the reasons for this discrepancy are unclear. However, there was a significant correlation between the number of training sessions recorded on the device and Δ PECF which suggests that improved cough ability may be IMT dosage dependent. Again this warrants further investigation.

6.8 Limitations of the cross-over RCT

The Brooke scale has been used as a standardised assessment tool for various NMD clinical trials, however as it only consists of six items it might not be sensitive enough to detect small changes in upper limb function for a variety of NMD with different clinical presentations. Furthermore, neither the Brooke nor MFM, reflect functional ability during ADL at different ages in DMD (Mazzone et al., 2012).

Therefore other measures for upper limb function, dexterity and ADL should be considered for future studies, including the Jebsen Hand function test, Performance of Upper Limb test (PUL), muscular dystrophy functional rating scale (MDFRS), upper limb module, distal upper limb/grip strength (e.g. MyoGrip) and self-reported measures (ABILHAND; capabilities of upper extremity questionnaire (CUE)) (Mazzone et al., 2012; Mercuri et al., 2012; Janssen et al., 2016; Ricotti et al., 2019).

Although the MFM is a validated tool for NMD, using ten items might have impacted the validity of the instrument, which is a minor limitation of this study. These items were however chosen to assess similar functional ability in both ambulant and non-ambulant children and to limit the duration of the study-related assessment and potentially avoidable exertion for participants in this study (Mazzone et al., 2012). In addition, other standardised tools for assessing motor ability, lower limb function and clinical progression such as the Hammersmith Functional Motor Scale and 6-minute walk test (6MWT) or North Star Ambulatory Assessment can be considered for non-ambulant and/or ambulant children with NMD (Main, Kairon, Mercuri & Muntoni, 2003; Bushby & Connor, 2011; McDonald et al., 2013; Messina et al., 2016). Future NMD studies in SA should investigate the use of complete standardised tools and validate instruments for our specific population and context.

While a correlation between functional ability and pulmonary function was not established in this cross-over study, other reports have indicated the association between the loss of upper limb function and pulmonary function regression (Meier et al., 2017; Ricotti et al., 2019; Corten & Morrow, 2020). The sample size was adequately powered for the primary outcome measure but may not have been sufficient to detect such an association. An estimated decrease in the primary outcome measure of two respiratory tract infections (respiratory morbidity) requiring antibiotics (SD:2) between groups might have been too high, especially for a three month intervention period. Therefore, the study might have been underpowered to detect any significance difference in primary outcomes between the training and the non-training period. However, there were no data available on which to base a sample size and power calculation. This study was explorative in nature, but the primary outcome sample size calculation constitutes a limitation of the study and should be adapted accordingly in future clinical trials.

The additional measures of inspiratory muscle strength (S-index, PIF and volume) were only assessed during the intervention period and therefore no between-group analyses could be performed. In addition, the validity and reliability of a single breath (such as S-index, PIF and volume) outcome measure versus three measurements of Pimax and SNIP are uncertain, but constitutes a limitation and should be considered in future assessments and trials. Furthermore, S-index, PIF and volume tests on the Powerbreathe K3[®] were not standardly recorded for all participants, as these measures did not form part of the original protocol, which could introduce bias. These measurements did however yield interesting and unexpected findings which were therefore reported but should be investigated in larger participant samples.

Another limitation to consider was that although normal speech and swallowing ability was used as a surrogate for sufficient bulbar function, similar to a prior report (Dohna-Schwake et al., 2006), oral control was not formally assessed and this may have impacted the ability to create a seal around the mouthpiece during assessment and IMT.

The lack of blinding of assessors to allocation could have introduced bias, which constitutes a limitation of the study. Data were collected by three different individuals, which may reflect a risk of bias owing to inter-rater inconsistencies. Confirmation of inter-rater reliability is recommended for future studies.

As with the pre-experimental study, the cross-over study also obtained subjective feedback from participants and their caregivers/clinicians related to their experiences of IMT, through open-text responses. Qualitative analysis of these responses was not done as this was beyond the scope of this study and future research is recommended to further explore participants' experience and perceptions of respiratory management techniques such as IMT.

6.9 Recommendations for clinical practice based on the cross-over RCT results

This cross-over study provides novel SA data related to children and adolescents with NMD. Based on the findings of this RCT, the use of daily IMT with a threshold device at an intensity of 30% Pimax for three months in children with a variety of NMD in SA seemed safe, well-tolerated and showed significant differences in inspiratory muscle strength and cough ability between and within groups (pre-post intervention). Even after IMT stopped, many of the improved pulmonary function values were maintained for three months, hence the advantages of IMT might be maintained. Therefore it is recommended that IMT could be considered as an adjunct intervention for the management of children (5-18 years) with NMD in SA, similar to other international findings (Winkler et al., 2000; Topin et al., 2002; Yeldan et al., 2008; Woszezenki et al., 2017).

In addition to the primary findings, during this cross-over RCT, discrepancies in the frequency and extent of pulmonary assessment (especially FVC and PEF) of participants were observed, as different institutions seem to follow different protocols, which do not all comply with the NMD clinical practice guidelines on assessment (Landfeldt et al., 2015; Chapter 2: 2.7.9). This highlights the need for regular, standardised pulmonary assessment, including measures of spirometry, cough ability and respiratory muscle strength (Pimax and Pemax) in order to monitor and plan appropriate respiratory management strategies. Pulmonary function assessment should be performed at least once a year.

As soon as the child becomes non-ambulant, present with a VC or FVC <80% predicted or turn 12 years old, they should be assessed twice a year, as recommended by clinical practice guidelines, as the risk for respiratory morbidity increases once ambulation is lost (Meier et al., 2017; Birnkrant et al., 2018; Finkel et al., 2018). A significant relationship between cough ability (PECF) and lung volumes/spirometry (PEF, FVC) has been shown in children with NMD, which implies that spirometry tests might be a valuable surrogate to identify patients at risk of respiratory morbidity if PECF values are not available and vice versa (Meier et al., 2017; Morrow et al., 2019). This might be especially helpful in resource-constrained countries such as SA and should be considered for clinical practice and research.

Similar to the findings from chapter 2, the importance of inclusion of cough augmentation and lung volume recruitment techniques as part of patients' home programme should be emphasised, as many participants in the cross-over trial only addressed cardiopulmonary complications once they arise and not as part of a preventative strategy.

6.10 Recommendations for research based on the cross-over RCT results

This study did not find a significant difference in the frequency of hospitalisations, respiratory infections, lung volumes and flow or total child/proxy PedsQL scores between the training and non-training period. Larger sampled and longer term studies might be needed to determine if the use of IMT can translate into decreased respiratory morbidity and improved overall HRQoL.

In answer to the question posed in Chapters 1 and 3, this RCT found that IMT seems to be safe, acceptable, well-tolerated and effective in children with a variety of NMD. This cross-over RCT showed that the use of IMT improves inspiratory muscle strength, the ability to create inspiratory flow and improved cough, which is all of clinical relevance to prevent secretion retention and maintain lung and chest compliance.

The results also indicated a significant difference in children's self-reported HRQoL in the Physical domain, which could suggest that IMT assisted participants to perform functional tasks better than before. However, these findings need to be confirmed with larger samples and longer duration RCT. This study has explored and found a possible alternative intervention for children with NMD which can be used as a foundation for future trials.

Future clinical trials evaluating the use of IMT in children and adolescents with NMD can consider investigating the effect of various training devices (threshold vs constant load) and titration of dose, frequency, duration and training intensity to determine if training at values higher than 30% of Pimax will be safe and/or more effective in this patient cohort. In larger study samples the different effect of IMT in conditions such as DMD, SMA, CMD can be determined. Furthermore, the effect of anthropometric measures such as BMI can be considered in future studies, as patients might respond differently to IMT. Unfortunately, novel therapies such as Idebenone (Mayer et al., 2017; Jalloh et al., 2018) are not yet available in SA and other alternative treatment strategies should therefore be investigated in order to improve HRQoL and maintain pulmonary function for as long as possible in children and adolescents with NMD.

Another consideration will be to develop and/or validate condition specific, age-appropriate standardised outcome measures to assess upper and lower limb function and perceived exertion which can be used across the progression of NMD, for both ambulant and non-ambulant patients (Pfeiffer et al., 2002; Mercuri et al., 2012; Mazzone et al., 2012; McDonald et al., 2013), and in particular for the SA context.

6.11 Conclusion

This cross-over RCT found no evidence of a difference in the number of hospitalisations and respiratory infections requiring antibiotics between the IMT intervention and control periods (non-inferiority); no adverse events related to IMT were reported and participant satisfaction and adherence were high. Inspiratory muscle strength (Pimax), cough ability (PECF) and HRQoL (child reported PedsQL Physical domain) showed a significant improvement with the intervention compared to control periods, which has clinical relevance for children with NMD. In addition, within-group changes occurred during the intervention period for parameters such as Pimax, SNIP, S-index, PIF, PECF and child reported PedsQL (Physical domain). Like other studies, no significant changes were observed between or within groups for spirometry and functional ability.

The use of IMT appears to be safe, acceptable, well-tolerated and effective in improving inspiratory muscle strength and cough efficacy in children with a variety of NMD, including dystrophinopathies and could be considered as an adjunct to respiratory management.

The results from this study within the broader context of literature, the clinical relevance of the findings, recommendations and the limitations of the study are described in Chapter 7.

Chapter 7: MAKE EVERY BREATH COUNT!

Discussion, recommendations, limitations of the study and conclusions

7.1 Introduction

The World Health Organisation (WHO) constitution states: “The enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social condition” (WHO constitution: <https://www.who.int/about/who-we-are/constitution>). Therefore, once children with neuromuscular disease (NMD) are diagnosed, assessment and anticipatory management should be provided to reduce pulmonary complications and improve their health-related quality of life (HRQoL) (Finder et al., 2004; loos et al., 2004; Wang et al., 2007; Bushby et al., 2010; Farrero et al., 2013; Goemans & Buyse, 2014; Birnkrant et al., 2018; Finkel et al., 2018; McDonald & Mercuri, 2018).

The influence of progressive respiratory muscle weakness, poor cough ability and subsequent respiratory morbidity was previously described (Chapter 1: 1.1.1; 1.1.2 ; 1.1.3). In Chapter 1 the possibility of using inspiratory muscle training (IMT) as part of respiratory management in children with NMD was proposed, in order to address the array of respiratory complications that commonly manifest in this patient cohort. The knowledge of South African (SA) physiotherapists on respiratory management, including their view on IMT, was explored, available literature appraised and an IMT protocol was developed. Thereafter a pre-experimental, pilot study and finally a cross-over randomised controlled trial (RCT) was implemented to describe and determine the safety and effect of IMT on clinical outcomes and HRQoL in children with NMD in SA.

This chapter describes the main findings of the study in relation to the objectives (1.3.1) and within the context of other literature. The generalisability of the findings, the clinical and research implications as well as limitations and recommendations for future research will be discussed.

7.2 Respiratory management strategies including the use of IMT for children with NMD: What did South African physiotherapists have to say?

The survey aimed to describe SA physiotherapists’ knowledge of clinical practice strategies in the respiratory management of non-ventilated children with NMD as well as describing the management strategies currently used in practice which included the use of IMT.

The survey findings suggested that few SA physiotherapists may have clinical experience and expertise regarding the respiratory management of children with NMD and although respondents were generally aware of international clinical practice guidelines/recommendations they still favoured traditional, manual airway clearance techniques (ACT) (McCool & Rosen, 2006; Finkel et al., 2018).

Physiotherapists who took part in the SA survey recommended and used respiratory muscle training (IMT and/or expiratory muscle training) as part of chronic management in children and adolescents with NMD (Chapter 2: 2.6.5.5; 2.6.6). Despite limited evidence and safety concerns as raised in literature and chapter 3, IMT, in particular, was supported by approximately 75% of survey respondents and clinically used by 67%. Inspiratory muscle training devices are available in SA, manual devices are relatively inexpensive and considered to be easy to administer and monitor. The high levels of adherence and participant satisfaction in both the pre-experimental, pilot study and cross-over RCT confirms the viability of using IMT in the SA context.

In general, SA physiotherapists included in the survey were aware of the indications for the implementation of other respiratory management strategies such as proximal ACT (cough augmentation), considering poor cough ability is evident in most children with NMD, particularly once the disease progresses and decreased pulmonary function becomes evident. Despite the numerous reported advantages of manual lung volume recruitment (LVR) techniques such as breath-stacking with an ambubag, which is easy to apply and has low cost implications, very few SA physiotherapists recommended or described using LVR techniques (Finder, 2010; Bianchi et al., 2014; Chiang et al., 2018; Katz et al., 2019). The reasons for this are unknown. Manual cough assistance is also cost-effective, easy to implement, can be used in patients from a young age, is applicable for the SA healthcare context, well supported by literature and was recommended and implemented by most of the SA physiotherapists (Farrero et al., 2013; Bianchi et al., 2014; Toussaint et al., 2016; Chatwin et al., 2018). Despite clinical practice guideline recommendations, mechanical cough assist (MI-E) was not well supported or used by SA physiotherapists. Possible reasons for the lack of implementation could be lack of knowledge and/or skill of SA physiotherapists, but also limited resources as these devices are costly and cannot be afforded by most parents/caregivers of children with NMD. Cough assist devices may also not be suitable for many patients in rural areas where electricity supply may be unreliable or unavailable.

Specifically for the SA context, the combination of manual insufflation with an ambubag and manually assisted cough (MAC) is recommended as cost-effective management strategies for children with NMD, which can be used at home and even in rural areas (Anderson et al., 2005; Finder, 2010). Clinical trials in children with NMD are essential to explore respiratory interventions which may reduce respiratory morbidity, increase HRQoL and bridge the gap between healthcare available for children in both public and private healthcare sectors in SA.

7.3 The use of inspiratory muscle training in children with neuromuscular disease: What does the literature say?

The systematic review suggested that IMT may be effective in improving inspiratory muscle strength in children with NMD, but also highlighted the need for clinical trials to determine the safety, practicality, acceptability and efficacy of IMT in children and adolescents (5-18 years) for clinically important outcome measures. The review was unable to determine the optimal intensity, dose, frequency and duration of IMT, but had similar findings to that of an integrative review published during the same year (Woszezenki et al., 2017).

Despite the hypothesised advantages of improved pulmonary function, decreased respiratory morbidity (Topin et al., 2002; Hull et al., 2012; Woszezenki et al., 2017; Silva et al., 2019) and the support seen for IMT in the SA survey (Chapter 2), management strategies such as respiratory muscle training have not yet been included as part of standard NMD clinical practice guidelines. This omission could be explained by the findings of the systematic review (Chapter 3), which highlighted the paucity of evidence on safety, practicality and acceptability of IMT. In addition, the controversy of IMT in patients with dystrophinopathies and the limited generalisability of results due to small sample sizes and high risk of bias have also been highlighted (Moseley et al., 2002; Bhowmik et al., 2009; Straub, 2013; Auger et al., 2017; Silva et al., 2019).

7.4 Inspiratory muscle training in children with neuromuscular disease: To train or not to train?

This thesis explored and tested the hypothesis that IMT might be an easily accessible, safe, cost-effective, viable and acceptable treatment strategy that could reduce respiratory symptoms, improve pulmonary function and decrease respiratory infections whilst also improving HRQoL in children with NMD. The question that required an answer was therefore whether or not inspiratory muscle training should be implemented in children with NMD and respiratory muscle weakness: “to train or not to train?”.

7.4.1 Adverse events, hospitalisations and respiratory tract infections

No adverse events related to IMT were reported during either the pre-experimental, pilot or cross-over RCT. Participant adherence was good and satisfaction was high to extremely high, which suggests that IMT with a threshold device at an intensity of 30% Pimax could be considered as an acceptable, safe and effective adjunct treatment strategy in children with NMD (Wanke et al., 1994; Winkler et al., 2000; Yeldan et al., 2008; Woszezenki et al., 2017).

Although the frequencies of respiratory infections and hospitalisations reported in this study were low, the cross-over RCT did not report any difference in respiratory morbidity (number of respiratory infections and/or hospitalisations) between the training and non-training periods ($p=0.20$; $p=0.60$). Further long-term research is needed to determine if IMT can reduce respiratory morbidity in children with NMD.

7.4.2 Pulmonary function: lung volumes and flow

The pre-experimental, pilot and cross-over RCT did not find a significant change in spontaneous and forced spirometry values namely vital capacity (VC), forced vital capacity (FVC), forced expiratory volume in one second (FEV_1) and peak expiratory flow (PEF)) within group and between groups, similar to findings from previous studies (Koessler et al., 2001; Yeldan et al., 2008; Silva et al., 2019). Even a significant increase in inspiratory muscle strength (Pimax) might not translate into improved lung volumes, owing to the sigmoid shape of the pressure-volume curve, especially with progressed restrictive pulmonary disease seen in study participants (Laghi & Tobin, 2003; Servera et al., 2003; Aboussouan, 2009).

Both the pre-experimental, pilot and cross-over RCT reported a significant increase in the ability to create airflow during inspiration (peak inspiratory flow (PIF)) ($p=0.02$; $p=0.0009$), which could indicate improved inspiratory muscle contraction ability. In addition, the cross-over RCT found evidence of a greater improvement of PIF after six weeks of IMT as compared to the pre-experimental, pilot study ($p=0.0003$), and with continued improvement until 12 weeks (3 months) of training. This trend could allude to a true improvement in inspiratory muscle strength (training effect) and not merely a learning effect.

7.4.3 Pulmonary function: inspiratory muscle strength

This pre-experimental, pilot and cross-over study, which included mostly non-ambulant participants, supported a significant improvement in inspiratory muscle strength measures (maximum inspiratory mouth pressure (Pimax), PIF and strength index (S-index)) pre-post intervention, despite participants' level of ambulation.

The cross-over RCT further reported an increase in median (IQR) Pimax of 14.0 (1.0 to 25.0)cmH₂O during the intervention period, compared to a change of 3(-5 to 7)cmH₂O during the non-training period (p=0.01). In addition, the cross-over trial provided evidence of a significant difference in Δ Pimax between the training and the non-training periods (p=0.01), which was not influenced by the type of NMD, presence of scoliosis or level of ambulation.

The Pimax values reported during the pre-experimental and cross-over RCT showed significant improvement pre- to post-IMT (p=0.01; p=0.0002) and over the IMT period. Although the sniff nasal inspiratory pressure (SNIP) values did not show significant change during the pre-experimental, pilot study (p=0.60) and were variable throughout the six-week and three month IMT period, there was a significant pre-post intervention improvement during the cross-over RCT (p=0.01). Therefore, the increase in PIF values, the significant pre-post intervention S-index improvement during the pre-experimental, pilot study (p=0.02) and cross-over RCT (p=0.002), as well as significant change during intervention, was not unexpected.

A variety of inspiratory muscle strength measures (Pimax, SNIP, PIF and S-index) all consistently showed significant change and continued improvement after the first two weeks of IMT, during both the pre-experimental and cross-over trials, which may allude to a training effect, over and above the initial learning effects and an improved coordinated effort when performing inspiratory assessment tests. Furthermore, the fact that improved Pimax and SNIP values did not significantly decrease for three months even after IMT was ceased could suggest a possible residual or carry-over effect of IMT which warrants further investigation.

The cross-over RCT found a significant association between Δ Pimax and participants' pre-intervention functional ability for both upper and lower limbs (Brooke: p=0.03; Vignos: p=0.02). This association between inspiratory muscle strength and functional ability supports previous suggestions that IMT may have greater clinical benefit if initiated earlier in the disease process when both physical and pulmonary function is relatively preserved (McCool & Tzelepis, 1995; Koessler et al., 2001; Eagle, 2002; Yeldan et al. 2008).

Conversely, it has been reported that patients with poor respiratory muscle strength and advanced respiratory disease are still able to perform IMT manoeuvres quite easily and may still benefit from this intervention (Topin et al., 2002; Human et al., 2019). Although patients with higher functional ability may respond better to IMT, the use of IMT in the pre-experimental and RCT studies was found to be both acceptable, well-tolerated and effective (Pimax, PIF, SNIP and peak expiratory cough flow (PECF)), even in participants who were mostly non-ambulant and with evidence of advanced respiratory disease. This suggests that IMT may be beneficial at various disease stages, both before and after ambulation is lost.

7.4.4 Pulmonary function: cough ability

Assisting a patient's inspiratory capacity through LVR or IMT can directly improve cough efficacy because it increases the volume of air that can be expelled during a cough effort (Aslan et al., 2013; Rose et al., 2018; Toussaint et al., 2018; Castrillo et al., 2019). Increasing voluntary inspiratory capacity, by improving inspiratory muscle strength, could have a similar effect. This RCT reported a median (IQR) Δ PECF of 20.0 (10.0 to 60.0)L/min during the IMT period, compared to a change (decline) in PECF of -15 (-40 to 10)L/min during the non-training period ($p=0.0001$). Evidence of a significant pre-post IMT improvement in PECF ($p=0.0005$) with a possible residual effect post three months of IMT was also found. On the contrary, there was no significant difference post intervention in PECF during the pre-experimental, pilot study ($p=0.63$), despite a significant improvement in Pimax ($p=0.01$). These findings might be attributed to the shorter (6-week) IMT duration and the small sample size of the pilot study. In addition, Δ PECF might be dependent on the number of IMT sessions completed, as suggested by the results of the cross-over RCT.

In the cross-over study, Δ PECF during intervention was not significantly influenced by participants' functional ability (Brooke, Vignos and Motor Function Measure (MFM)) before IMT, despite the reported association between inspiratory muscle strength (Δ Pimax) and pre-intervention Brooke and Vignos scores. In addition, the Δ PECF during intervention was not significantly influenced by the type of NMD, presence of spinal deformities or the participants' level of mobility (ambulant/non-ambulant). This suggests that IMT has the potential to improve cough ability regardless of the patient's functional ability, or presence of postural deformities, although Pimax improvement might be greater if IMT were instituted earlier during the course of the disease.

7.4.5 Functional ability, health-related quality of life (PedsQL), perceived exertion (OMNI), participant adherence and participant/parent/caregiver/clinician feedback

Limited evidence is available on the functional ability of children with NMD

(Eagle, 2002; Janssen et al., 2016). This study provided novel data about the functional ability of 31 children and adolescents with NMD (pilot study n=8; cross-over RCT n=23) and is the first to record Brooke, Vignos and items of the MFM in this cohort in SA. Due to the age range of participants and disease progression, the majority of participants were non-ambulant (Vignos: 9) and a change in functional ability was not expected, even after three months of IMT. Despite the participants' clinical presentation, age range and restrictive pulmonary disease, upper limb function (Brooke scale) was relatively preserved in both the pre-experimental, pilot study and cross-over RCT with a median score of 3/6 and 2/6 respectively. In both studies, participants also presented with good upper limb function and coordination based on the MFM (mean MFM 26 (± 1.83) and median 27 (16-29) respectively). The pre-experimental, pilot study indicated a significant change in upper limb function and coordination post-IMT (MFM: $p=0.03$), which was not observed in the cross-over RCT ($p=0.64$).

Few studies have reported the effect of respiratory management techniques on HRQoL or compliance with these treatment strategies (McCool & Rosen, 2006), both of which were measured in the pre-experimental, pilot and cross-over studies. A surprising finding was the suggested effect of IMT on HRQoL. Although none of the pre-post changes in the self-reported/child PedsQL total, Physical domain or Psychosocial domain was statistically significant, the child PedsQL total score and Psychosocial domain in the pre-experimental, pilot study showed a medium and large effect size respectively (0.52; 0.81). During the cross-over RCT, there was evidence of a significant change in self-reported/child proxy PedsQL Physical domain within ($p=0.002$) and between groups ($p=0.003$). This suggests that improved inspiratory muscle strength, breathing and cough ability may translate into improved perceived physical as well as psychosocial function. Larger, longer-term clinical trials are required to confirm or refute these findings.

The OMNI scale has been used in children with NMD to assess the level of perceived exertion during exercise (Jansen et al., 2013) and during both the pre-experimental, pilot and cross-over study low to moderate OMNI scores were reported. Based on these reported OMNI scores, IMT did not cause severe fatigue in this cohort of patients.

Participant adherence with the IMT programmes for the six weeks, pre-experimental, pilot study and the three month cross-over study was good, as evident from both the self-reported number of training sessions (training diaries) and electronically recorded (Powerbreathe[®]) training sessions, which had a high level of agreement. The median number of training sessions, out of a maximum of sixty, over six weeks recorded by clinicians and the Powerbreathe[®] devices were similar (52 and 51 respectively). Over the three-month IMT period, the median number of training sessions recorded by parents/caregivers/clinicians and the Powerbreathe[®] devices were 95 and 93 respectively. The majority of participants in both clinical studies had the same number of training sessions recorded in their training diaries and the Powerbreathe[®] devices. The good participant adherence could be explained by the high levels of satisfaction reported by participants based on a 10-point visual analogue scale (VAS) during the pre-experimental (median: 9/10) and cross-over trial (median: 8/10). Most participants (n=26/31) indicated that they would like to continue with IMT as part of their home programme after the conclusion of the data collection. The open-text responses from participants and parents/caregivers/clinicians supported the hypothesis that IMT could provide symptomatic respiratory relief, improve physical ability and performance of activities of daily living, enhance participation and even have a positive effect on the psychosocial well-being of children with NMD.

Based on the results from this study and contrary to the literature (Winkler et al., 2000), Δ Pimax did not seem to be dependent on training adherence or the number of IMT sessions completed. The cross-over study could also not find evidence of a significant correlation between Δ SNIP and the number of IMT sessions, whether self-reported or recorded. Conversely, Δ PECF was significantly correlated with the number of training sessions recorded by participants ($p=0.02$) and electronically on the Powerbreathe[®] devices ($p=0.03$). Clinically this suggests that improvement in Pimax could be evident early during IMT intervention, while translation into improved cough ability might take longer and this should be considered with the implementation of IMT in children with NMD.

7.5 Recommendations for clinical practice in children with neuromuscular disease

7.5.1 Implementation of cost-effective and safe respiratory management strategies such as inspiratory muscle training and cough augmentation

Despite the availability of IMT devices and their use being well supported by SA physiotherapists as part of chronic management for children with NMD, none of the participants in the pre-experimental, pilot and RCT had previously used IMT.

The findings of the pre-experimental, pilot and cross-over RCT provide novel data regarding the safety, suitability, acceptability and efficacy of IMT and could provide a readily available, inexpensive option to mitigate inspiratory muscle weakness and poor cough ability which is so evident in this patient cohort. The use of threshold IMT devices at 30% Pimax, 30 breaths, twice a day appears safe and was effective in improving several relevant outcome measures. This regime may therefore be recommended as an adjunct treatment for SA children and adolescents with NMD. Training can be started at 10 breaths, with three sets, until the patient can complete 30 consecutive breaths, twice a day for three months. It is recommended that patients make use of IMT training diaries because it assisted participants and their parents/caregivers to monitor progress (date, repetitions, sets, time, duration), levels of exertion (OMNI scale) and establishing a daily IMT routine (Topin et al., 2002; Yeldan et al., 2008; Woszezenki et al., 2017; Katz et al., 2019; Wenninger et al., 2019).

Based on the results of the pre-experimental, pilot and cross-over studies, it may be suggested that IMT should be started prior to losing ambulation, as pulmonary function starts to decline with decreased functional ability and the risk of respiratory complications become higher (Birnkrant et al., 2018). Even patients with progressed disease, non-ambulant and/or with decreased oral control can perform and may benefit from IMT in terms of improved inspiratory muscle strength and cough efficacy with potential symptomatic relief (Human et al., 2019). The ideal time to start IMT may therefore be prior to loss of ambulation, but even patients that are already non-ambulant should be provided the opportunity to train, while being monitored by parents/caregivers and healthcare professionals. The manufacturers of the Powerbreathe[®] device suggest that after the three-month foundational training has been completed, patients could continue with IMT twice, every second day to maintain their inspiratory muscle function for as long as possible. This suggestion has not been evaluated in this study and requires further research over a longer period.

An improved ability to take a deep breath has numerous advantages. These benefits include maintaining chest wall and lung compliance, assisting with secretion mobilisation and the optimisation of the length-tension relationship of the respiratory muscles resulting in a stronger cough (expiratory flow), with subsequent effective airway clearance (Boitano, 2006; McCool & Rosen, 2006; Finder, 2010; Farrero et al., 2013; Chatwin et al., 2018; Finkel et al., 2018). As Chapters 2 and 3 have indicated, there is no clear evidence of superiority for physiotherapy respiratory management techniques to address the array of respiratory complications observed in children with NMD. Therefore cost, healthcare context, patient preference and ability, therapist knowledge/proficiency, and equipment availability should be considered when deciding on intervention strategies.

Novel therapies such as Idebenone for patients with Duchenne muscular dystrophy (DMD) aim to improve mobility for longer and decrease the pulmonary regression (Boentert et al., 2017; Mayer et al., 2017), but these costly therapies are not readily available in SA. Therefore alternative, cost-effective strategies such as IMT that have the potential to improve clinical outcomes and HRQoL could be considered as part of management in children with NMD in SA. Despite the known efficacy and low cost of LVR and MAC (McCool & Rosen, 2006; Chiang et al., 2018; Toussaint et al., 2018), none of the participants in the pre-experimental, pilot study and only two from the cross-over RCT indicated that they used LVR. Lack of lung volume recruitment or insufflation therapy in the study participants could be attributed to a lack of knowledge on how to use devices such as mechanical insufflation-exsufflation and resuscitation bags, but also limited resources to acquire the necessary equipment. Improved resource allocation in schools and NMD clinics at hospitals is therefore needed to ensure the implementation of NMD assessment and management practice guidelines.

As cost is not such a great consideration with the use of ambubags, physiotherapists' knowledge and skill in this regard need to be addressed. Safe and cost-effective airway clearance techniques such as LVR (with an ambubag) and MAC are recommended for use in children with NMD in SA. Focused education and training is needed to improve SA physiotherapists' skills and knowledge regarding available and cost-effective treatment strategies.

7.5.2 Evidence-based practice and education for improved respiratory management for children in South Africa

Anticipatory treatment strategies with a renewed focus on safety, viability, HRQoL and education are recommended for patients with NMD in SA (Wang et al., 2007; Bushby et al., 2010; Birnkrant et al., 2018; Goemans & Buyse, 2014; Toussaint et al., 2018). The use of evidence-based physiotherapy is essential to improve professional practice and maintain standards of healthcare service delivery (Stander et al., 2020). Clinical practice guidelines can improve the efficiency of healthcare which will free up resources for more equitably distributed healthcare services (Woolf et al., 1999).

Despite the advances in management strategies for children with NMD, physiotherapists and parents/caregivers might also not always be aware of, or receive sufficient information about, available management strategies for respiratory complications (Finder et al., 2004).

Suboptimal access to specialised care and poor adherence with NMD clinical practice guidelines could be attributed to the public health care sector not funding these services or that healthcare workers with special expertise in NMD are scarce (Avendaño & Güell, 2003; Servera et al., 2003; Landfeldt et al., 2015; Vry et al., 2016). Standardisation of assessment and management strategies, aligned with clinical practice guidelines, for children with NMD in SA is therefore recommended. In addition, education of parents/caregivers and members of the multi-disciplinary team needs to be done so that ventilatory support, LVR, cough augmentation and IMT can be implemented as required (Birnkrant et al., 2018; Finkel et al., 2018; Toussaint et al., 2018). Advocacy, training and the dissemination of information are essential to promote cost and clinically effective physiotherapy respiratory management strategies.

Although the majority of participants were already non-ambulant at the time of the study, it was notable that they were not undergoing regular pulmonary monitoring as recommended (Toussaint et al., 2018; Birnkrant et al., 2018). Spirometry was performed in most cases during patients' annual follow-up appointments at the hospital (NMD clinic) and PEF, Pimax and expiratory muscle strength (Pemax) were not documented. As recommended by other studies and guidelines, pulmonary monitoring, including spirometry (lung volumes and flow), PEF, Pimax and Pemax should be performed for children with NMD in SA with every clinic visit, at least once per annum, and every six months as soon as patients become non-ambulant, their FVC or VC falls below 80% predicted value, and/or they reach 12 years of age (Miske et al., 2004; Mayer et al., 2017; Chatwin et al., 2018; Chiang et al., 2018; Finkel et al., 2018; Kinane et al., 2018; Stephan et al., 2020).

7.6 Recommendations for future research

Research and surveys among children with NMD in SA are limited, hence this study provides the foundation for further research to be conducted. The sample size of the cross-over RCT (n=23) compares well with similar international clinical studies and provides context-specific data for children in SA, which could inform the planning of future NMD clinical trials.

7.6.1 Pulmonary function

The effect of IMT and improved inspiratory muscle strength translating into improved cough ability may only become evident with longer training periods. It is therefore suggested that to improve cough ability, IMT programmes of longer than six weeks should be considered in children with NMD. To ascertain if the use of IMT can improve, maintain or reduce the regression of lung volumes in children with NMD, longer-term and larger sample size clinical trials are warranted.

A study conducted by Huang et al. (2003) using a training intensity of 75% of Pimax for 24 breaths per day, for four weeks, increased by 36% of Pimax. This might indicate that an increased intensity could improve outcomes beyond what was reported in this study. The titration of training intensities, optimal dose, frequency and duration of IMT in children with NMD need to be determined in future research. Future clinical trials evaluating the use of IMT in children and adolescents with NMD can consider investigating the effect of various training devices (threshold vs constant load) and titration of dose, frequency, duration and training intensity to determine if training at values higher than 30% of Pimax will be safe and/or more effective in this patient cohort. In larger study samples the difference of IMT in conditions such as DMD, spinal muscular atrophy (SMA), congenital muscular dystrophy (CMD) can be determined. Furthermore, the effect of anthropometric measures such as body mass index (BMI) and scoliosis can be considered in future studies, as patients might respond differently to IMT.

Further studies are also recommended to assess the clinical effect of dual-way training in patients with NMD, with both in- and expiratory muscle training, which was beyond the scope of this research (Yeldan et al., 2008; Wenninger et al., 2020).

Volitional respiratory muscle strength tests can usually be performed easily, but it may be difficult to ensure a maximal effort, especially in the presence of poor oral control (ERS, 2002; Nicot et al., 2006; Caruso et al., 2015; Boentert et al., 2017). Therefore, alternative inspiratory muscle strength measures besides Pimax and SNIP such as magnetic phrenic nerve stimulation, transdiaphragmatic pressures (Pdi), twitch mouth pressure and tension-time index (TTi) of the inspiratory muscles could be considered for future studies (Winkler et al., 2000; Perrin et al., 2004; Hull et al., 2012; Hulzebos et al., 2018; Dassios & Dimitriou, 2019). Non-volitional tests such as phrenic nerve stimulation could be of particular value when patients have difficulty in performing volitional tests, present with low values (e.g. Pimax) or if there is a great variation in assessment values (Nicot et al., 2006; Caruso et al., 2015; Boentert et al., 2017; Hulzebos et al., 2018). These interventions are however invasive and might not be readily available in SA. Other alternative assessment techniques such as the use of scans (MRI and/or CT) and ultrasound to determine diaphragm placement, thickness and excursion of the diaphragm might be considered for future trials (Boentert et al., 2017; Harlaar, Ciet, van der Ploeg, Brusse, van der Beek, Wielopolski & van Doorn, 2018).

These devices are however costly and expertise are not always readily available (Nicot et al., 2006; Farrero et al., 2013). Measuring the thickness of the diaphragm in the zone of apposition using ultrasound is a potentially feasible outcome, as diaphragm thickness correlates with the strength of the diaphragm and is non-invasive, portable and requires little cooperation from the patient (Farrero et al., 2013; Harlaar et al., 2018).

The threshold PEF values to predict outcomes such as weaning from the ventilator and indication of cough augmentation in young children might be lower than the general threshold of 270L/min and 160L/min, as these levels were determined in adult studies (Dohna-Schwake et al., 2006; Panitch, 2006; Sejerson & Bushby, 2009). Further investigation is needed to determine threshold values in children with NMD.

7.6.2 Functional ability, health-related quality of life and addressing the needs of patients and their families

As NMD are chronic conditions, long-term studies are required to determine the effect of respiratory management such as IMT not only on clinical outcome measure including lung volumes and inspiratory muscle strength, but also respiratory morbidity, HRQoL and patient experience (Gozal & Thiriet, 1999; McCool & Rosen, 2006; Schechter, 2007; Auger et al., 2017; Wenninger et al., 2019). To optimise healthcare service delivery, the needs and perspectives of children with NMD and their parents need to be understood. This pre-experimental, pilot study and RCT asked participants, clinicians and caregivers for their opinion about the use of IMT, but in-depth qualitative studies are recommended to better explore the perspectives of SA children with NMD and their caregivers in order to adapt treatment strategies accordingly.

Functional tests such as Brooke and MFM were developed for a variety of NMD and might not account for specific clinical differences, hence disease specific outcome measures should also be considered in future studies (Mazzone et al., 2012). Scales such as the Comprehensive Functional Scale for DMD (CFSD), Muscular Dystrophy Functional Rating Scale (MDFRS) which is a 4-point grading system, Performance of Upper Limb test (PUL), ACTIVLIM, Egen Klassifikation (EK) scale and the Northstar ambulatory test should be considered for future research among children with NMD in SA (Lue et al., 2009; Mazzone et al., 2012; Mercuri et al., 2012; Kim, Jung, Kim, Lee, Park, Shin et al. 2018; Ricotti et al., 2019). Alternatively, context-specific measurement tools need to be developed, disseminated and implemented to improve assessment, monitoring and clinical practice in SA. Also, the effect of improved inspiratory muscle strength on upper limb function and coordination should therefore be confirmed with larger, randomised controlled trials.

Younger participants may have had difficulty in understanding the OMNI scale's abstract concepts and expressing their perceived levels of exertion. Therefore it is recommended that the OMNI scale be adapted and validated for the SA socio-geographical and cultural context and for all age groups.

Geographical and logistical challenges limited the number of participants that could be recruited over two years. Due to the lack of an NMD database/patient registry and the limited number of specialised NMD centres/clinics in SA (Vry et al., 2016; Jalloh et al., 2018), it was challenging to identify an adequate sample of patients with the same diagnosis, level of mobility and similar clinical presentation. These challenges and the need to travel long distances for follow-up assessments need to be considered with the planning of future clinical trials.

7.7 Strengths of the study

This study provided novel data regarding the knowledge and implementation of respiratory management strategies supported and implemented by SA physiotherapists among children and adolescents with NMD. The survey findings also highlighted areas to be explored with future research.

To address the hypoventilation and decreased cough ability caused by progressive inspiratory muscle weakness, IMT as an adjunct treatment was investigated, despite controversy and contradictory findings in literature. The systematic review indicated the need for further clinical trials to be conducted in order to determine the safety and efficacy of IMT in this particular patient cohort. This review provided the foundation for the pre-experimental, pilot study and cross-over RCT, but also for future clinical trials to be conducted in the field of NMD.

The pre-experimental, pilot study provided valuable information for the planning of the cross-over RCT, but also for future research. The cross-over RCT sample size was similar to international IMT studies and provided novel findings on the clinical value of IMT in children and adolescents with NMD in SA, in particular, to improve inspiratory muscle strength and cough ability. Limited data are available on the use of IMT in this population and the results from this study can also provide guidance for other clinical trials.

In addition, the findings identified current gaps in literature and what is known about healthcare management strategies for children with NMD in SA and highlights opportunities for future research.

7.8 Limitations

Similar to other studies in NMD, participants differed regarding diagnosis, disease progression and distribution of muscle weakness (Aslan et al., 2013). Although the majority of participants in this study were diagnosed with DMD, the heterogeneity of participants constitutes a limitation (Dohna-Schwake et al., 2006). Inspiratory muscle training might have a positive and clinically relevant effect for children with a wide variety of NMD, a suggestion supported by the finding that the type of NMD did not affect either the ΔP_{imax} or ΔP_{ECF} significantly. However, considering the majority of participants had DMD, this may skew the results of this study. Results from studies primarily consisting of patients with DMD cannot be extrapolated to all other NMD, due to the sex bias and possible cognitive involvement commonly observed in dystrophinopathies such as DMD and congenital/childhood myotonic dystrophy (Guglieri & Bushby, 2011; Ho et al., 2015; Morrow et al., 2019). These are factors that could influence the outcome of IMT and should be considered in future research.

The validity and reliability of using selected items of MFM have not been determined, which is a limitation of this study, as only ten items were used as part of the assessment.

The pre-experimental, pilot and RCT studies made use of a peak flow meter and mouthpiece to determine PEF, however, the use of face mask interfaces for measuring PEF is recommended for future research as standard practice among children with and without oral control (Chatwin et al., 2018; Chiang et al., 2018). The mouthpiece interface used for measuring PEF may have influenced the results, particularly if oral control were affected. It is therefore recommended that future studies use a face mask interface for testing PEF in all subjects with NMD, as outlined in guidelines published after the start of this study (Chatwin et al., 2018). In addition, PEF was not measured using a pneumatograph, but with a handheld Wright peak flow meter, similar to other studies (Dohna-Schwake et al., 2006; Chiang et al., 2018). This could influence measurements and might be viewed as a limitation; however, peak flow meters are inexpensive and readily available for the monitoring of NMD, especially in resource-constrained countries such as SA.

Another possible limitation of this study was that the PedsQL generic score was used, which might be unable to describe the subtle differences and effects of NMD on HRQoL (Iannaccone et al., 2009; Messina et al., 2016). Although using the generic score makes it easier to compare results with other studies (Messina et al., 2016), future studies in children with NMD can consider using disease specific modules or instruments.

Similar to other clinical trials among children with NMD (Jansen et al., 2013), the assessors during the pre-experimental, pilot study and cross-over RCT were not blinded to group allocation, as this was not feasible. The researcher and research assistants had to teach participants how to perform IMT, monitor their level of exertion and adjust their training programme accordingly.

The findings from the pre-experimental, pilot study and cross-over RCT suggest that participants tolerated IMT well, but the validity and reliability of the OMNI scale in the SA context is unknown, and this constitutes a limitation of this study. The OMNI scale might also not be generalisable to all age groups of children and adolescents (Pfeiffer et al., 2002).

7.9 Conclusion

Early childhood intervention is essential and in SA, with its limited resources and the envisioned implementation of a national health insurance programme, interventions should be used effectively and efficiently, whilst ensuring safety and improved outcomes for patients with NMD. The results from the various phases of this research provide novel data about physiotherapists' knowledge and implementation of respiratory treatment strategies in SA as well as the use of IMT in children and adolescents with NMD. Although the published literature was inconclusive on whether IMT in children with NMD should be included as a standard management strategy, SA physiotherapists recommended and reported using this technique in clinical practice. Clinical studies were therefore implemented to describe the safety, practicality, acceptability and efficacy of IMT in SA children with NMD, for the first time.

The results from both the pre-experimental, pilot study and RCT suggest that the proposed IMT protocol, using a Powerbreathe K3[®] device, is viable, safe, well-tolerated and acceptable in this cohort of patients and was associated with objective improvement in clinical outcomes such as inspiratory strength, flow, cough ability and self-reported HRQoL (Physical domain). Larger, clinical trials are recommended to identify the optimal dose and frequency of IMT over a longer term.

This thesis suggests that IMT is a safe, effective, low-cost adjunct treatment that should be considered to improve inspiratory muscle strength, cough efficacy and HRQoL in children with NMD presenting with respiratory muscle weakness.

To train or not to train-yes, you can!

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APPENDICES

Appendix Ai: Information letter and informed consent for validation of standard of care questionnaire

Dear doctor/professor,

RE: Validation of questionnaire to determine standard of care

My name is Anri Human and I am a registered PhD student in Physiotherapy at the University of Cape Town. We are doing a research study on the physiotherapy methods used on children and adolescents with neuromuscular diseases (NMDs) including Duchenne's muscular dystrophy (DMD), myopathy, and spinal muscular atrophy (SMA). Firstly, our research aims to determine how effective different cough assist techniques are for children with NMDs who are admitted to hospital with chest infections. Secondly we would like to investigate the effect of a three month inspiratory muscle training programme as an adjunct to standardised care. The research will be conducted at Red Cross War memorial Children's Hospital (RCWMCH) in Cape Town as well as Doctor George Mukhari Academic Hospital (DGMHAH) in Pretoria.

In order to be able to conduct randomised controlled trials comparing standard chest physiotherapy (CPT) with alternative interventions, it will be necessary to define what constitutes standardised CPT in South Africa. Comparing an alternative intervention/adjunct to conventional therapy/standardised care can assist in concluding more rigorously that any significant changes seen between the experimental and control groups are in fact due to the intervention that is being assessed.

The attached questionnaire has been developed to determine what constitutes current CPT standard practice for paediatric and adolescent patients with neuromuscular diseases. The aim is to determine what is implemented as part of CPT for these patients in an acute (hospital) and chronic (home/school environment) setting. Due to the fact that this is a self-constructed questionnaire, validation of its content is needed.

Your input and feedback as a specialist in this field will therefore be highly appreciated. Validation requires that you comment and give feedback on specifically the content of the questionnaire attached (content validity) as well as its "look and feel" (face validity). If any possible treatment strategies or management options have been omitted, please be so kind as to highlight this in your feedback also.

This study has been approved by the University of Cape Town's Faculty of Health Sciences' Human Research Ethics Committee (HREC). The HREC number is **513/2015**.

If you have any questions about this study or you would like more information, please do not hesitate to contact the researchers. We will gladly answer your questions or provide additional information.

Anri Human

074 362 4055/(012) 521-4047

anrihuman@gmail.com

Brenda Morrow (research supervisor)

(021) 658-5074

Brenda.Morrow@uct.ac.za

If you agree to assist in the validation of this questionnaire, kindly complete the following informed consent documentation. Your feedback on the questionnaire and completed informed consent form can be returned to anrihuman@gmail.com.

Thank you for your time!

SPECIALIST SURVEY VALIDATION:

CONSENT FORM

Name of study:

Standard chest physiotherapy management of paediatric and adolescent patients with neuromuscular diseases in an acute and chronic setting

I have read the information pertaining to the abovementioned study, and understand the aims and objectives of the proposed study. I have been provided the opportunity to ask questions, and where applicable, all the questions I had were answered to my satisfaction. I understand that participation in this study validation is completely voluntary and that I may withdraw from participating in this study at any time and without supplying reasons. I will not be prejudiced in any way if I choose not to participate, and I have not been coerced in any way to participate.

I am aware of the fact that this study has been approved by the Human Research Ethics Committee (HREC) of the University of Cape Town; HREC: **513/2015**. I am fully aware that the results of this study will be used for scientific purposes and may be published. I agree to participation, provided my privacy is guaranteed.

I hereby give consent to participate in this study.

.....

Name and qualification of specialist

Signature

Place.....

Date.....

Witness.....

Statement by the Researcher

I have provided written information regarding this study to the specialists and experts in the field.

I agree to answer any future questions concerning the study to the best of my ability.

I will adhere to the approved protocol.

Name of researcher: Anri Human

Signature of researcher:

Signed on this 3rd day of December 2015 at Pretoria.

Appendix Aii: Physiotherapy experts in the field of Respiratory physiotherapy to provide input in standard of care questionnaire

The following experts were approached to complete the standard of care questionnaire, as they were not SASP members, but are specialised in the field of respiratory/paediatric physiotherapy:

South African experts in the field of Respiratory physiotherapy

Name	Institution
Janine Verstraete	RCWMCH
Sam Van Deventer	RCWMCH
Glynn Gribble	RCWMCH
Leigh Waterhouse	RCWMCH
Silmara Hanekom	Kalafong hospital
Lieselotte Corten	UCT/RCWMCH



Molotlegi Street, Ga-Rankuwa, Gauteng, 0208
Physiotherapy Department, Health Sciences
Building
Office N219, 2nd Floor, PO Box 239, MEDUNSA,

30 May 2016

Dear,

RE: Survey on standard of care

My name is Anri Human, I am a physiotherapist currently registered for my PhD at UCT, under the supervision of profs. Brenda Morrow and Jennifer Jelsma. We are doing the following research study: "The effect of mechanical insufflation-exsufflation and inspiratory muscle training on clinical outcomes and health-related quality of life in paediatric and adolescent patients with neuromuscular diseases presenting with respiratory muscle weakness: a multi-centre trial." The research will be conducted at Red Cross War Memorial Children's Hospital (RCWMCH) in Cape Town as well as Doctor George Mukhari Academic Hospital (DGMH) in Pretoria.

In order to be able to conduct randomised controlled trials comparing standard chest physiotherapy (CPT) with alternative interventions, it will be necessary to define what physiotherapists view as standard CPT for children and adolescents with neuromuscular diseases in an acute and chronic setting. Determining what constitutes standard of care will be done by means of a questionnaire distributed via Survey Monkey. This questionnaire has been validated by an expert panel and piloted among physiotherapists. Furthermore, this study has been approved by the University of Cape Town's Faculty of Health Sciences' Human Research Ethics Committee (513/2015).

You have been identified as an expert in the field of respiratory/paediatric physiotherapy and therefore we would like to invite you to complete this standard of care questionnaire. If you should agree, you can follow the link

<https://www.surveymonkey.com/r/8RF3F5J>.

We would truly appreciate your assistance in this matter.

If you have any questions, please do not hesitate to contact either myself or my supervisor (A/Prof. Brenda Morrow: (021) 658-5074)

Kind regards

Anri Human

Appendix Aiii: South African physiotherapy survey: feedback provided by expert panel and pilot study participants

The developed questionnaire was distributed to a selected expert panel that consisted of pulmonologists, neurologists, paediatricians and respiratory physiotherapists from RCWMCH and DGMAH/Sefako Makgatho University (during December 2015 -February 2016).

Speciality	Institution	Comments	Confirmation (comments)
Paediatric neurologist	RCWMCH	No response received. Numerous emails were sent, no response to date. Neurological input was however received from a neurologist (DGMAH).	N/A
Paediatric pulmonologist	RCWMCH	04/01/2016: Add an “unsure” tick box especially under subheadings such as secretion mobilisation techniques (time and frequency)	She was satisfied with the final questionnaire
Paediatric pulmonologist	RCWMCH	Responded on 20/01/2016 However, completed the questionnaire and submitted signed informed consent later (07/02/2016). What came out from the completion of the questionnaire was the following: • Under General respiratory (nebulisation): hypertonic saline. Decided to rather add mucolytics • Bag mask manual insufflation followed by MAC was added to OTHER techniques. So maybe we can add bagging/hyperinflation/breath-stacking under MAC? • Did not complete anything under muscle training and lung compliance • Hypertonic saline was added as nebulisation (as needed with infections twice a day) • The specialist did not understand the question under MI-E (time settings for inspiration, expiration). It needs to be noted that physiotherapists that have worked with MI-E will understand the settings. Via email the following comments were made: “I am very excited to see some research happening in this field and that hopefully your work will elevate the importance of CPT in these vulnerable children. I suspect you will find, specialists like me will have little idea about Physio in these kids so hopefully your survey will demonstrate this as well as lack of consensus and standardisation- hence why this research is so important!”	General comments: Regarding the target Population of the survey: (Dr. was concerned that only a limited number of physiotherapists (? n=5) in our country will be able to answer these questions). He made the suggestion that we look internationally in settings where there is more expertise with neuromuscular patients. However the protocol was designed to determine knowledge of S.A physiotherapists Some comments made in the document regarding type of ventilation support, especially if the questionnaire will only be sent to physiotherapists (as we do not prescribe ventilation in our country).
Paediatric physiotherapist	RCWMCH	Completed the questionnaire, but no specific comments about the validity. He did state (on further follow-up) that there was a few comments he wanted to make on the content and face validity-but did not send any. • What did come out from the completion of the questionnaire is that another option might need to be added: As needed/depending on the patient’s requirements for MAC, MI-E (acute and chronic management)	No response

		• Maybe add precautionary measures regarding cardiomyopathy • Poor adherence from family members, child and school (no standard practice) • Maybe change under ventilation/support: frequency per treatment; frequency per day; hours per day (range), short term or long-term ventilation. • 24hour postural management to optimise respiratory function, for example seating	
Pulmonologist	DGMAH/SMU	Addition of general practitioner (under medical vocation). Medications such as mucolytics (Yes/No) under assistance (acute & chronic) Otherwise (looks good!)	No changes to be made. Satisfied.
Paediatrician	DGMAH/SMU	Never responded. Followed up numerous times (email and telephone calls); did not respond within three weeks. Dr. C Lombard was also contacted via email (no response). Another paediatrician (Dr. Honey) who consults once a week at DGMAH was approached for feedback.	N/A
Paediatrician (special interest in genetics)	DGMAH	Response was given on 15/02 (Completed the questionnaire and gave general comments): General respiratory: Nocturnal NIV initially; supplemental O₂ > 50% Secretion mobilisation techniques: Percussion, vibrations, PD, adapted PD, positioning, AD (10 min maximum, 2-3 times per day). Breathing exercises (not specified), 5 minutes application every hour. Manual cough assistance: 3-4x per treatment, one to two hourly per day (Thoracic, abdominal and both). Not used to MI-E (not familiar with the device) Suctioning: 2-3x per treatment, every 2-3 hours. Chronic management: Breath-stacking (independent and assisted), no devices specified. Inspiratory and expiratory muscle training (no specifics given) Breathing exercises: suggests passive inspiration with forced expiration can assist in opening alveoli (2-3x per treatment, 5-6x per day) Nebulisation (depending if electricity is available): saline, salbutamol Once per treatment (depending on the condition of the child) 2-4x per day. Oscillatory device Percussions (by parent) 10 min max; 2-3x per day Vibrations (by parent) 10 min max; 2-3x per day Postural drainage (Trendelenburg) PD (Non-Trendelenburg) 5 min max; 3-4x per day	Satisfied with the final product, we can proceed.

		Positioning (by parent) 5min max, 3-4x per day Autogenic drainage (by parent) 5 min max; 3-4x per day Cough assistance (MAC) (by parents): 3-4 x per treatment 4-5x per day Abdominal, thoracic compression and both MI-E (yes), not sure of specifications Suctioning: 2-3x per treatment; 4-5x per day Other comments: Frequency should be less, but increased frequency during the day. "I don't think in SA any of the mechanical devices are standard treatment. In fact in our rural settings not even standard treatment are used." Ventilation/support: BiPAP, CPAP yes but frequencies not specified NIV: only in hospitals	
Neurologist	DGMAH/SMU	No additions/changes suggested (looks good)	Satisfied, we can continue
Respiratory Physiotherapist	DGMAH	Response given 15/01: Awareness regarding: • The role of physiotherapy in the prevention of respiratory complications due to bed rest (arising out of NMD adolescents). This questionnaire aims to determine what constitutes CPT. Mobilisation, positioning and transfers will fall more under rehabilitation, therefore not applicable. • Roles of Anatomy and Physiology in neonates that influences treatment protocol and approaches . Not applicable, as inclusion criteria states 5-18 years of age. • Do physiotherapists understand their roles in the prevention and management of respiratory complications associated with NMD diagnoses? A question was added regarding prevention and management of complications, or other techniques/modalities that might be applicable. • Do Musculoskeletal clinicians understand the role of PT in the prevention and management of the complications arising out of immobilisation due to NMDs? • Need to identify the role that PT plays in the prevention and management of complications in patients with NMD diagnoses. As stated previously, an open ended question was added.	No response

Paediatric specialist (Physiotherapist)	RCWMCH	Suggestions about corrections to be made (mostly to be made on Survey monkey), implemented 28/02/2016: 1. I think question 8 is a repeat of Qu. 6 2. Manually assisted cough – there are a number of choices for no. of repetitions, but the one I am looking for is that it depends on the patient – if no more secretions, I might stop at 3, if a lot of secretions, and the patient tolerates it I might carry on more than 15 MACs. However, even if still secretions, I might stop sooner if the pt. is tired... 3. Qu. 30 – only allows either independent or assisted breath-stacking, but in this patient I might use either or both and see what works best. This option is not given... 4. It is not clear when the questions change to referring to a home program – I think this should be clearer, it seems at first that the questions are just being repeated. I also think a new presentation description should be provided at this point ie. In what state is the pt being discharged? A 7 year old with Duchenne's would be expected to be discharged with complete resolution of the respiratory infection, still ambulant which implies no resp. support is needed. However, if lung function still poor then he might need cough augmentation- more info is needed, I think. In fact, I might change the case a bit to being a 12 year old DMD, still mobilising on admission, but needing wheelchair support at times (about the time that they would need to start cough therapy).	Survey monkey link was sent: Satisfied for questionnaire to be distributed.
Paediatric physiotherapist	UCT (Division of Physiotherapy)	Asked the question regarding: do we want to determine what is currently being done as standard CPT (management) in S.A? The aim is to determine what is best practice (based on literature and clinical expertise), therefore experts/PT specialists in the field are asked for their input. In order to gain knowledge on what is currently being done in S.A, Section D was added. Also, the suggestion was made that the case scenario should maybe not be as specific to age, functionality, diagnosis and vital signs, respiratory function (to limit the treatment options), or otherwise be removed completely and ask what have they used recently (past 6/12 months).	Can't comment on the content, but made suggestions regarding the formatting: Not to use symbols, but rather yes/no answers (this will be corrected on Survey Monkey) Also to rather ask participants to give the number of months/years that they have worked with NMDs (for statistical value) and not give a category (BM disagreed on the categories, in order to decrease completion time). Link was sent: satisfied for questionnaire to be distributed.
Fellow paediatric PhD	UCT (Division of Physiotherapy)	(Majority of corrections to be made on Survey monkey): Write MI-E and IMT in full the first time used. Evidence-based practice should be based on literature as well as expertise, ensure that this	Satisfied with final draft content.

student/research assistant		comes out clearly in the introduction. Will you consult research evidence as well? Under eligibility criteria: add that it's physios and specialists working with children AND/OR NMD. It is unclear that OT's and nurses are considered under 'medical specialists' described. Add 'university' or 'research centre' or 'other' under this section as you might have specialists who are doing research however are not working in clinical practice? Or they should be able to leave blank, which is not an option... If you add 'other' you could maybe add a 'please specify' option. If they are currently not treating children with NMD but might have treated them e.g, researchers who aren't currently working in practice but are doing research on the topic etc. Add 'ventilation' after the 'invasive' option = 'invasive ventilation' Maybe you should more clearly specify what you see as adapted postural drainage and positioning as many physios might use 'positioning' and 'ADP' as one technique. Only AD or do you include AAD? As NMD patients most likely won't be able to do individual AD (esp at young age or at severe progressed disease) Breathing exercises: you can't select option 'yes' and add the selection to specify so rather put 'yes, please specify' and 'no' or change the setting so you can select both options Would you consider active movements as part of secretion mobilisations? The cough assist settings need to be determined individually so is it possible to give a clear answer? Patients who have been using it for a long time will have most likely higher pressures as they are used to it, when you start with the machine patients prefer lower pressures. Also in-and expiration might be individually determined Would you like to know if they do nasal suctioning or via the mouth. Breath-stacking can also be done without a device, when using frog breathing. So maybe rather change it to the 'method of breath-stacking' rather than 'device used' Please change the title : secretions = secretions (is also wrong in titles used later on in the questionnaire) Rather remove 'flutter' and just say in the question 'oscillating device (eg Flutter, Acapella) and then give them the option to specify which oscillating device they use. Isn't CPAP and BiPAP a form of non-invasive ventilation? Not sure if here in SA they use vests? Would gross motor activity be included as removing secretions?	

After the first round of feedback from the expert panel was received the applicable changes were implemented:

Background of participants: It was suggested to add “university” and “rehabilitation centres” as additional options in order to ensure all work-related contexts were covered. Those physiotherapists that might not be working with NMD patients when completing the questionnaire, but are experts in the field, were then able to also complete the survey, as their opinions will add value.

Case scenarios:

The case scenarios were adapted in order to not be too specific regarding age and stage of disease, functionality, diagnosis, vital signs and respiratory function as it may differ depending on the type of NMD. The guideline was changed to reflect patients older than five years.

General additions and changes:

- These included adding an “unsure” option, over and above the “yes” or “no” for the description of frequencies and durations of treatment/intervention, as some participants might be unsure.
- Another valuable input was to add another option that can be selected namely “patient dependent” because some intervention(s) and frequencies will depend on the patient’s reaction.
- Making use of a “flutter” was changed to oscillatory device (in order to not limit the option to one brand name) and participants were given the opportunity to specify which device they prefer to use.
- Another elaboration was adding the option of “both” for techniques such as breath-stacking: namely independent, dependent and/or both, based on the patient’s condition and reaction to treatment.
- Device used for breath-stacking was changed to method of breath-stacking, as a device might not always be indicated. The suggestion was made to also add “assisted autogenic drainage”, as some patients might be too young to be able to do AD independently. Additions: Additions made based on suggestions were: hyperinflation/bagging/breath-stacking,
- Instead of saline usage to rather refer to the use of mucolytics.
- Cardiomyopathy as a precautionary measure when applying cough augmentation techniques (what would the therapist do in such a case?).
- Ventilatory support was elaborated on pertaining to frequency per treatment; frequency per day; hours per day (range), description of short term or long-term ventilation.

- It was suggested to add 24-hour postural management to optimise respiratory function, for example seating.
- One reviewer asked if physiotherapists are aware of their role in the prevention and management of respiratory complications associated with NMD. For this reason, an open ended question was added asking about prevention and management of complications, or other techniques/modalities that might be applicable in these patients.

South African context (specificity): The aim of the survey was to determine what is best practice (based on literature and clinical expertise), as perceived by experts/PT specialists. In order to gain knowledge on what is currently being done in S.A for NMD patients, Section D was added. This section asked the participant to indicate which CPT techniques they have been using for NMD paediatric and adolescent patients within the last six months.

Technical changes:

Lastly, minor corrections were made to clarify that participants should answer based on their expertise as well as literature (evidence-based), the researcher wrote out abbreviations when first used (MAC, MI-E), ensured consistency throughout the document as well as the “flow” of the questionnaire, removed repetitions, added subheadings with more explanation (clarity/distinction between acute and chronic management), and corrected spelling/grammar.

Second round of feedback (expert panel):

After the questionnaire was adapted and returned to the expert panel (March 2016), some minor comments were made regarding response rate, as many physiotherapists might not be familiar with clinical guidelines for NMD. This emphasised what the researcher wanted to determine, the number of South African physiotherapists that have had exposure to/worked with children in this field.

A few recommendations were made regarding ventilation settings, but this is not prescribed by physiotherapists and was therefore not changed.

Some general comments were made that very few specialists and even physiotherapists in South Africa might be aware of techniques such as MI-E, hence the response rate might be low. Therefore, the suggestion was to send the survey to international physiotherapists as well. The researcher was aware of the implications of a lack of knowledge/exposure, but the aim of this survey was to determine the knowledge and perception of South African physiotherapists. The researcher was interested in ascertaining if determine if South African clinicians are aware of devices/interventions despite not having access to it.

One of the physiotherapists raised the issue of musculo-skeletal management involvement in the prevention of complications caused by immobility and bed rest in patients living with NMD. The researchers were of the opinion that this topic was outside the scope of the questionnaire's aims and objectives, as the focus was primarily on CPT. Positioning and transfers can be categorised under physiotherapy rehabilitation, therefore not applicable to this survey. The same physiotherapist also highlighted the role of Anatomy and Physiology in neonates, as these underlying differences will influence the physiotherapy management of patients with NMD. This comment was not applicable to this survey, as the inclusion criteria states 5-18 years of age, and therefore neonates will be excluded. Gross motor development and activity monitoring and management was suggested, but not included in the questionnaire as it does not fall within the scope of this survey.

The final suggestions/corrections made after resending to the expert panel were therefore either implemented or refuted, based on applicability/relevance after discussing with the primary supervisor.

In conclusion:

Minor adaptations were made, based on the first round of feedback received, such as including universities and rehabilitation centres in order to be more inclusive of all work-contexts. Physiotherapists that might not currently be working with patients with NMD, but have expertise in this particular field, were then also able to complete the survey, as their opinions would add value to the results. It was also specified in the introduction and throughout the questionnaire that participants' answers should be based on their knowledge of literature (EBP) as well as their clinical experiences.

The expert panel suggested the case scenarios should be made more generalised and not be too prescriptive regarding age, but rather state "patient older than five", stage of disease, functional and respiratory status, as these factors would be dependent on the type of NMD and co-morbidities. General feedback included the addition of "unsure" besides "yes" and "no" as answer options, in order to indicate if a participant was uncertain if a specific technique should be used in these patients. The option of "patient dependent" was also added for cases when the intervention was dependent on patient presentation and reaction to treatment. In addition, open ended questions about the role of physiotherapists in prevention and management of respiratory complications, were recommended. Lastly, to align with the objectives of the survey and determine which respiratory management strategies are being used in South Africa, Section D was added to the questionnaire.

After corrections, the adapted questionnaire was once more distributed to the expert panel for confirmation and the majority was satisfied and agreed that the instrument was ready for distribution (piloted). Minor suggestions were made after re-submission and these final suggestions were either implemented or refuted, based on clinical applicability/relevance, as decided in consultation with the supervisor.

Appendix Aiv: Letter of confirmation of questionnaire to expert panel



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Email: anri.human@smu.ac.za; Telephone: 012 5214047/5828

10 March 2016

Dear prof.,

RE: Confirmation of questionnaire by expert panel

Thank you kindly for your input and feedback on the standard of care questionnaire. After careful consideration and discussions with my supervisors, certain changes have been made, based on the feedback received from the expert panel.

The questionnaire is more comprehensive thanks to your suggestions.

If possible, could you please have a look at the final product? If you have any concerns, questions or comments to be raised, we would appreciate your feedback. If however you are satisfied with the questionnaire, we will also appreciate it if you can indicate that to us either via email or sms.

We realise that, for a specialist as yourself, time is limited; therefore if I do not receive any feedback by Thursday 17 March, will it be in order to assume that you are satisfied with the questionnaire as is? If that is the case, we will continue with the pilot study towards the end of next week before distributing the questionnaire to physiotherapists.

May I take this opportunity once again to thank you for your input and support of this research project, it is truly appreciated.

If you have any questions, please do not hesitate to contact either myself or my supervisor (A/Prof. Brenda Morrow: (021) 658-5074).

Kind regards

Ms. A. Human

Lecturer: Physiotherapy department

Appendix Av: Standard of care questionnaire

This was the final version of the standard of care questionnaire that was used to develop the Survey Monkey questionnaire.

Standard of Care Questionnaire: “Chest physiotherapy (ACT) practice in paediatric and adolescent patients with neuromuscular diseases”

Thank you for taking the time to complete this questionnaire. Data obtained from this questionnaire will be used to formulate a broad definition of chest physiotherapy (ACT) practice among physiotherapists treating patients with neuromuscular diseases/disorders (NMDs).

Instructions:

In order to complete the questionnaire please answer yes, no or unsure where applicable. Where values are required please use the allocated space to indicate the value.

Section A: Background	
Please complete the following questions regarding your vocational background (Please tick all applicable options):	
1. What type of medical institution(s) do you currently work / practice in?	
Hospital (General Wards)	☐
Hospital (Specialised wards, i.e. NICU, PICU)	☐
Clinics	☐
Private Practice	☐
Special School	☐
University (academic, lecturer, researcher)	☐
Rehabilitation centre	☐
Other (please specify)	
2. Have you treated children and/or adolescents with NMDs? (Please tick all applicable options).	
Yes	☐
No	☐
I am a researcher and/or academic conducting research in this field or physiotherapist that is an expert in this area (NMDs).	☐
3. If Yes, How long have you treated children and/or adolescents with NMDs?	
<12 Months	☐
1 – 5 Years	☐

6-10 Years	☐
>10 Years	☐

Section B: Acute management of non-ventilated paediatric and adolescent patients with NMD	
Please read through the following and answer the questions based on the scenario for an acute patient.	
SCENARIO 1 (hospital): <i>Patient X has been diagnosed with a NMD and is older than five years of age and has recently become wheelchair-bound. He has been admitted to hospital due to a respiratory infection and is presenting with a weak cough. He is haemodynamically stable, but oxygen saturation is 91%, and he is retaining secretions due to an ineffective cough.</i>	
1. What do you consider (based on literature and clinical expertise) as standard management of a patient such as patient X? Please tick all applicable options:	
General Respiratory	
Mechanical ventilatory support:	☐ No ☐ Yes ☐ Unsure
If Yes , please specify:	
Non-invasive ventilation (NIV)	☐
Invasive ventilation	☐
Short-term ventilation	☐
Other (Please Specify):	
Supplemental Oxygen	☐ No ☐ Yes ☐ Unsure
If Yes , please specify % or litres	
Nebulisation	☐ No ☐ Yes ☐ Unsure
If Yes , which type of nebulised/aerosol medication would you use?	
If Yes , Frequency (per treatment)	
If Yes , Frequency (per day)	
24 hour postural management, for example supported sitting.	☐ No ☐ Yes ☐ Unsure
If Yes , Specify the postural management technique(s) to be used (example seating):	
Other comments regarding general respiratory management of patients with NMDs:	
Secretion Mobilisation Techniques	
Percussions	☐ No ☐ Yes ☐ Unsure
If Yes , estimated time (per treatment)	

If Yes , Frequency (per day)	
Vibrations	☐ No ☐ Yes ☐ Unsure
If Yes , estimated time (per treatment)	
If Yes , Frequency (per day)	
Oscillatory device (e.g. Flutter, Acapella, IPV)	☐ No ☐ Yes ☐ Unsure
If Yes , please specify device	
Postural drainage (Trendelenburg/"head down position")	☐ No ☐ Yes ☐ Unsure
If Yes , estimated time (per treatment)	
If Yes , Frequency (per day)	
Adapted postural drainage (No Trendelenburg)	☐ No ☐ Yes ☐ Unsure
If Yes , estimated time (per treatment)	
If Yes , Frequency (per day)	
Positioning	☐ No ☐ Yes ☐ Unsure
If Yes , estimated time (per treatment)	
If Yes , Frequency (per day)	
Autogenic Drainage (including assisted autogenic drainage)	☐ No ☐ Yes ☐ Unsure
If Yes , estimated time (per treatment)	
If Yes , Frequency (per day)	
Breathing Exercises	☐ No ☐ Yes ☐ Unsure
If Yes , Specify the type of breathing exercises to be used:	
If Yes , estimated time (per treatment)	
If Yes , Frequency (per day)	
Other comments regarding secretion mobilisation techniques:	

Airway clearance techniques/Cough Assistance:	
Manually Assisted Cough (MAC)	☐ No ☐ Yes ☐ Unsure
If Yes , which MAC technique will you use? (tick all applicable options)	
Abdominal compression	☐
Thoracic compression	☐
Both	☐
Frequency of manually assisted cough(s) (MAC) (per treatment):	

Frequency of treatment (per day):	
Once a day	☐
Twice a day	☐
>Twice a day	☐
Patient dependent	☐
If the patient is tired, will you continue with cough assistance or rather stop? Tick the applicable option:	
Continue	☐
Stop	☐
Change technique/procedure	☐
Unsure	☐
Mechanical Insufflation-Exsufflation (MI-E)	☐ No ☐ Yes ☐ Unsure
If Yes , indicate which setting is used:	
Manual Setting	☐
Automatic Settings: If Yes , which settings are mostly used? (Please tick all the appropriate options)	☐
Basic Auto	☐
Timed programmable auto	☐
Triggered programmable auto	☐
Pressure Settings for Inspiration (Please give ranges of cmH ₂ O)	
Pressure Settings for Expiration (Please give ranges of cmH ₂ O)	
Repetitions of Insufflation – Exsufflation (Cycle repeat)	
Time settings (Ti): Inspiration (seconds)	
Time settings (Te): Expiration (seconds)	
Pause between breaths (seconds)	
Sets used during a treatment	
Pause/rest-interval in-between sets	
Depending on the patient's requirements/as needed	☐
If the patient presents with cardiomyopathy, will you still use MI-E?	
Yes	☐
No	☐
Unsure	☐
Please motivate your answer:	
Suctioning	☐ No ☐ Yes ☐ Unsure
If Yes , Frequency (per treatment)	
If Yes , Frequency (per day)	

Other comments regarding airway clearance/cough assistance:
Which other physiotherapy techniques (as part of the role of the physiotherapist) should be implemented regarding prevention and management of respiratory complications associated with NMDs?
Other (general): What other general management techniques, not mentioned above, should be used for acute management of these patients? Please motivate your answer:

Section C: Chronic management of non-ventilated paediatric and adolescent patients with NMD	
Please read through the following and answer the questions based on the scenario for a chronic patient.	
Scenario 2 (home/school): <i>Patient Y has been diagnosed with a NMD and is older than five years of age. He recently became wheelchair-bound and attends follow-up visits to the Neuro clinic every 3-6 months, depending on the need. Currently his Vital Capacity is <80% predicted value for his age and he presents with a weak cough.</i>	
1. What do you consider (based on literature and clinical expertise) as standard management of a patient such as Patient Y? Please tick all applicable options.	
Home Programme (Muscle Training and Lung Compliance):	
Breath-stacking (Hyperinflation):	☐ No ☐ Yes ☐ Unsure
Independent (only)	☐
Assisted (only)	☐
Independent or assisted or both, depending on what works best	☐
If Yes , Specify the method of breath-stacking:	
Other comments regarding breath-stacking/hyperinflation techniques:	
Respiratory Muscle Training:	

Inspiratory Muscle Training	☐ No ☐ Yes ☐ Unsure
If Yes , Specify the device:	
Threshold Device	☐
Resistance Device	☐
Flow Device	☐
If yes, specify the application:	
Repetitions (per Day)	
Frequency (per Day)	
Expiratory Muscle Training	☐ No ☐ Yes ☐ Unsure
If Yes , Specify the device:	
Threshold Device	☐
Resistance Device	☐
Flow Device	☐
If yes, specify the application:	
Repetitions (per Day)	
Frequency (per Day)	
Breathing Exercises	☐ No ☐ Yes ☐ Unsure
If Yes , Specify the type of breathing exercise(s) to be used:	
Estimated time (per Treatment)	
Frequency (per Day)	
Other comments regarding respiratory muscle training:	

Home programme (secretion mobilisation):	
Nebulisation	☐ No ☐ Yes ☐ Unsure
If Yes , which type of Nebulised/aerosol medication would you use?	
If Yes , Frequency (per treatment)	
If Yes , Frequency (per day)	
Oscillatory device (e.g. Flutter, Acapella, IPV)	☐ No ☐ Yes ☐ Unsure
If Yes , please specify device	
If yes, specify the application:	
If Yes , Frequency (per treatment)	
If Yes , Frequency (per day)	
Percussions	☐ No ☐ Yes ☐ Unsure
If Yes , estimated time (per treatment)	
If Yes , Frequency (per day)	

Vibrations	☐ No ☐ Yes ☐ Unsure
If Yes , estimated time (per treatment)	
If Yes , Frequency (per day)	
Postural drainage (Trendelenburg/"head down position")	☐ No ☐ Yes ☐ Unsure
If Yes , estimated time (per treatment)	
If Yes , Frequency (per day)	
Adapted postural drainage (No Trendelenburg)	☐ No ☐ Yes ☐ Unsure
If Yes , estimated time (per treatment)	
If Yes , Frequency (per day)	
Positioning	☐ No ☐ Yes ☐ Unsure
If Yes , estimated time (per treatment)	
If Yes , Frequency (per day)	
Autogenic Drainage (including assisted autogenic drainage)	☐ No ☐ Yes ☐ Unsure
If Yes , estimated time (per treatment)	
If Yes , Frequency (per day)	
Other comments regarding secretion mobilisation techniques:	
Airway clearance techniques/Cough Assistance:	
Manually Assisted Cough (MAC)	☐ No ☐ Yes ☐ Unsure
If Yes, which MAC technique will you use? (tick all applicable options):	
Abdominal compression	☐
Thoracic compression	☐
Both	☐
Frequency of manually assisted cough(s) (MAC) (per treatment):	
Frequency of treatment (per day):	
Once a day	☐
Twice a day	☐
>Twice a day	☐
Patient dependent	☐
If the patient is tired, will you continue with cough assistance or rather stop? Tick the applicable option:	
Continue	☐
Stop	☐
Change technique/procedure	☐
Unsure	☐

Mechanical Insufflation-Exsufflation (MI-E)	☐ No ☐ Yes ☐ Unsure
If Yes , indicate which setting is used:	
Manual Setting	☐
Automatic Settings: If Yes , which settings are mostly used? (Multiple selection allowed)	☐
Basic Auto	☐
Timed programmable auto	☐
Triggered programmable auto	☐
Pressure Settings for Inspiration (Please give ranges of cmH ₂ O)	
Pressure Settings for Expiration (Please give ranges of cmH ₂ O)	
Inspiratory repeat (Ins Rpt) (how many insufflations before exsufflation)	
Repetitions of Insufflation – Exsufflation (Cycle repeat)	
Time settings (Ti): Inspiration (seconds)	
Time settings (Te): Expiration (seconds)	
Pause between breaths (seconds)	
Sets used during a treatment	
Pause/rest-interval in-between sets	
Depending on the patient's requirements/as needed	☐
Suctioning	☐ No ☐ Yes ☐ Unsure
If Yes , Frequency (per treatment)	
If Yes , Frequency (per day)	
Other comments regarding airway clearance techniques/cough assistance:	
Ventilation / Support	
Non-Invasive Ventilation (NIV)	☐ No ☐ Yes ☐ Unsure
Diurnal	☐
Nocturnal	☐
Both/24 hours	☐
Short-term ventilation	☐
Long-term ventilation	☐

Intermittently (as required by patient)	☐
Bi-PAP	☐ No ☐ Yes ☐ Unsure
If Yes , average hours per day/night (range, e.g. 2-3 hours)	
CPAP	☐ No ☐ Yes ☐ Unsure
If Yes , average hours per day/night (range, e.g. 2-3 hours)	
Supplemental Oxygen	☐ No ☐ Yes ☐ Unsure
If Yes , please specify % or litres	
24 hour postural management, for example supported sitting.	☐ No ☐ Yes ☐ Unsure
If Yes , Specify the postural management technique(s) to be used (example seating):	
Other comments regarding ventilation/support:	
What other techniques (as part of the role of the physiotherapist) regarding prevention and management of respiratory complications associated with NMDs should be implemented?	
Other (general): What other techniques, not mentioned, should be used for chronic management of these patients? Please motivate your answer:	

Section D: Current practice at your institution for children and adolescents with neuromuscular disease (NMD). Please tick the applicable option and continue if indicated.	
I do not see NMD patients on a regular basis ☐	
If Yes , thank you for your time, you do not have to complete Section D.	
I do see NMD patients on a regular basis ☐	
If Yes, please continue with Section D and answer the following questions:	
Which of the following techniques have you used in the past 6 months (acute/hospital management)?	
Physiotherapy techniques	
Secretion Mobilisation Techniques:	
Percussions	☐ No ☐ Yes
Vibrations	☐ No ☐ Yes
Postural drainage (Trendelenburg/"head down position")	☐ No ☐ Yes
Adapted postural drainage (No Trendelenburg)	☐ No ☐ Yes
Positioning	☐ No ☐ Yes
Autogenic Drainage (including assisted autogenic drainage)	☐ No ☐ Yes
Breathing Exercises	☐ No ☐ Yes
Suctioning	☐ No ☐ Yes
Nebulisation (including mucolytics)	☐ No ☐ Yes
Breath-stacking (hyperinflation)	☐ No ☐ Yes
Others:	
24 hour postural management, for example supported sitting	☐ No ☐ Yes
Supplemental Oxygen	☐ No ☐ Yes
Airway clearance techniques/Cough assistance:	
Manually Assisted Cough (MAC)	☐ No ☐ Yes
Mechanical insufflation-exsufflation (MI-E)	☐ No ☐ Yes
Which of the following techniques have you used in the past 6 months (chronic/home management)?	
Physiotherapy techniques	

Home Programme (Muscle Training and Lung Compliance):	
Breath-stacking (hyperinflation)	☐ No ☐ Yes
Inspiratory muscle training	☐ No ☐ Yes
Expiratory muscle training	☐ No ☐ Yes
Breathing exercises	☐ No ☐ Yes
24 hour postural management, for example supported sitting	☐ No ☐ Yes
Secretion Mobilisation Techniques:	
Nebulisation (including mucolytics)	☐ No ☐ Yes
Oscillatory device (e.g. Flutter, Acapella, IPV)	☐ No ☐ Yes
Percussions	☐ No ☐ Yes
Vibrations	☐ No ☐ Yes
Postural drainage (Trendelenburg/"head down position")	☐ No ☐ Yes
Adapted postural drainage (No Trendelenburg)	☐ No ☐ Yes
Positioning	☐ No ☐ Yes
Autogenic Drainage (including assisted autogenic drainage)	☐ No ☐ Yes
Suctioning	☐ No ☐ Yes
Airway clearance techniques/Cough assistance:	
Manually Assisted Cough (MAC)	☐ No ☐ Yes
Mechanical insufflation-exsufflation (MI-E)	☐ No ☐ Yes

Other: What other techniques have you used? Please motivate your answer:

Thank you for your time

References

Wang, C.H. et al. 2007. Consensus statement for standard of care in spinal muscular atrophy. *Journal of Child Neurology*, 22(8), pp.1027–1049.

Appendix Avi: Information letter and informed consent for pilot study



Molotlegi Street, Ga-Rankuwa, Gauteng, 0208
Physiotherapy Department, Health Sciences Building
Office N219, 2nd Floor, PO Box 239, MEDUNSA, 0204

March/April 2016

Dear,

RE: Pilot study (standard of care)

Thank you kindly for your willingness to assist. We are doing the following research study: “The effect of mechanical insufflation-exsufflation and inspiratory muscle training on clinical outcomes and health-related quality of life in paediatric and adolescent patients with neuromuscular diseases presenting with respiratory muscle weakness: a multi-centre trial.” The research will be conducted at Red Cross War memorial Children’s Hospital (RCWMCH) in Cape Town as well as Doctor George Mukhari Academic Hospital (DGMH) in Pretoria.

In order to be able to conduct randomised controlled trials comparing standard chest physiotherapy (CPT) with alternative interventions, it will be necessary to define what physiotherapists view as standard CPT for children and adolescents with NMDs in an acute and chronic setting. Comparing an alternative intervention/adjunct to conventional therapy/standardised care can assist in concluding more rigorously that any significant changes seen between the experimental and control groups are in fact due to the intervention that is being assessed. This study has been approved by the University of Cape Town’s Faculty of Health Sciences’ Human Research Ethics Committee (HREC). The HREC number is 513/2015.

The questionnaire has been validated (content validity) by an expert panel. Your input and feedback as a specialist in this field regarding the following aspects will be highly appreciated:

- The “look and feel” of the questionnaire and if the questions are clear and unambiguous (face validity)
- The approximate time that it took to complete the questionnaire
- Any other relevant comments

If you have any questions, please do not hesitate to contact either myself or my supervisor (A/Prof. Brenda Morrow: (021) 658-5074)

Kind regards

Ms. A. Human

Lecturer: Physiotherapy department

Please indicate your comments in the spaces given below, this can be submitted together with the completed questionnaire to anrihuman@gmail.com

Approximately how long did it take you to complete the questionnaire? (minutes)

Comments on face validity (“look and feel”)

Are the questions clear and unambiguous? If not, please specify.

Other comments

Thank you for your time!

Appendix Avii: Pilot study participants and feedback on South African survey on standard of care

Physiotherapists included in pilot study:

Name	Institution
Mrs. Ilze Bole	Private practice Akasia hospital and Eugene Marais (ICU, general wards and out patients)
Mrs. Marlize Cochrane-Boeyens	Lecturer at SMU (Neurology)
Prof. Heleen Van Aswegen	Lecturer at WITS (Respiratory)
Ms. Ina Finger	Clinician DGMAH
Rozelle Conradie	Clinician RCWMCH
Nicole Comminellis	Clinician RCWMCH: Default (did not respond)

Feedback from the five respondents are outlined in the table below:

Respondent	Time to complete	Face validity	Clarity of questions
1	45 minutes	Good outlay, easy to follow the flow	Yes
2	Approximately 35 minutes	User-friendly, all aspects of CPT covered. Relevant to the topic at hand.	Yes, easy to understand. Options are applicable and sufficient to cover all aspects.
3	Approximately 12 minutes	Lay-out is nice and clear The shading in different areas helps the reader to identify different aspects being assessed. I suggest using a more descriptive title for the questionnaire so that those not familiar with its content will know immediately what it is about	Not specifically mentioned
4	30-45 minutes	Easy to follow	Clear unambiguous questions
5	Approximately 60 minutes	Felt like I repeated myself a lot	Yes

The researcher added a general section titled “Other comments” for additional feedback from the pilot study participants. These comments included:

- Various techniques will be dependent on the patient’s reaction (some answers might have to include: patient dependent), similar to what some of the expert panel also suggested.
- Furthermore, a suggestion was made that the clinician could stop and give the patient a rest, if the secretion clearance technique was still ineffective, try a different technique. Otherwise suctioning might be indicated in order to clear secretions.

- In some cases, elaboration on answers might be needed. This was addressed by adding open-ended areas to comment at the end of each section of the questionnaire.
- It was further suggested that standard management should be emphasised, as this was not always clear, if participants should answer based on their knowledge or what is currently done in hospitals/clinics. This matter was addressed by highlighting certain phrases in the introductory statement as well as the heading of each section (differentiation between standard and current management).
- Limitations are caused by staff shortages and resources (not having access to MI-E for instance), which could also influence answering, hence Section D would give a description of the reality in South African institutions and what is currently being used.
- Consistency with the use of abbreviations was advised. Also one typing error and two technical errors were highlighted. Participants also made suggestions on improving the “flow” of the questionnaire.

The above suggestions were discussed with the research assistant and supervisors and adaptations were made where needed. Thereafter the questionnaire on Survey Monkey was refined and prepared for distribution. Because minor alterations were made to the questionnaire after the pilot study, data captured from the pilot study were included in the main analysis.

Appendix Aviii: Survey Monkey opening statement and consent



Standard of Care Questionnaire: Chest physiotherapy practice (ACT) in paediatric and adolescent patients with neuromuscular disease.

1. Introduction

Research Background:

This survey forms part of research being conducted by Anri Human for her PhD at the University of Cape Town. The research focuses on chest physiotherapy (CPT) methods used on children and adolescents with neuromuscular diseases (NMDs) such as Duchenne's muscular dystrophy (DMD), myopathy, and spinal muscular atrophy (SMA). Firstly, the research aims to determine the efficacy of various cough assist techniques for children with NMDs admitted to hospital with chest infections. Secondly the study aims to investigate the effect of a three month inspiratory muscle training programme as an adjunct to standard care in patients with NMDs.

In order to be able to conduct randomised controlled trials comparing standard chest physiotherapy (CPT) with alternative interventions, it will be necessary to define what physiotherapists view as standard CPT for children and adolescents with NMDs based on literature/research and their clinical expertise. Comparing an alternative intervention/adjunct to conventional therapy/standardised care can assist in concluding more rigorously that any significant changes seen between the experimental and control groups are in fact due to the intervention that is being assessed. The aim of this survey is to determine what is viewed as standard CPT by physiotherapists (although may not always be implemented, due to reasons such as limited resources) in acute (hospital) and chronic settings (home/school) (Section B & C). Furthermore, to determine what is currently being used by physiotherapists in South Africa for patients with NMDs in an acute and chronic context (Section D).

Target Participants:

- Physiotherapists who work with children and/or adolescents with NMDs and/or having a special interest in Cardiopulmonary and/or Paediatrics
- Experts in the field of Respiratory Paediatrics in South Africa (based on publications, presentations and expertise in the field).

Eligibility Criteria:

This survey is restricted to physiotherapists involved in the treatment/management of paediatric and adolescent NMD patients or who are experts in this field. This is a purposive study, however if a participant should indicate that they do not work with paediatric and adolescent NMD patients, then they will be excluded.

Participation, data collection and analysis:

This questionnaire has been validated and confirmed by an expert panel. Your input and feedback will be highly appreciated. This survey is completed on an individual basis and is completely anonymous. Results received will be coded hence ensuring anonymity of participants. There will be no risks to any participant and participation is voluntary. Feedback obtained from the survey will be sent to the primary researcher who will collate the data for analysis.

Depending on the number of sections applicable to you, it should take approximately 20 minutes to complete this survey. Based on literature and the results from this survey, a standard care guideline for patients with NMDs will be compiled.

Should you have any questions regarding this survey or the NMD study as a whole; please do not hesitate to contact the researchers:

Anri Human

anrihuman@gmail.com

(012) 521-4047

A/Prof. Brenda Morrow

Brenda.Morrow@uct.ac.za

(021) 658-5074

***1. I have read the information pertaining to this survey, and understand the aims and objectives thereof. I have been provided the opportunity to ask questions, and where applicable, all questions were answered to my satisfaction.**

I understand that participation in this survey is completely voluntary and that I may withdraw from participating in this survey at any time and without supplying reasons. I will not be prejudiced in any way if I choose not to participate. I have not been coerced in any way to participate in this survey.

I am aware of the fact that this study has been approved by the Human Research Ethics Committee (HREC) of the University of Cape Town; HREC: 513/2015. I am fully aware that the results of this survey will be used for scientific purposes and may be published. I agree to participation, provided my privacy is guaranteed.

I hereby give consent that I have read through and understand the abovementioned terms and conditions and that I give my full consent to participate in this survey; and that any or all information provided by myself may be used as part of research data to be published at the discretion of the researchers. All personal information will remain strictly confidential.

- ☐ I hereby **agree** that I have read and understand the abovementioned terms and conditions, and grant my permission that data supplied by myself may be used for research and publishing purposes.
- ☐ I **do not agree** to the terms and conditions as set out above.

Appendix Aix: Response rate on Survey Monkey

The following table depicts the response rate trends over the duration of the survey:

Week	Number of responses
Week 1 (23/05/2016)	10
Week 2 (30/05/2016)	8
Week 3 (06/06/2016)	21
Week 4 (13/06/2016)	1
Week 5 (20/06/2016)	19
Week 6 (27/06/2016)	5
Week 7 (04/07/2016)	7
Week 8 (11/07/2016)	0
Week 9 (18/07/2016)	3
Week 10 (25/07/2016)	0
Week 11	Survey Monkey closed

Appendix Ax: Additional responses/data from survey participants (standard of care): Section A-D

SECTION A:

Vocational background of all participants that completed Section A (n=74) presented as frequencies

Place of work	Number of participants
Hospital (General wards)	34
Hospital (Specialised wards e.g. NICU, PICU)	29
Clinics	1
Private practice	47
Special school	10
Rehabilitation centre	7
University (Academic, lecturer, researcher)	8
Other	2
Total	138

Note: Several respondents worked in multiple workplaces.

Vocational background of all participants that completed Section A (n=74) presented as percentages

Place of work	% of responses
Hospital (general wards)	24.6
Hospital (specialised wards)	21.0
Private practice	34.0
Special school, rehabilitation centre, clinic, academics & other	20.3

Vocational background of participants with NMD experience (n=64) presented as frequencies

Place of work	Number of participants
Hospital (General wards)	21
Hospital (Specialised wards e.g. NICU, PICU)	18
Private practice	27
Special school	7
Rehabilitation centre	5
University (Academic, lecturer, researcher)	5
Other (GICU & CICU)	1
Total	84

Note: Several respondents worked in multiple workplaces.

Vocational background of participants with NMD experience (n=64) presented as percentage

Place of work	% of responses
Hospital (general wards)	25.0
Hospital (specialised wards)	21.4
Private practice	32.0
Special school, rehabilitation centre, clinic, academics & other	21.4

Years of experience in the field of NMD (N=65) presented as frequencies

Years of experience	Number of participants
< 12 months	10
1-5 years	27
6-10 years	16
> 10 years	12
Total	65

SECTION B:

Acute management in patients with NMD (Summary of responses)

Questionnaire Section B: Acute Management	Intervention/technique	Number of “yes” responses (total number of responses per section)	If yes, details provided/description
General respiratory care	Mechanical ventilation	11 (44)	
		14 (44 ⁴²)	NIV ⁴³
		2 (14)	Short-term ventilation
	Supplemental oxygen	37 (44)	
		10 (37)	<u>Specify dosage</u> (% or litres): 40%
		9 (37)	2 litres/2-5 L
	Nebulisation	36 (44)	
		16 (31)	<u>Type of nebulisation:</u> Saline (mostly 0.9%)
		4 (31)	Saline combined with others. (e.g. bronchodilators/mucolytics)
		16 (28)	<u>Frequency per Rx⁴⁴:</u> Once
		11 (34)	<u>Frequency per day:</u> Twice
	24-hour postural management	37 (44)	
			<u>Specify the technique:</u>

⁴² More participants answered the specifications for ventilation (e.g. NIV, short-term) (n=14) than those that stated that they will use ventilation (yes=11)

⁴³ More than one option was allowed, one pilot study participant did not complete the specification of ventilation

⁴⁴ Frequencies per treatment/per day were not asked for all modalities.

		14 (34)	Supported sitting
		14 (34)	(Alternate) side-lying
		9 (34)	Semi-Fowler's; Fowler's; head elevated
Secretion mobilisation	Percussions	33 (41)	
		5 (31) 4 (31)	<u>Time per Rx:</u> 10 minutes 15 minutes
		23 (31)	<u>Frequency per day:</u> Twice
	Vibrations	36 (41)	
		7 (33) 5 (33)	<u>Time per Rx:</u> 5 minutes 10 minutes
		24 (33)	<u>Frequency per day:</u> Twice
	Oscillatory device (e.g. Flutter, Acapella, IPV)	24 ⁴⁵ (36)	
		16 (24)	<u>Type of device:</u> Flutter
	Postural drainage (Trendelenburg/"head down position")	8 (41)	
		No consensus among participants (n=8)	<u>Time per Rx:</u> No consensus (ranging from 1 to 20 minutes)
		6 (8)	<u>Frequency per day:</u> Twice

⁴⁵ This question was not included in the pilot study

	Adapted postural drainage (No Trendelenburg)	33 (41)	
		3 (30) 4 (30)	<u>Time per Rx:</u> 10 minutes 20 minutes <u>Frequency per day:</u> Twice
	Positioning	18 (28) 36 (41)	
		3 (32) 2 (32) 3 (32)	<u>Time per Rx:</u> 10 minutes 20 minutes 30 minutes <u>Frequency per day:</u> Twice
	Autogenic drainage (including assisted autogenic drainage)	15 (29) 20 (41)	
		2 (19) 4 (19)	<u>Time per Rx:</u> 5 min 10 min <u>Frequency per day:</u> Twice
	Breathing exercises	13 (18) 40 ⁴⁶ (41)	
		18 (36 ⁴⁷) 9 (36 ⁴⁸)	<u>Type of breathing exercises:</u> Active cycle of breathing (ACBT) (including modified ACBT) Deep breathing exercises (DBE) (alone or in combination)

⁴⁶ One pilot study participant said they will not use breathing exercises

⁴⁷ Although they said yes, four participants did not specify the exercises to be used

⁴⁸ Although they said yes, four participants did not specify the exercises to be used

		7 (35) 3 (35) 5 (35)	<u>Time per Rx:</u> 5 min 5-10 min 10 min
		18 (32)	<u>Frequency per day:</u> Twice
Cough augmentation/ airway clearance	Manually Assisted Cough (MAC)	38 (39 ⁴⁹)	
		19 (38)	<u>Type of MAC:</u> (Abd & Tx compression combined)
		No consensus among participants (n=32) 6 (32)	<u>Frequency per Rx:</u> No consensus (ranging from two to 10 times) 3-5; 5 or 5-10 times
			<u>Frequency per day:</u>
		27 (38)	Patient dependent
		10 ⁵⁰ (38)	Twice a day
		22 (38 ⁵¹)	<u>Action to take if patient gets tired:</u> Change technique/procedure
		15 (38)	Stop
	Mechanical assisted coughing/mechanical insufflation exsufflation (MI-E)	7 ⁵² (39)	

⁴⁹ One participant was unsure of the use of MAC

⁵⁰ One participant stated twice a day as well as patient dependent

⁵¹ One participant was unsure

⁵² 22 participants was unsure of the use of MI-E

		2 (7 ⁵³)	Manual setting
		4 (7 ⁵⁴)	<u>Automatic setting:</u>
		3 (4)	Basic auto
		1 (4)	Timed programmed
			<u>Inspiratory pressure (cmH₂O)</u>
		1 (7)	10-20
		1 (7)	30
			<u>Expiratory pressure (cmH₂O):</u>
		1 (7)	0-10
		1 (7)	30
			<u>Repetitions</u>
			<u>(insufflation-exsufflation) per cycle:</u>
		1 (7)	3-4
		1 (7)	5
			<u>Inspiratory time [Ti] (seconds):</u>
		1 (7)	2
		1 (7)	3 (patient dependent)
			<u>Expiration time [Te] (seconds):</u>
		1 (7)	1
		1 (7)	3
			<u>Pause between breaths (seconds):</u>
		1 (7)	1 or 2
		1 (7)	2
			<u>Sets used during a treatment:</u>
		1 (7)	5
		1 (7)	

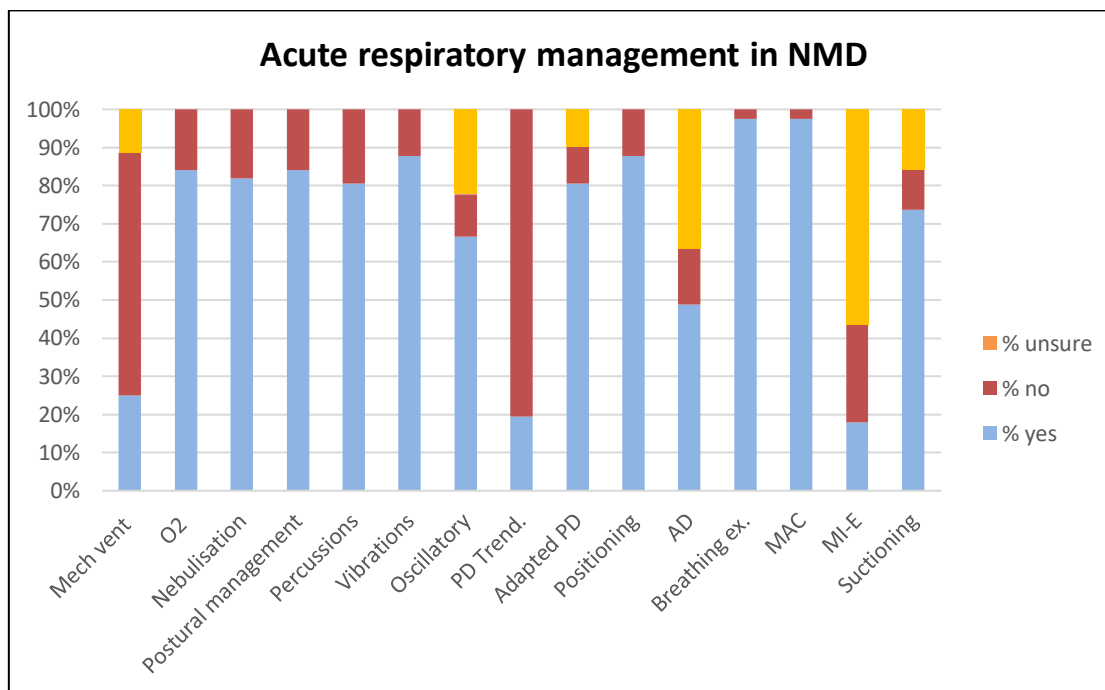
⁵³ One pilot study participant stated that they would use MI-E (manual setting), but have not used it on a patient before

⁵⁴ One participant stated that they know MI-E (automatic settings) is used internationally, but would not view it as part of standard care in SA

		1 (7) 1 (7) 2 (7)	Patient dependent <u>Pause/rest-interval between sets:</u> 30-60s 2 minutes <u>Settings dependent on the patient's requirements/as needed:</u> Yes, for all settings
	Cardiomyopathy	0 (35 ⁵⁵)	Use of MI-E in patients presenting with cardiomyopathy
	Suctioning	28 (38)	
		8 (26) 6 (26) 4 (26) 10 (22) 8 (22)	<u>Frequency per Rx:</u> Once As needed/patient dependent Twice <u>Frequency per day:</u> Twice As needed/patient dependent

⁵⁵ 22 participants were unsure if MI-E should be continued; 9 stated that they will not continue

Acute respiratory management responses expressed as a percentage (yes, no and unsure)



Open ended responses South African survey (Section B: acute care)

General respiratory management (n=11)	Secretion mobilisation (n=12)	Airway clearance techniques, including cough augmentation (n=12)	Other physiotherapy techniques (prevent and manage respiratory complications) (n=19)	General recommendations for acute care (n=10)
Retraining respiratory muscles as condition resolves	Tailored to child. Blow bottle if likes using it.	Care with pressure so as to not rupture small bowel	IPPB to maintain volume which could also be used for IMT. Power breathe devices for IMT	Infection control. Parent caregiver education.
Breathing control is important with inspiration: expiration	Caregiver training	Suctioning used as an assessment technique for this patient as well as for a treatment technique. Not necessary to continue with when not needed	Exercise and mobilisation	Education of parents and care givers. Demonstrations and carryover of what to continue with at home ADL activities
Chest physiotherapy: percussions and vibrations as tolerable, a bubble bottle, an incentive spirometer, breathing exercises, assisted coughing and trachy stimulation if necessary	Include saline in nebulizer	Pt education (self Mx). Being cautious to fatigue the pt	Muscle strengthening; Passives Mobilizations; ADL activities	Emotional support for child and family. This develops a better relationship with child and this will lead to improved co operation
Blowbottle and similar breathing exercises	Mobilising thoracic and upper limbs	Suctioning only when unable to clear secretions, I have never used MI-E, so not sure how that affects the need for suctioning	Patient and parent education regarding positioning and assisted coughing	Mobilisation of patient
I have done trachy stimulations and occasionally suctioned. I would nebulise with saline or a mucolytic to enable easier coughing if patient is not too weak.	Airstacking (independent by patient or mechanical, could be done by IPV)	Suctioning will be used if child is unable to expectorate despite assistance	Thoracic mobility exercises and stretching of the trunk	Exercise and mobilisation
A home programme is essential for maintenance of the respiratory function	Huffing, blowing of bubbles, windmill blowing	Carer training	Thoracic upper limb mobility	Noninvasive ventilation can be used to rest patient overnight in some cases as respiratory muscle exhaustion should be avoided
Treat what is needed and required for the patient. Focus on chest	Depends on LOC and cooperation from patient	Suction orally to clear upper airway	Education to child and caregiver	Vibromat if percussions and/or vibes are painful

requirements first but incorporate other aspects of functional ADL activities and try to maintain level of function of what the patient currently has. Bring in other members of the MDT for assistance as is needed				
Cough assistance, manually or with IPPB; IPPB to increase ventilation and mobilise secretions. Suction if necessary	Position bed into chair; Mobilize into chair; Mobilize and encourage breathing exercises etc. ASAP once off assisted ventilation and coping better (All if patient is stable and can tolerate)	Use IPPB as insufflation with peak pressures of 20 to 30 cmH ₂ O	Infection control techniques. Teach family home management of secretion and MAC	Warm humidification would be ideal and feeding with soft diet or nasal gastric tube to prevent aspiration.possible feeding assessment,oral hygiene
Teaching of adapted cough/breathing exercises, blowing activities, PEP etc	Cough assistance manually or with IPPB. Suction if cough not clearing lungs or cough exhausts patient	MIE: I use both automatic and manual settings depending on the child. Manual is easier to immediately change the time of inspiration-expiration-rest	Some form of cardio exercise. General muscle strengthening	As above ⁵⁶ (Breathe stacking/Deep breathing with ambubag).
Suctioning if necessary	Needs to be tailored to the individual	Nurses stay with patients and suction the remainder of the day	Active and passive movements	Would see if patient can cope with PEP (Flutter/bubble PEP bottle) so he can clear secretions more frequently-depends on severity of NMD
Nasal cannula with humidification	Active cycle of breathing technique used extensively in sputum induction	Suctioning only when intubated or unable to cough mostly in very young children.	Mobilisation (if appropriate)	
	Breath-stacking or DBE with bagging	Suctioning if unable to clear secretions	Mobilisation (2 responses)	
			Airstacking	
			Thoracic movements	

⁵⁶ With reference to the previous open-ended question on the prevention and Mx of respiratory complications

			Upper limb exercises for demand ventilation (sic)	
			Thoracic mobility, active assisted movements of limbs, circulatory activities	
			Home exercises	
			Breathe stacking/Deep breathing with ambubag	

SECTION C

Chronic management in patients with NMD (Summary of responses)

Questionnaire Section C: Chronic management	Intervention/technique	Number of “yes” responses (total number of responses per section)	If yes, details provided/description
Mechanical ventilation and support	NIV	16 (27)	
		1 (17) 7 (17) 0 (17) 2 (17) 0 (17) 9 (17)	<u>Type of NIV⁵⁷:</u> Diurnal Nocturnal Both/24 hours Short-term ventilation Long-term ventilation Intermittent (as required by patient/patient dependent)
		10 (28) 1 (9) 1 (9) 2 (9) 4 (9)	<u>BiPAP</u> <u>Average hours per day/night:</u> 2 2-4 6-8 Intermittent/ As needed/ patient dependent
		8 (27) ⁵⁸ 3 (7)	<u>CPAP</u> <u>Average hours per day/night:</u> As needed/required
	Supplemental O ₂	15 (27) ⁵⁹	

⁵⁷ Two participants chose more than one answer/option

⁵⁸ 10 participants indicated that they will not use CPAP

⁵⁹ One participant stated that they will use supplemental oxygen, if needed

		1 (13) 2 (13) 1 (13) 3 (13)	<u>Specify dosage</u> <u>(% or litres):</u> 25-40% 40% 2 litres As required/ patient dependent
	24-hour postural management	19 (28)	
		10 (15) 3 (15)	<u>Specify the technique</u> ⁶⁰ : Sitting (supported/high sitting) Head lifted (semi-Fowler's; 30 degrees)
Chronic management (Secretion Mobilisation/ peripheral ACT)	Nebulisation	24 (28)	
		7 (19) 3 (19)	<u>Type of nebulisation:</u> Saline (0.9%) alone Saline combined with others. (e.g. mucolytics)
		6 (19) 3 (19) 9 (20) 4 (20)	<u>Frequency per Rx:</u> Once As needed <u>Frequency per day:</u> Twice Patient dependent
	Oscillatory device (e.g. Flutter, Acapella, IPV)	20 (28) ⁶¹	

⁶⁰ Some participants provided more than one answer

⁶¹ One participant reported that they would use IPV

		13 (18) 2 (18) 2 (18)	<u>Type of device:</u> Flutter Flutter and/or Acapella Acapella
		3 (18) 4 (18) 3 (18) 3 (18) 7 (18) 4 (18)	<u>Frequency per Rx:</u> Once Ten times Patient dependent <u>Frequency per day:</u> Once Twice Three times
	Percussions	15 (27) ⁶²	
		5 (12) 2 (12) 2 (12) 8 (12)	<u>Time per Rx:</u> Ten minutes Two minutes per position/side <u>Frequency per day:</u> Once Twice
	Vibrations (One participant stated that they will use only if indicated)	15 (28) ⁶³	
		4 (12) 2 (12) 2 (12) 5 (12)	<u>Time per Rx:</u> Five minutes Ten minutes <u>Frequency per day:</u> Once Twice

⁶² One participant stated that they will use percussions only if indicated

⁶³ One participant stated that they will use vibrations only if indicated

	Postural drainage (Trendelenburg/ "head down position")	4 (28) ⁶⁴	
		2 (4) 1 (4)	<u>Time per Rx⁶⁵:</u> 10 min 10-15 min
		1 (3) 1 (3) 1 (3)	<u>Frequency per day:</u> Once 1-2 times (with treatment) 3 times
	Adapted postural drainage	17 (28) ⁶⁶	
		2 (14) 2 (14)	<u>Time per Rx:</u> 10 min 20 min
		2 (14) 6 (14) 2 (14)	<u>Frequency per day:</u> 1-2 times 2 times Patient dependent
	Positioning	23 (28)	
		2 (19) 2 (19) 4 (19)	<u>Time per Rx:</u> 30 minutes Every 2-4 hours Patient dependent
		2 (17) 5 (17) 4 (17)	<u>Frequency per day:</u> Throughout the day Twice Patient dependent

⁶⁴ 18 participants indicated that they will not use head down tilt/Trendelenburg

⁶⁵ One participant did not specify time per treatment and frequency per day

⁶⁶ Seven participants indicated that they will not use adapted PD

	Autogenic drainage (including assisted autogenic drainage)	12 (28)	
		2 (10) 3 (10)	<u>Time per Rx:</u> 5 min Patient dependent
		5 (10) 3 (10)	<u>Frequency per day:</u> Twice Patient dependent
Chronic management (Cough augmentation/proximal ACT)	Manually Assisted Cough (MAC)	22 (28)	
		1 (23) 9 (23) 13 (23)	<u>Type of MAC⁶⁷:</u> Abdominal Thoracic Abd & Tx combined
		2 (17) 9 (17)	<u>Frequency of coughs per Rx:</u> 2-3 As needed/ patient dependent
		1 (26) 6 (26) 0 (26) 19 (26)	<u>Frequency of coughs per day:</u> Once Twice >Twice Patient dependent
		8 (24) 16 (24)	<u>Action to take if patient gets tired:</u> Change technique/procedure Stop

⁶⁷ One participant that was unsure of the use of MAC, stated that if they should use this technique they will use a combination of thoracic and abdominal technique

	Mechanical assisted coughing/mechanical insufflation exsufflation (MI-E) ⁶⁸	4 (27) ⁶⁹	
		0 (3)	Manual setting
		3 (3)	<u>Automatic setting:</u>
		1 (2 ⁷⁰)	Basic auto
		0 (1)	Timed programmed
		1 (2)	Triggered programmable auto
		2 (2 ⁷¹)	<u>Inspiratory pressure (cmH₂O)</u>
			30
		1 (2)	<u>Expiratory pressure (cmH₂O):</u>
		1 (2)	20
			30
			<u>Repetitions</u>
			<u>(insufflation-exsufflation) per cycle:</u>
		1 (2)	3
		1 (2)	5
		1 (2)	<u>Inspiratory time [Ti] (seconds):</u>
		1 (2)	1.5
			2
		1 (2)	<u>Expiration time [Te] (seconds):</u>
		1 (2)	1.5
			3

⁶⁸ One participant stated that MI-E is used for home management internationally, but doubt if it is used in S.A

⁶⁹ 16 participants were unsure if MI-E should be used

⁷⁰ One participant did not specify the automatic mode

⁷¹ One participant that said yes for MI-E automatic mode did not specify which mode to use

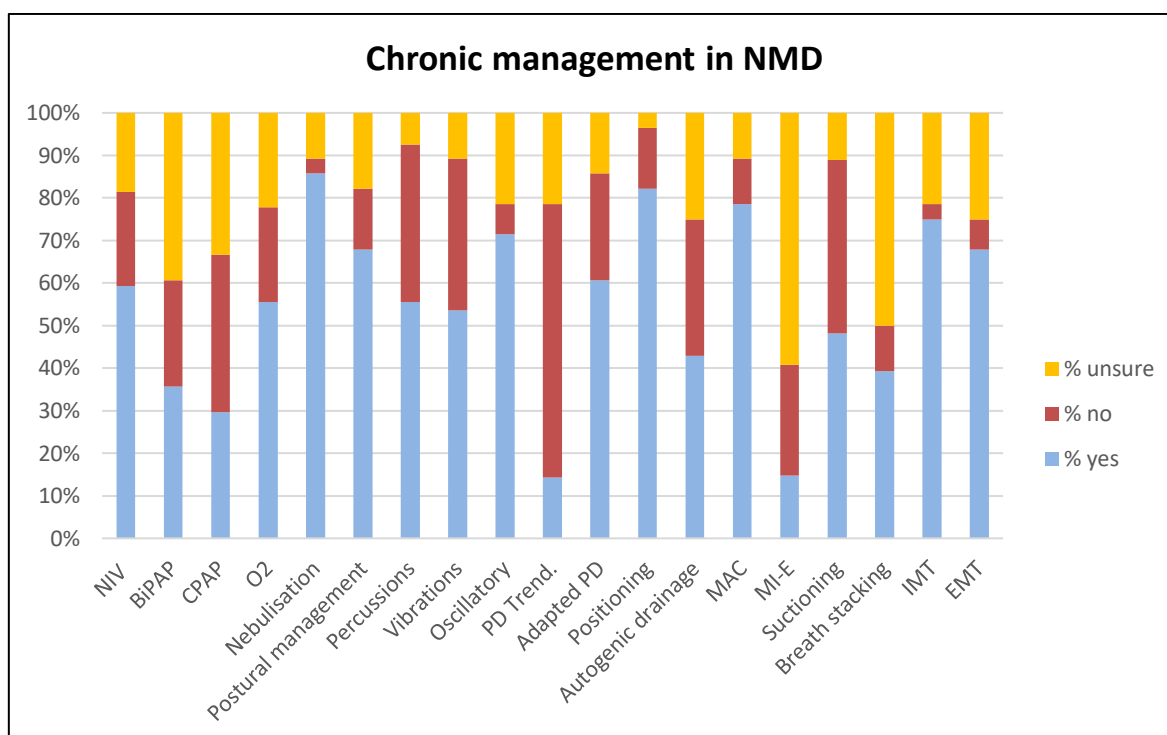
		1 (2) 1 (2) 1 (1 ⁷²) 1 (1) 2 (2)	<u>Pause between breaths (seconds):</u> 1 to 2 2 <u>Sets used during a treatment:</u> 5 <u>Pause/rest-interval between sets:</u> 1 minute <u>Settings dependent on the patient's requirements/as needed:</u> Yes, for all settings
	Suctioning	13 (27)	
		2 (12) 2 (12) 6 (12) 3 (9) 6 (9)	<u>Frequency per treatment:</u> Once Twice As required/ patient dependent <u>Frequency per day:</u> Twice As required/ patient dependent
Lung volume recruitment, breathing exercises and respiratory muscle training	Breath-stacking	11 (28) ⁷³	
		2 (11) 3 (11)	<u>Variety suggested:</u> Independent breath-stacking only Independent/assisted

⁷² Two participants did not provide an answer

⁷³ 14 participants were unsure about the use of hyperinflation

		6 (11)	Independent/assisted/both; depending on patient
	Breathing exercises	27 (28)	
		4 (22) 9 (22) 6 (22)	<u>Type of breathing exercises:</u> Active cycle of breathing (ACBT) alone ACBT in combination with other techniques, including modified ACBT Deep breathing exercises (DBE)
		3 (22) 5 (22) 3 (22) 11 (22) 4 (22)	<u>Time per Rx:</u> 2 min 5 min 5-10 min <u>Frequency per day:</u> Twice Three times
	Expiratory muscle training (EMT)	19(28)	
		10 (18) 6 (18) 1(18) 1 (18)	<u>Specific device:</u> Resistance device only Threshold device only Resistance, threshold or flow device Resistance and flow device (combination)
	Inspiratory muscle training (IMT)	21 (28)	
		9 (21) 8 (21) 2 (21)	<u>Specify device:</u> Resistance device only Threshold device only Resistance and flow device (combination)

Chronic respiratory management responses expressed as a percentage (yes, no and unsure)



SECTION C:

Open ended responses South African survey (Section C: chronic care)

Breathing exercises, respiratory muscle training and lung compliance	Airway clearance techniques, including cough augmentation (n=5)	Other physiotherapy techniques (prevent and manage respiratory complications) (n=19)
Breathing exercises (n=17): Active cycle of breathing (ACBT)	Saline nebulisations with and/or between the medicated nebulisations,	IPPB to maintain volume which could also be used for IMT. Power breathe devices for IMT
Localised breathing, basal apical abdominal	Percussions only to be used when secretions are not mobilising easily if the patient has an increase in secretions or change in secretions we encourage hospital admission	Exercise and mobilisation
Inspiratory and forced expiratory techniques e.g. active cycle of breathing	Hydrotherapy could be used to deepen the breathing and strengthen respiratory muscles	Muscle strengthening; Passives Mobilizations; ADL activities
ACBT, Deep breathing exercises (DBE)	Suction as necessary	Patient and parent education regarding positioning and assisted coughing

Blowing toys (not sure if they are considered breathing exercises or a device)	MIE both manual and automatic used, manual easier to change time settings during sets and child dependent	Thoracic mobility exercises and stretching of the trunk
ACBT, blowing exercises	Other physiotherapy techniques to prevent complications (role of the physiotherapist) (n=6)	Thoracic upper limb mobility
Deep inspiratory with forced expiration	Passive and active limb exercise and trunk stretching	Education to child and caregiver
Diaphragmatic and localised	General strengthening and some forms of cardio exercise if possible	Infection control techniques. Teach family home management of secretion and MAC
Positive pressure	Maintenance of ranges; strengthen core and diaphragm; mobility of upper quadrant	Some form of cardio exercise. General muscle strengthening
Glove Blowing; ACBT; Autogenic Drainage; IMT; Spirometer	Active and passive movements	Active and passive movements
Incentive spirometer	Stretching of thoracic musculature and shoulder mobility	Mobilisation (if appropriate)
ACBT and autogenic drainage	Postural support to reduce secondary changes e.g. scoliosis and management of weight	Mobilisation (2 responses)
Modified ACBT, autogenic drainage	Other general management techniques for chronic care (not previously mentioned) (n=3)	Airstacking
ACBT	Prevent RTIs with pharmacological intervention and nutrition and home hygiene	Thoracic movements
ACBT's, relaxed and controlled breathing, deep breathing exercises	Home exercises; play in mobility	Upper limb exercises for demand ventilation (sic)
ACBT	Exercise and games to improve respiratory function	Thoracic mobility, active assisted movements of limbs, circulatory activities
DBE and glossopharyngeal breathing		Home exercises
Respiratory muscle training (n=3): General cardiovascular exercise		Breathe stacking/Deep breathing with ambubag
LUFT		

As maintenance breathing exercises in a play or fun activity is necessary for compliance		
Breath-stacking/hyperinflation/lung volume recruitment techniques suggested (n=8)		
Active exercise with holds at end of breath		
Depending on age teach small inspirations, holding breath in between and maximally full use manual inflation bag with mask or mouthpiece		
Frog breathing or using mask with a one way valve		
Independent by frog breathing Assisted, could be done by IPV device or balloon inflation		
Independent-fear of injury (barotrauma)		
IPPB with a mouthpiece		
Short exhalations with deeper and deeper inhalations		
With an ambubag with a mouthpiece or mask depending on mouth closure followed by MAC		
With an ambubag with a mouthpiece or mask depending on mouth closure followed by MAC		

SECTION D

Current practice in patients with NMD in SA (Summary of responses)

Acute management	Intervention	Yes	Total
Secretion mobilisation techniques	Percussions	5	6
	Vibrations	6	6
	Postural drainage (Trendelenburg)	1	6
	Adapted postural drainage (No Trendelenburg)	6	6
	Positioning	6	6
	Autogenic drainage (Including AAD)	1	6
	Breathing exercises	6	6
	Suctioning	4	6
	Nebulisation (including mucolytics)	4	6
	Breath-stacking (hyperinflation)	4	6
Others	24 hour postural management	3	5
	Supplemental O ₂	4	6
Airway clearance/cough assistance	MAC	4	6
	MI-E No (n=6)	0	6

Chronic management	Intervention	Yes	Total
Home programme (muscle training & compliance)	Breath-stacking	3	6
	IMT	4	6
	EMT	5	6
	Breathing exercises	6	6
	24 hour postural management	4	6
Secretion mobilisation	Nebulisation (including mucolytics)	3	6
	Oscillatory device	3	6
	Percussions	5	6
	Vibrations	4	6
	Postural drainage (Trendelenburg)	1	6
	Adapted postural drainage (No Trendelenburg)	6	6
	Positioning	6	6
	Autogenic drainage (Including AAD)	0	6
	Suctioning	2	6
Airway clearance/cough assistance	MAC	4	6
	MI-E No(n=6)	0	6

Summary of preferred techniques in acute and chronic management of children with NMD

(survey on standard of care)

Management	Acute	Chronic
General respiratory care/respiratory support	<i>Non-invasive ventilation (NIV)</i> <i>Nebulisation (normal saline)</i> <i>Supplemental O₂</i> <i>24-hour postural management</i>	<i>Non-invasive ventilation (NIV)</i> <i>24-hour postural management</i> <i>Supplemental O₂</i>
Secretion mobilisation	<i>Percussions</i> <i>Vibrations</i> <i>Adapted postural drainage</i> <i>(No Trendelenburg)</i> <i>Positioning</i> <i>Oscillatory devices (e.g. Flutter)</i> <i>Breathing exercises</i>	<i>Nebulisation</i> <i>Adapted postural drainage</i> <i>(No Trendelenburg)</i> <i>Positioning</i> <i>Oscillatory devices</i>
Airway clearance and cough augmentation/assistance	<i>Manually assisted cough (MAC)</i> <i>(combination of thoracic and abdominal compressions)</i> <i>Suctioning</i> <i>*The majority either did not know of mechanical insufflation-exsufflation (MI-E) as an alternative cough augmentation option or was aware of the device, but have never used it before.</i>	<i>Manually assisted cough (MAC)</i> <i>(Thoracic and abdominal)</i>
Lung compliance exercises and respiratory muscle training	Not included as part of acute management	<i>Breathing exercises</i> <i>Inspiratory and expiratory muscle training</i> <i>*50% of participants were unsure about the use of breath-stacking/hyperinflation/glossopharyngeal breathing (GPB)</i>

**Frequency of techniques was mostly recommended as twice a day.*

Appendix Axi: International clinical practice guidelines and publications on respiratory management of children with neuromuscular disease or respiratory muscle weakness

- Guidelines on pulmonary rehabilitation, with specific reference to COPD (Nici et al., 2006);
- British Thoracic Society guideline for management of children presenting with neuromuscular weakness (Hull et al., 2012);
- American Thoracic Society consensus statement: Respiratory care of the patient with DMD (Finder et al., 2004);
- Consensus statement for standard of care in congenital muscular dystrophies and SMA (Wang et al., 2007; Wang et al., 2010);
- Airway clearance techniques in NMD (Panitch, 2006; Finder, 2010; Chatwin et al., 2018; Toussaint et al., 2018);
- Airway clearance in neuromuscular weakness (Gauld, 2009);
- Diagnosis and management of DMD, part 2: implementation of multi-disciplinary care (Bushby et al., 2010);
- Diagnosis and management of DMD, part 2: respiratory, cardiac, bone health and orthopaedic management (Birnkrant et al., 2018);
- Respiratory implications of Pediatric Neuromuscular Disease (Panitch, 2017);
- Guidelines for the management of respiratory complications in patients with neuromuscular disease (Farrero et al., 2013);
- 228th ENMC International Workshop: Airway clearance techniques in neuromuscular disorders. Naarden, the Netherlands, 3-5 March 2017 (Toussaint et al., 2018).

Appendix Bi: Search strategies (in alphabetical order)

Africa-Wide information search strategy

Africa-Wide Information is an aggregation of 50 databases sourced from Africa, Europe and North America. This database collection integrates contents from African Studies, South African Studies, and African Healthline to form a multidisciplinary aggregation offering unique and extensive coverage of all facets of Africa and African studies.

Keywords were determined by investigating MeSH terms in literature and databases. The final keywords to be used are firstly conditions, then intervention and lastly type of study: neuromuscular diseases OR neuromuscular disorders OR NMD OR muscular dystrophy OR Duchenne* OR DMD OR spinal muscular atrophy OR central core disease OR congenital myopathy OR restrictive lung dis* OR respiratory muscle condition OR diaphragm* weakness combined with respirat* mus* training OR respirat* mus* strength* OR respiratory mus* endurance OR inspirat* mus* training OR inspirat* mus* strength* OR inspirit* mus* endurance OR IMT OR diaphragm* strength*. These keywords will then be combined with random* OR trial* OR clinical trial OR placebo OR comparative stud* OR controlled trial OR CCT OR RCT OR double-blind* OR single-blind*.

To note:

The search strategy was adapted accordingly (refer to table below):

Date of search	
Years covered	20 th century to present
Complete strategy	First line: neuromuscular diseases OR neuromuscular disorders OR NMD OR muscular dystrophy OR Duchenne* OR DMD OR spinal muscular atrophy OR central core disease OR congenital myopathy OR restrictive lung dis* OR respiratory muscle condition OR diaphragm* weakness OR diaphragm* strength* Combined with (AND) Second line: respirat* mus* training OR respirat* mus* strength* OR respiratory mus* endurance OR inspirat* mus* training OR inspirat* mus* strength* OR inspirit* mus* endurance OR IMT First line: neuromuscular diseases OR neuromuscular disorders OR NMD OR muscular dystrophy OR Duchenne* OR DMD OR spinal muscular atrophy OR central core disease OR congenital myopathy OR restrictive lung dis* OR respiratory muscle condition OR diaphragm* weakness Combined with (AND) Second line: random* OR trial* OR clinical trial OR placebo OR comparative stud* OR controlled trial OR CCT OR RCT OR double-blind* OR single-blind*.

	First line: respirat* mus* training OR respirat* mus* strength* OR respiratory mus* endurance OR inspirat* mus* training OR inspirat* mus* strength* OR inspirit* mus* endurance OR IMT OR diaphragm* strength* Second line: random* OR trial* OR clinical trial OR placebo OR comparative stud* OR controlled trial OR CCT OR RCT OR double-blind* OR single-blind*. First line: neuromuscular diseases OR neuromuscular disorders OR NMD OR muscular dystrophy OR Duchenne* OR DMD OR spinal muscular atrophy OR central core disease OR congenital myopathy OR restrictive lung dis* OR respiratory muscle condition OR diaphragm* weakness Second line: respirat* mus* training OR respirat* mus* strength* OR respiratory mus* endurance OR inspirat* mus* training OR inspirat* mus* strength* OR inspirit* mus* endurance OR IMT OR diaphragm* strength* Third line: random* OR trial* OR clinical trial OR placebo OR comparative stud* OR controlled trial OR CCT OR RCT OR double-blind* OR single-blind*.
Summary of strategy	An <u>advanced search</u> will be done. Three lines are given initially. No specific field is selected. Search modes and expanders is set to Boolean/Phrase. All other dropdown options including publication type, language, document type and data contributor are kept at <u>ALL</u> (in order to ensure that all possible options are included). Firstly condition will be combined with intervention, then condition and intervention will be combined with study type/design (separately) and lastly condition, intervention and type of study will be combined.
Language restrictions	None

The Cochrane Central Register of Controlled Trials (CENTRAL) search strategy

<http://www.cochrane.org/editorial-and-publishing-policy-resource/cochrane-central-register-controlled-trials-central>

CENTRAL is a bibliographic database that provides a highly concentrated source of reports of randomized controlled trials. Records contain the list of authors, the title of the article, the source, volume, issue, page numbers, and, in many cases, a summary of the article (abstract). They do not contain the full text of the article.

Keywords were determined by investigating MeSH terms in literature and databases. The final keywords to be used are firstly conditions, then intervention and lastly type of study: neuromuscular diseases OR neuromuscular disorders OR NMD OR muscular dystrophy OR Duchenne* OR DMD OR spinal muscular atrophy OR central core disease OR congenital myopathy OR restrictive lung dis* OR respiratory muscle condition OR diaphragm* weakness combined with respirat* musc* training OR respirat* musc* strength* OR respiratory musc* endurance OR inspirat* musc* training OR inspirat* musc* strength* OR inspirit* musc* endurance OR IMT OR diaphragm* strength*. These keywords will then be combined with random* OR trial* OR clinical trial OR placebo OR comparative stud* OR controlled trial OR CCT OR RCT OR double-blind* OR single-blind*.

To note, the search strategy was adapted accordingly (refer to table below):

Date of search	
Years covered	From inception to present
Complete strategy	First search: Conditions: neuromuscular diseases OR neuromuscular disorders OR NMD OR muscular dystrophy OR Duchenne* OR DMD OR spinal muscular atrophy OR central core disease OR congenital myopathy OR restrictive lung dis* OR respiratory muscle condition OR diaphragm* weakness Combined with (AND) Interventions: respirat* musc* training OR respirat* musc* strength* OR respiratory musc* endurance OR inspirat* musc* training OR inspirat* musc* strength* OR inspirit* musc* endurance OR IMT OR diaphragm* strength* Second search: Conditions: neuromuscular diseases OR neuromuscular disorders OR NMD OR muscular dystrophy OR Duchenne* OR DMD OR spinal muscular atrophy OR central core disease OR congenital myopathy OR restrictive lung dis* OR respiratory muscle condition OR diaphragm* weakness Combined with (AND) Study type/design: random* OR trial* OR clinical trial OR placebo OR comparative stud* OR controlled trial OR CCT OR RCT OR double-blind* OR single-blind*.

	Third search: Interventions: respirat* musc* training AND respirat* musc* strength* OR respiratory musc* endurance OR inspirat* musc* training OR inspirat* musc* strength* OR inspirit* musc* endurance OR IMT OR diaphragm* strength Combined with (AND) Type of study/design: random* OR trial* OR clinical trial OR placebo OR comparative stud* OR controlled trial OR CCT OR RCT OR double-blind* OR single-blind*. All three will then be combined namely condition, intervention and type of study/design.
Summary of strategy	Go to the Cochrane Library and then click on: The Cochrane Central Register of Controlled Trials (CENTRAL) Search for trials. Only one search option is given (no basic or advanced search). In search: "Search all text" will be used. Firstly the condition and intervention will be combined, then the condition and intervention will be combined with the type of study (individually). Lastly all three (condition, intervention and type of study) will be combined.
Language restrictions	None

CINAHL via Ebsco Host search strategy

CINAHL is a database that covers a wide range of topics including nursing, biomedicine, health sciences librarianship, alternative/complementary medicine, consumer health and 17 allied health disciplines. Currently CINAHL indexes more than 3000 journals and more than 70 full-text journals. In addition, CINAHL provides access to health care books, nursing dissertations, selected conference proceedings, standards of practice, audiovisuals and book chapters, as well as legal cases, clinical innovations, critical paths, research instruments and clinical trials (<http://www.ebscohost.com/biomedical-libraries/the-cinahl-database>).

Keywords were determined by investigating MeSH terms in literature and databases. The final keywords to be used are firstly conditions, then intervention and lastly type of study: neuromuscular diseases OR neuromuscular dis* OR NMD OR muscular dystrophy OR Duchenne* OR DMD OR spinal muscular atrophy OR central core disease OR congenital myopathy OR restrictive lung dis* OR respiratory muscle condition OR diaphragm* weakness combined with respirat* musc* training OR respirat* musc* strength* OR respiratory musc* endurance OR inspirat* musc* training OR inspirat* musc* strength* OR inspirit* musc* endurance OR IMT OR diaphragm* strength*. These keywords will then be combined with random* OR trial* OR clinical trial OR placebo OR comparative stud* OR controlled trial OR CCT OR RCT OR double-blind* OR single-blind*.

To note: The search strategy was adapted accordingly (refer to table below):

Date of search	
Years covered	1981 to present
Complete strategy	Firstly condition(s) and intervention(s) will be combined and the applicable CINAHL headings will be chosen. 1) ALL subheadings were included: All the <u>condition</u> keywords as described above were entered and CINAHL headings were searched. Those that could “explode all trees” were chosen: • Duchenne Muscular Dystrophies • Lung Diseases • Mitochondrial Myopathies • Muscular Atrophy, Spinal • Muscular Disorders, Atrophic • Muscular Dystrophy • Neuromuscular Diseases • Neuromuscular Junction Diseases • Respiratory Airflow • Respiratory Muscles

	Those that could not, “major concept” was chosen.⁷⁴ 2) ALL subheadings were included: All the <u>intervention</u> keywords as described above were entered and CINAHL headings were searched. Those that could “explode all trees” were chosen: • Muscle Strength • Muscle Strengthening • Physical Endurance • Respiratory Airflow • Respiratory Failure • Respiratory System Abnormalities • Respiratory Tract Infections Those that could not, “major concept” was chosen.⁷⁵ 3) ALL subheadings were included: All the type of study/design keywords as described above were entered and CINAHL headings were searched. Those that could “explode all trees” were chosen: • Clinical Trials • Non-experimental Studies • Random Sample Those that could not, “major concept” was chosen.⁷⁶ ALL the keywords that were searched in the CINAHL headings will also be included in the search list (ticked) e.g. neuromuscular dis* for all the three searches. 4) Combinations: Search 1 and 2 will then be combined: condition(s) and intervention(s) by selecting the two searches and clicking on “search with AND”. Search 1 and 3 will then be combined: condition(s) and type of study/design by selecting the two searches and clicking on “search with AND”. Search 2 and 3 will then be combined: Intervention(s) and type of study/design by selecting the two searches and clicking on “search with AND”. Lastly search 1, 2 and 3 will be combined (condition(s), intervention(s) and type of study/design).
Summary of strategy	An <u>advanced search</u> will be done. Three lines are given initially. No specific field is selected. Search modes and expanders is set to Boolean/Phrase. All other dropdown options including clinical queries, journal subset, publication

⁷⁴ CINAHL headings used are described at the end of the table

⁷⁵ CINAHL headings used are described at the end of the table

⁷⁶ CINAHL headings used are described at the end of the table

	type, sex, special interest, geographic subset, language and age groups are kept at <u>ALL</u> (in order to ensure that all possible options are included). Firstly the correct CINAHL headings will be sourced and selected by making use of the specified keywords for condition(s), intervention(s) and type of study/design. Based on these terms a search will be done. Condition(s), intervention(s) and type of study/design will be searched separately and then they will be combined. Condition and intervention will be combined, then condition and type of study/design, thereafter intervention and type of study/study design will be combined. Lastly all three will be combined (condition(s), intervention(s) and type of study/design will be combined for a more focused result.
Language restrictions	None

Conditions (CINAHL headings chosen):

"(MH "Neuromuscular Junction Diseases+") OR (MH "Neuromuscular Diseases+") OR (MM "Myotonic Dystrophy") OR "neuromuscular dis*" OR "NMD" OR (MH "Muscular Dystrophy+") OR "muscular dystrophy" OR (MM "Becker Muscular Dystrophy") OR (MM "Muscular Dystrophy, Oculopharyngeal") OR (MH "Duchenne Muscular Dystrophy+") OR "central core disease" OR (MH "Muscular Atrophy, Spinal+") OR (MM "Bulbo-Spinal Atrophy, X-Linked") OR (MH "Muscular Disorders, Atrophic+") OR (MM "Muscular Atrophy") OR (MM "Charcot-Marie-Tooth Disease") OR "spinal muscular atrophy" OR (MH "Mitochondrial Myopathies+") OR "congenital myopathy" OR (MH "Lung Diseases+") OR "restrictive lung disease" OR (MH "Respiratory Muscles+") OR (MH "Respiratory Airflow+") OR "respiratory muscle condition" OR (MM "Muscle Weakness") OR "diaphragm* weakness"

Interventions (CINAHL headings chosen):

"(MH "Respiratory Airflow+") OR (MH "Respiratory Tract Infections+") OR (MH "Respiratory System Abnormalities+") OR "respiratory musc* training" OR "respiratory musc* strength" OR (MH "Respiratory Failure+") OR (MH "Physical Endurance+") OR "respiratory musc* endurance" OR (MM "Training Effect (Physiology)") OR (MM "Resistance Training") OR "inspiratory musc* training" OR (MH "Muscle Strength+") OR "inspiratory musc* strength" OR "inspiratory musc* endurance" OR "IMT" OR "diaphragm* strength*" OR (MH "Muscle Strengthening+")

Type of study/design (CINAHL headings chosen):

"(MM "Stratified Random Sample") OR (MM "Systematic Random Sample") OR (MM "Simple Random Sample") OR (MH "Random Sample+") OR "random" OR "trial*" OR (MM "Clinical Trial Registry") OR (MM "Randomized Controlled Trials") OR (MH "Clinical Trials+") OR "clinical trial" OR (MM "Placebo Effect") OR "placebo" OR (MM "Comparative Studies") OR (MM "Concurrent Prospective Studies") OR (MM "Cross Sectional Studies") OR (MH "Nonexperimental Studies+") OR (MM "Multicenter Studies") OR (MM "Quantitative Studies") OR (MM "Physiological Studies") OR "comparative study" OR (MM "Cochrane Library") OR "controlled trial" OR "CCT" OR "RCT" OR (MM "Double-Blind Studies") OR "double blind*" OR (MM "Single-Blind Studies") OR "single blind*"

Clinicaltrials.gov search strategy

<https://clinicaltrials.gov/>

ClinicalTrials.gov is a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world and is run by the United States Library of Medicine (NLM) at the national Institutes of Health. ClinicalTrials.gov currently lists 172,691 studies with locations in all 50 states and in 187 countries. Keywords were determined by investigating MeSH terms in literature and databases. The final keywords to be used are firstly conditions, then intervention and lastly type of study: neuromuscular diseases OR neuromuscular disorders OR NMD OR muscular dystrophy OR Duchenne* OR DMD OR spinal muscular atrophy OR central core disease OR congenital myopathy OR restrictive lung dis* OR respiratory muscle condition OR diaphragm* weakness combined with respirat* musc* training OR respirat* musc* strength* OR respiratory musc* endurance OR inspirat* musc* training OR inspirat* musc* strength* OR inspirit* musc* endurance OR IMT OR diaphragm* strength*. These keywords will then be combined with random* OR trial* OR clinical trial OR placebo OR comparative stud* OR controlled trial OR CCT OR RCT OR double-blind* OR single-blind*.

To note, this search strategy was adapted accordingly (refer to table below):

Date of search	
Years covered	2000 to present
Complete strategy	Conditions: neuromuscular diseases OR neuromuscular disorders OR NMD OR muscular dystrophy OR Duchenne* OR DMD OR spinal muscular atrophy OR central core disease OR congenital myopathy OR restrictive lung dis* OR respiratory muscle condition OR diaphragm* weakness Combined with (AND) Interventions: respirat* musc* training OR respirat* musc* strength* OR respiratory musc* endurance OR inspirat* musc* training OR inspirat* musc* strength* OR inspirit* musc* endurance OR IMT OR diaphragm* strength* Study type: "all studies" will be chosen.
Summary of strategy	An <u>advanced search</u> will be done. The first line (Search terms) represents a basic search. Under targeted search (specific), in the line labelled "conditions" all the relevant search terms will be entered with "OR" in-between. In the next line for "interventions" the relevant search terms/keywords with "OR" in-between will be entered. Recruitment, study results, study types, sex and age will be kept on "all studies" (in order to ensure that all relevant studies are found, even those that include both adult and paediatric patients). The type of study keywords will not be applied in this database, as study type is catered for in the advanced search option and therefore "all studies" will be chosen.
Language restrictions	None

The Cochrane Neuromuscular Disease Group Specialized Register search strategy

<http://neuromuscular.cochrane.org/cochrane-neuromuscular-disease-group>

The Neuromuscular Disease Group was registered with the Cochrane Collaboration in March 1998 and aims to provide systematic reviews of all interventions for all neuromuscular diseases, including amyotrophic lateral sclerosis/motor neuron disease, peripheral nerve disorders, myasthenia gravis and neuromuscular function disorders, and muscle diseases. Since 2008 the Group has begun to prepare systematic reviews of diagnostic test accuracy.

Keywords were determined by investigating MeSH terms in literature and databases. The final keywords to be used are firstly conditions, then intervention and lastly type of study: neuromuscular diseases OR neuromuscular disorders OR NMD OR muscular dystrophy OR Duchenne* OR DMD OR spinal muscular atrophy OR central core disease OR congenital myopathy OR restrictive lung dis* OR respiratory muscle condition OR diaphragm* weakness combined with respirat* mus* training OR respirat* mus* strength* OR respiratory mus* endurance OR inspirat* mus* training OR inspirat* mus* strength* OR inspirit* mus* endurance OR IMT OR diaphragm* strength*. These keywords will then be combined with random* OR trial* OR clinical trial OR placebo OR comparative stud* OR controlled trial OR CCT OR RCT OR double-blind* OR single-blind*.

To note: The search strategy was adapted accordingly (refer to table below):

Date of search	
Years covered	Inception (?1998) to present
Complete strategy	From the Cochrane Library page, click on the Neuromuscular Disease Group. Then on "Our reviews". Trials are given as a "full list" or categorised under subtopics and each subtopic is then divided again: Subtopics: • Complications of Neuromuscular Disease (4) • Generic Neuromuscular Symptoms (22) • Generic treatments (4) • Motor Neuron Disorder (39) • Muscle Diseases (33) • Neuromuscular Junction Disorders (19) • Other disorders related to neuromuscular disease (1) • Peripheral Neuropathy (142) All of the above subtopics will be searched by the researcher, except for generic Neuromuscular Symptoms and peripheral neuropathy, to assess if any of the reviews might be applicable to this study topic.
Summary of strategy	Trials are given as a "full list" or categorised under subtopics. Trial Subtopics (all except for generic Neuromuscular Symptoms and peripheral neuropathy) will be manually searched by the researcher for studies applicable to the study topic. Keyword/phrase searches with condition(s), intervention(s) and type of study/design will therefore not be applied for this database.
Language restrictions	None

Medline search strategy

MEDLINE is a bibliographic database that contains over 21 million references to journal articles in life sciences with a concentration on biomedicine. The subject scope of MEDLINE is biomedicine and health, broadly defined to encompass those areas of the life sciences, behavioral sciences, chemical sciences, and bioengineering needed by health professionals and others engaged in basic research and clinical care, public health, health policy development, or related educational activities. The majority of the publications covered in MEDLINE are scholarly journals; a small number of newspapers, magazines, and newsletters are also included. A distinctive feature of MEDLINE is that the records are indexed with NLM Medical Subject Headings (MeSH®). Currently Medline has 5 600 citations from worldwide journals in about 40 languages; and about 60 languages for older journals (<http://www.nlm.nih.gov/pubs/factsheets/medline.html>).

Keywords were determined by investigating MeSH terms in literature and databases. The final keywords to be used are firstly conditions, then intervention and lastly type of study: neuromuscular diseases OR neuromuscular disorders OR NMD OR muscular dystrophy OR Duchenne* OR DMD OR spinal muscular atrophy OR central core disease OR congenital myopathy OR restrictive lung dis* OR respiratory muscle condition OR diaphragm* weakness combined with respirat* musc* training OR respirat* musc* strength* OR respiratory musc* endurance OR inspirat* musc* training OR inspirat* musc* strength* OR inspirit* musc* endurance OR IMT OR diaphragm* strength*. These keywords will then be combined with random* OR trial* OR clinical trial OR placebo OR comparative stud* OR controlled trial OR CCT OR RCT OR double-blind* OR single-blind*.

The search strategy was adapted accordingly (refer to table below):

Date of search	
Years covered	Inception (?1946) to present.
Complete strategy	Firstly condition(s) will be searched and the applicable MeSH terms will be sourced. ALL subheadings were included: All the <u>condition</u> keywords as described above were entered and MeSH 2014 keywords were searched. Those that could “explode all trees” were chosen: • Lung diseases • Motor neuron diseases • Muscles • Muscular Atrophy, Spinal • Muscular Disorders, Atrophic • Muscular Dystrophies • Muscular Dystrophies, Limb-Girdle • Myopathies, structural, congenital • Neuromuscular Diseases • Neuromuscular Junction Diseases

	• Respiratory Muscles Respiratory System Those that could not, “major concept” was chosen.⁷⁷ Secondly intervention(s) will be searched and the applicable MeSH terms will be sourced. ALL subheadings were included: All the <u>intervention</u> keywords as described above were entered and MeSH 2014 keywords were searched. Those that could “explode all trees” were chosen: • Breathing exercises • Inspiratory Capacity • Muscle Strength • Respiratory Mechanics • Respiratory Muscles • Respiratory System • Respiratory Therapy Those that could not, “major concept” was chosen.⁷⁸ Thirdly, type of study/design will be searched and the applicable MeSH terms will be sourced. ALL subheadings were included: All the type of study/design keywords as described above were entered and MeSH 2014 keywords were searched. Those that could “explode all trees” were chosen: • Case Control • Clinical Trial • Clinical Trials as Topic • Cohort Studies • Controlled Clinical Trial as Topic • Longitudinal Studies • Placebo effect • Randomized Controlled Trials • Randomized Controlled Trials as Topic Those that could not, “major concept” was chosen.⁷⁹ ALL the keywords that were searched in the MeSH 2014 will also be included in the list e.g. neuromuscular dis* for all the three searches. Lastly the searches will be combined in order to get the most applicable to this specific search. Various combinations will be used. Combinations: Search 1 and 2 will then be combined: condition(s) and intervention(s) by selecting the two searches and clicking on “search with AND”. Search 1 and 3 will then be combined: condition(s) and type of study/design by selecting the two searches and clicking on “search with AND”. Search 2 and 3 will then be combined:

⁷⁷ MeSH terms used are described at the end of the table

⁷⁸ MeSH terms used are described at the end of the table

⁷⁹ MeSH terms used are described at the end of the table

	Intervention(s) and type of study/design by selecting the two searches and clicking on "search with AND". Lastly search 1, 2 and 3 will be combined (condition(s), intervention(s) and type of study/design).
Summary of strategy	An advanced search will be done. Three lines are given initially. No specific field is selected. Search modes and expanders is set to Boolean/Phrase. All other dropdown options including sex, general queries, journal & citation subset, language, age, subject subset, publication type and animals are kept at <u>ALL</u> (in order to ensure that all possible options are included). Firstly the correct MeSH terms will be sourced and selected by making use of the specified keywords for condition(s), intervention(s) and type of study/design. Based on these terms a search will be done. Condition(s), intervention(s) and type of study/design will be searched separately and then they will be combined. Condition and intervention will be combined, then condition and type of study/design, thereafter intervention and type of study/design will be combined. Lastly all three will be combined (condition(s), intervention(s) and type of study/design will be combined for a more focused result.
Language restrictions	None

Conditions (MeSH terms chosen):

(MH "Neuromuscular Diseases+") OR (MH "Neuromuscular Junction Diseases+") OR (MH "Motor Neuron Disease+") OR "neuromuscular dis*" OR (MM "Muscular Dystrophy, Duchenne") OR (MM "Muscular Dystrophy, Facioscapulohumeral") OR (MM "Muscular Dystrophy, Emery-Dreifuss") OR (MM "Muscular Dystrophy, Oculopharyngeal") OR (MH "Muscular Dystrophies, Limb-Girdle+") OR (MM "Distal Myopathies") OR (MH "Muscular Dystrophies+") OR (MM "Sarcoglycanopathies") OR "muscular dystrophy" OR (MH "Muscular Atrophy, Spinal+") OR (MM "Spinal Muscular Atrophies of Childhood") OR (MM "Bulbo-Spinal Atrophy, X-Linked") OR (MH "Muscular Disorders, Atrophic+") OR (MM "Myopathy, Central Core") OR "central core disease" OR (MH "Myopathies, Structural, Congenital+") OR (MM "Myotonia Congenita") OR "congenital myopathy" OR (MM "Cardiomyopathy, Restrictive") OR (MH "Lung Diseases+") OR "restrictive lung disease" OR (MH "Respiratory Muscles+") OR (MM "Respiratory Paralysis") OR (MH "Respiratory System+") OR (MH "Muscles+") OR (MM "Muscle Hypotonia") OR "respiratory muscle condition" OR (MM "Muscle Weakness") OR "diaphragm* weakness"

Interventions (MeSH terms chosen):

"(MH "Breathing Exercises+") OR (MM "Resistance Training") OR (MH "Respiratory System+") OR (MM "Respiratory Paralysis") OR (MH "Respiratory Therapy+") OR (MM "Respiratory Rate") OR "respiratory musc* training" OR (MH "Muscle Strength+") OR "respiiratory musc* strength" OR (MH

"Respiratory Muscles+") OR (MH "Respiratory Mechanics+") OR "respiratory musc* endurance" OR (MH "Inspiratory Capacity+") OR (MM "Inspiratory Reserve Volume") OR "inspiratory musc* strength" OR "inspiratory musc* endurance" OR "IMT" OR "diaphragm* strength*"

Type of study/design (MeSH terms chosen):

"(MM "Random Allocation") OR (MH "Randomized Controlled Trials as Topic+") OR (MH "Randomized Controlled Trial+") OR "trial*" OR (MM "Cross-Over Studies") OR (MH "Clinical Trial+") OR "clinical trial" OR (MM "Pragmatic Clinical Trial") OR (MM "Controlled Clinical Trial") OR (MM "Clinical Trial, Phase IV") OR (MM "Clinical Trial, Phase III") OR (MM "Clinical Trial, Phase II") OR (MM "Clinical Trial, Phase I") OR (MH "Clinical Trials as Topic+") OR (MM "Pragmatic Clinical Trials as Topic") OR (MM "Meta-Analysis as Topic") OR (MH "Placebo Effect+") OR (MM "Placebos") OR (MH "Controlled Clinical Trials as Topic+") OR "placebo" OR (MM "Comparative Study") OR "comparative study" OR (MH "Case-Control Studies+") OR (MH "Cohort Studies+") OR (MM "Retrospective Studies") OR (MM "Prospective Studies") OR (MH "Longitudinal Studies+") OR (MM "Intervention Studies") OR (MM "Interdisciplinary Studies") OR "controlled trial" OR "CCT" OR "RCT" OR (MM "Double-Blind Method") OR (MM "Double Bind Interaction") OR "double blind*" OR (MM "Single-Blind Method") OR "single blind*" OR "cross-over"

Pan African Clinical trials registry (PACTR) search strategy

<http://www.pactr.org/>

The Pan African Clinical Trials Registry (PACTR) is a regional register of clinical trials conducted in Africa. The registry is an African initiative serving the needs of Africans. It provides an open-access platform where clinical trials can be registered free of charge. The PACTR is currently funded by the EDCTP and managed by the South African Cochrane Centre (SACC), an intra-mural research unit of the South African Medical Research Council (MRC).

Keywords were determined by investigating MeSH terms in literature and databases. The final keywords to be used are firstly conditions, then intervention and lastly type of study: neuromuscular diseases OR neuromuscular disorders OR NMD OR muscular dystrophy OR Duchenne* OR DMD OR spinal muscular atrophy OR central core disease OR congenital myopathy OR restrictive lung dis* OR respiratory muscle condition OR diaphragm* weakness combined with respirat* mus* training OR respirat* mus* strength* OR respiratory mus* endurance OR inspirat* mus* training OR inspirat* mus* strength* OR inspirit* mus* endurance OR IMT OR diaphragm* strength*. These keywords will then be combined with random* OR trial* OR clinical trial OR placebo OR comparative stud* OR controlled trial OR CCT OR RCT OR double-blind* OR single-blind*. The search strategy was adapted accordingly (refer to table below):

Date of search	
Years covered	Inception (?2012) to present
Complete strategy	First search (line for keywords): Conditions: neuromuscular diseases OR neuromuscular disorders OR NMD OR muscular dystrophy OR Duchenne* OR DMD OR spinal muscular atrophy OR central core disease OR congenital myopathy OR restrictive lung dis* OR respiratory muscle condition OR diaphragm* weakness Second search (line for keywords): Interventions: respirat* mus* training OR respirat* mus* strength* OR respiratory mus* endurance OR inspirat* mus* training OR inspirat* mus* strength* OR inspirit* mus* endurance OR IMT OR diaphragm* strength* Third search (line for “other conditions”): neuromuscular diseases OR neuromuscular disorders OR NMD OR muscular dystrophy OR Duchenne* OR DMD OR spinal muscular atrophy OR central core disease OR congenital myopathy OR restrictive lung dis* OR respiratory muscle condition OR diaphragm* weakness (As described by the database, as an alternative search the “OR” will be omitted from the “other condition” line and only a space will be kept between the different conditions. Combined with types of studies (line with keywords): random* OR trial* OR clinical trial OR placebo OR comparative stud* OR controlled trial OR CCT OR RCT OR double-blind* OR single-blind*.

Summary of strategy	Go to the home page of PACTR, click on search. A <u>basic</u> search will be done as an advanced search's required fields are very specific such as primary investigators, recruitment phase, trial dates (commence and end) and other very specific trial information. Under the basic search there are four condition options namely: HIV/AIDS, Tuberculosis, Malaria, and Other. "Other" will be chosen under diseases of interest. Firstly in the line for keywords the relevant keywords for conditions will be entered with "OR" in-between. Second search: in the line for keywords the relevant keywords for interventions will be entered with "OR" in-between. Thirdly under "other" the condition keywords will be added to the open line and in the keyword line "intervention keywords" will be entered. (The "OR" will also be removed in the "other condition" line and only a space will be kept between the conditions (as an alternative search). Thirdly under "others" the condition keywords are entered and then in the keyword line the relevant type of study will be entered. The type of study keywords will not otherwise be applied in this database.
Language restrictions	None

PEDro search strategy

Keywords were determined by investigating MeSH terms in literature and databases. The final keywords to be used are firstly conditions, then intervention and lastly type of study: neuromuscular diseases OR neuromuscular disorders OR NMD OR muscular dystrophy OR Duchenne* OR DMD OR spinal muscular atrophy OR central core disease OR congenital myopathy OR restrictive lung dis* OR respiratory muscle condition OR diaphragm* weakness OR diaphragm* strength* combined with respirat* mus* training AND respirat* mus* strength* OR respiratory mus* endurance OR inspirat* mus* training OR inspirat* mus* strength* OR inspirit* mus* endurance OR IMT. These keywords will then be combined with random* OR trial* OR clinical trial OR placebo OR comparative stud* OR controlled trial OR CCT OR RCT OR double-blind* OR single-blind*.

To note: On a simple search when all the options of type of disease/condition and intervention was combined no results were found. On the advanced search the search functions are limited to abstract & title, therapy, problem, body part, subdiscipline, topic and method (with drop-down boxes), therefore it is difficult to make use of the pre-set search strategy. The search strategy was adapted accordingly (refer to table below):

Date of search	
Years covered	1929 to present
Complete strategy	1. Neuromuscular diseases 2. Neuromuscular disorders 3. NMD 4. Muscular dystrophy 5. Duchenne 6. DMD 7. Spinal muscular atrophy 8. Central core disease 9. Congenital myopathy 10. Restrictive lung dis* 11. Respiratory muscle condition 12. Diaphragm* weakness 13. Diaphragm* strength All of the above conditions with "OR" 14. respirat* mus* training 15. respirat* mus* strength* 16. respiratory mus* endurance 17. inspirat* mus* training 18. inspirat* mus* strength* 19. inspirit* mus* endurance 20. IMT All of the above interventions with "OR", divided based on the categories (colours). All of the above individually combined with the "clinical trial" for the design component of the search.
Summary of strategy	The simple search strategy will be used at first. The disease/condition as well as the intervention search terms will be searched separately, with

	“OR” but keywords were limited to maximum of four (clustered together as indicated by the different colours) otherwise the search will be ineffective. For the trial design, the advanced search strategy will be followed. Each of the condition/intervention search terms will be individually combined (inserted in the “title and abstract” section) with method option: clinical trial. The returned citations will be manually combined to be specific to the review question.
Language restrictions	None

Pubmed search strategy

PubMed comprises more than 24 million citations for biomedical literature from MEDLINE, life science journals, and online books.

Keywords were determined by investigating MeSH terms in literature and databases. The final keywords to be used are firstly conditions, then intervention and lastly type of study: neuromuscular diseases OR neuromuscular disorders OR NMD OR muscular dystrophy OR Duchenne* OR DMD OR spinal muscular atrophy OR central core disease OR congenital myopathy OR restrictive lung dis* OR respiratory muscle condition OR diaphragm* weakness combined with respirat* musc* training AND respirat* musc* strength* OR respiratory musc* endurance OR inspirat* musc* training OR inspirat* musc* strength* OR inspirit* musc* endurance OR IMT OR diaphragm* strength*. These keywords will then be combined with random* OR trial* OR clinical trial OR placebo OR comparative stud* OR controlled trial OR CCT OR RCT OR double-blind* OR single-blind*.

The search strategy was adapted accordingly (refer to table below):

Date of search	
Years covered	Inception (?1946) to present
Complete strategy	First line: neuromuscular diseases OR neuromuscular disorders OR NMD OR muscular dystrophy OR Duchenne* OR DMD OR spinal muscular atrophy OR central core disease OR congenital myopathy OR restrictive lung dis* OR respiratory muscle condition OR diaphragm* weakness Combined with (AND) Second line: respirat* musc* training AND respirat* musc* strength* OR respiratory musc* endurance OR inspirat* musc* training OR inspirat* musc* strength* OR inspirit* musc* endurance OR IMT OR diaphragm* strength* First line: neuromuscular diseases OR neuromuscular disorders OR NMD OR muscular dystrophy OR Duchenne* OR DMD OR spinal muscular atrophy OR central core disease OR congenital myopathy OR restrictive lung dis* OR respiratory muscle condition OR diaphragm* weakness Combined with (AND) Second line: random* OR trial* OR clinical trial OR placebo OR comparative stud* OR controlled trial OR CCT OR RCT OR double-blind* OR single-blind*. First line: respirat* musc* training AND respirat* musc* strength* OR respiratory musc* endurance OR inspirat* musc* training OR inspirat* musc* strength* OR inspirit* musc* endurance OR IMT OR diaphragm* strength Combined with (AND) Second line: random* OR trial* OR clinical trial OR placebo OR comparative stud* OR controlled trial OR CCT OR RCT OR double-blind* OR single-blind*. Then all three will be combined namely condition, intervention and type of study/design:

	First line: neuromuscular diseases OR neuromuscular disorders OR NMD OR muscular dystrophy OR Duchenne* OR DMD OR spinal muscular atrophy OR central core disease OR congenital myopathy OR restrictive lung dis* OR respiratory muscle condition OR diaphragm* weakness Second line: respirat* musc* training AND respirat* musc* strength* OR respiratory musc* endurance OR inspirat* musc* training OR inspirat* musc* strength* OR inspirit* musc* endurance OR IMT OR diaphragm* strength Third line: random* OR trial* OR clinical trial OR placebo OR comparative stud* OR controlled trial OR CCT OR RCT OR double-blind* OR single-blind*.
Summary of strategy	An <u>advanced search</u> will be done. The “builder” option will be used, and all lines will be kept to “all fields”. Firstly the condition and intervention will be combined, then the condition and intervention will be combined with the type of study (individually). Lastly all three (condition, intervention and type of study) will be combined.
Language restrictions	None

Respiratory care journals online search strategy

<http://rc.rcjournal.com/>

National research registry is a register of unpublished research in progress in the National Institute for Health Research (NHS). It includes five databases: NRR database of research projects; MRC Clinical Trials Directory; Reviews in progress Health Research at York and Register of Registers and this database allows unrestricted access.

Keywords were determined by investigating MeSH terms in literature and databases. The final keywords to be used are firstly conditions, then intervention and lastly type of study: neuromuscular diseases OR neuromuscular disorders OR NMD OR muscular dystrophy OR Duchenne* OR DMD OR spinal muscular atrophy OR central core disease OR congenital myopathy OR restrictive lung dis* OR respiratory muscle condition OR diaphragm* weakness combined with respirat* mus* training OR respirat* mus* strength* OR respiratory mus* endurance OR inspirat* mus* training OR inspirat* mus* strength* OR inspirit* mus* endurance OR IMT OR diaphragm* strength*. These keywords will then be combined with random* OR trial* OR clinical trial OR placebo OR comparative stud* OR controlled trial OR CCT OR RCT OR double-blind* OR single-blind*.

To note: The search strategy was adapted accordingly (refer to table below):

Date of search	
Years covered	January 2003 to present
Complete strategy	<u>Search 1 (under text/abstract/title)</u> Conditions will be searched: neuromuscular diseases OR neuromuscular disorders OR NMD OR muscular dystrophy OR Duchenne* OR DMD OR spinal muscular atrophy OR central core disease OR congenital myopathy OR restrictive lung dis* OR respiratory muscle condition OR diaphragm* weakness <u>Search 2 (under text/abstract/title)</u> Interventions will be searched: respirat* mus* training OR respirat* mus* strength* OR respiratory mus* endurance OR inspirat* mus* training OR inspirat* mus* strength* OR inspirit* mus* endurance OR IMT OR diaphragm* strength* Article types: all sections will be chosen. (A separate/combined search with study design cannot be performed as article types only included original research, reviews, clinical practice guidelines and all sections).
Summary of strategy	An <u>advanced search</u> will be done. Under specify authors, keywords "Text/abstract/title" will be chosen and "any" will be chosen (compared to "all" and "phrase") after the keywords are entered. Article types will be kept to "all sections" and no date limitation is set. For conditions all the relevant search terms will be entered with "OR" in-between. Click on "submit" For the next search under text/abstract/title "interventions" will be searched and the relevant search terms/keywords with "OR" in-between will be entered. The type of study keywords will not be applied in this database, as study type is catered for, and "all sections" will be chosen.
Language restrictions	None

Sabinet search strategy

Based in South Africa, Sabinet has been a leader in facilitating access to electronic information for more than 30 years. Sabinet has been offering an aggregation service to the Southern African publishing community since 2001, and it has developed into the most comprehensive, searchable collection of full-text electronic African journals in the world (including reviews and studies), covering subjects such as business, education, humanities, science, medical and health sciences, law and theology. These more than 350 journals represent research carried out in Africa and the content is not restricted to information about Africa.

Keywords were determined by investigating MeSH terms in literature and databases. The final keywords to be used are firstly conditions, then intervention and lastly type of study: neuromuscular diseases OR neuromuscular disorders OR NMD OR muscular dystrophy OR Duchenne* OR DMD OR spinal muscular atrophy OR central core disease OR congenital myopathy OR restrictive lung dis* OR respiratory muscle condition OR diaphragm* weakness combined with respirat* mus* training AND respirat* mus* strength* OR respiratory mus* endurance OR inspirat* mus* training OR inspirat* mus* strength* OR inspirit* mus* endurance OR IMT OR diaphragm* strength*. These keywords will then be combined with random* OR trial* OR clinical trial OR placebo OR comparative stud* OR controlled trial OR CCT OR RCT OR double-blind* OR single-blind*.

The search strategy was adapted accordingly (refer to table below):

Date of search	
Years covered	ISAP (since 1987) SA e-publications (since 2001) Current & completed research (since 1950) SA theses (since 1918) SACat(since 1800)
Complete strategy	First line: neuromuscular diseases OR neuromuscular disorders OR NMD OR muscular dystrophy OR Duchenne* OR DMD OR spinal muscular atrophy OR central core disease OR congenital myopathy OR restrictive lung dis* OR respiratory muscle condition OR diaphragm* weakness Combined with (AND) Second line: respirat* mus* training AND respirat* mus* strength* OR respiratory mus* endurance OR inspirat* mus* training OR inspirat* mus* strength* OR inspirit* mus* endurance OR IMT OR diaphragm* strength* First line: neuromuscular diseases OR neuromuscular disorders OR NMD OR muscular dystrophy OR Duchenne* OR DMD OR spinal muscular atrophy OR central core disease OR congenital myopathy OR restrictive lung dis* OR respiratory muscle condition OR diaphragm* weakness Combined with (AND) Second line: random* OR trial* OR clinical trial OR placebo OR comparative stud* OR controlled trial OR CCT OR RCT OR double-blind* OR single-blind*.

	First line: respirat* mus* training AND respirat* mus* strength* OR respiratory mus* endurance OR inspirat* mus* training OR inspirat* mus* strength* OR inspirit* mus* endurance OR IMT OR diaphragm* strength Combined with (AND) Second line: random* OR trial* OR clinical trial OR placebo OR comparative stud* OR controlled trial OR CCT OR RCT OR double-blind* OR single-blind*. All three combinations cannot be combined on this database. The above will be searched with WorldCat, SACat and SANB respectively.
Summary of strategy	Via UCT website go to SACat via Sabinet reference: Then go to the Sabinet Home page (Sabinet reference platform). Click on searching “theses and dissertations”, choose ALL databases (African Digital Repository & Current and completed research) except (NDLTD). Then the following journals will be chosen: SA and African Electronic Journals (SA ePublications), African Journal Archive, Index to South African Periodicals (ISAP), African Digital Repository, ArchUP. Current and completed research will be chosen as option. Firstly WorldCat will be chosen as “library” and under news “SA Media”. Then “search form” will be clicked. The “keywords” function/search line will be used and not that of the title or author. All of the above combinations will be searched with “WorldCat”, “SACat” and “SANB” chosen as library respectively. Firstly, the condition will be combined with intervention, then condition and lastly intervention will be combined with study type/design (separately).
Language restrictions	None

South African National Clinical Trial Register (SANCTR) search strategy

<http://www.sanctr.gov.za/Homebrnbsp/tabid/135/Default.aspx>

The South African National Clinical Trials Register provides information on clinical trials on human participants being conducted in South Africa, namely information on a trial's purpose; who can participate, where the trial is located and contact details.

The South African National Clinical Trials Register forms part of international calls for making trial information publicly available. The International Committee of Medical Journal Editors, which includes peer reviewed journals from around the world, recently made a statement that from 1 July 2005 no trials will be considered for publication unless they are included on a research register. Keywords were determined by investigating MeSH terms in literature and databases. The final keywords to be used are firstly conditions, then intervention and lastly type of study: neuromuscular diseases OR neuromuscular disorders OR NMD OR muscular dystrophy OR Duchenne* OR DMD OR spinal muscular atrophy OR central core disease OR congenital myopathy OR restrictive lung dis* OR respiratory muscle condition OR diaphragm* weakness combined with respirat* mus* training OR respirat* mus* strength* OR respiratory mus* endurance OR inspirat* mus* training OR inspirat* mus* strength* OR inspirit* mus* endurance OR IMT OR diaphragm* strength*. These keywords will then be combined with random* OR trial* OR clinical trial OR placebo OR comparative stud* OR controlled trial OR CCT OR RCT OR double-blind* OR single-blind*.

To note, the search strategy was adapted accordingly (refer to table below):

Date of search	
Years covered	Inception (?2005) to present
Complete strategy	For this database trials are categorised based on the condition/type of disease. Therefore the keywords and strategies used in previous databases will not apply to SANCTR. On the home page of SANCTR click on "SA clinical trial data listed by disease". Searches will be done under: "Muscle, bone and cartilage diseases", "Rare diseases" and "Respiratory tract". Under "Muscle, bone and cartilage diseases" the following will be chosen: • Musculoskeletal abnormalities • Other Under "Rare diseases" the following will be chosen: • Other Under "Respiratory Tract" the following will be chosen: • Other Under "Nervous system diseases" no applicable subheading could be found, therefore it will be omitted in the search strategy. Under these subcategories applicable titles will be sought. There are no "keywords, abstract and title" search functions on this website, therefore

	the search strategy followed for most other databases will not be applied here.
Summary of strategy	The search will be done by clicking on the headings and subheadings that could be applicable to neuromuscular diseases and inspiratory muscle training namely: "Muscle, bone and cartilage diseases", "Rare diseases" and "Respiratory tract" as well as "musculoskeletal abnormalities" and "Other"
Language restrictions	None

Science Direct search strategy

Science Direct is a leading full-text scientific database offering journal articles and book chapters from nearly 2,500 journals and 26,000 books.

Keywords were determined by investigating MeSH terms in literature and databases. The final keywords to be used are firstly conditions, then intervention and lastly type of study: neuromuscular diseases OR neuromuscular disorders OR NMD OR muscular dystrophy OR Duchenne* OR DMD OR spinal muscular atrophy OR central core disease OR congenital myopathy OR restrictive lung dis* OR respiratory muscle condition OR diaphragm* weakness combined with respirat* mus* training OR respirat* mus* strength* OR respiratory mus* endurance OR inspirat* mus* training OR inspirat* mus* strength* OR inspirit* mus* endurance OR IMT OR diaphragm* strength*. These keywords will then be combined with random* OR trial* OR clinical trial OR placebo OR comparative stud* OR controlled trial OR CCT OR RCT OR double-blind* OR single-blind*.

To note: The search strategy was adapted accordingly (refer to table below):

Date of search	
Years covered	1823 to present
Complete strategy	First search: Conditions: neuromuscular diseases OR neuromuscular disorders OR NMD OR muscular dystrophy OR Duchenne* OR DMD OR spinal muscular atrophy OR central core disease OR congenital myopathy OR restrictive lung dis* OR respiratory muscle condition OR diaphragm* weakness Combined with (AND): Interventions: respirat* mus* training AND respirat* mus* strength* OR respiratory mus* endurance OR inspirat* mus* training OR inspirat* mus* strength* OR inspirit* mus* endurance OR IMT OR diaphragm* strength* Second search: Conditions: neuromuscular diseases OR neuromuscular disorders OR NMD OR muscular dystrophy OR Duchenne* OR DMD OR spinal muscular atrophy OR central core disease OR congenital myopathy OR restrictive lung dis* OR respiratory muscle condition OR diaphragm* weakness Combined with (AND): Type of study/design: random* OR trial* OR clinical trial OR placebo OR comparative stud* OR controlled trial OR CCT OR RCT OR double-blind* OR single-blind*. Third search: Interventions: respirat* mus* training OR respirat* mus* strength* OR respiratory mus* endurance OR inspirat* mus* training OR inspirat* mus* strength* OR inspirit* mus* endurance OR IMT OR diaphragm* strength

	Combined with (AND): Type of study/design: random* OR trial* OR clinical trial OR placebo OR comparative stud* OR controlled trial OR CCT OR RCT OR double-blind* OR single-blind*.
Summary of strategy	An <u>advanced search</u> will be done. All sources will be searched and keywords will be searched in ALL fields also. Journals and "ALL" will be ticked. Dates will be kept at "all years" and field/Science will be kept on "All Sciences". Operators "OR" are used between keywords (in order to ensure that all possible options are included). Firstly condition(s) will be combined with intervention(s) and then with types of study/design. Lastly intervention(s) will be combined with types of study/design.
Language restrictions	None

Scopus search strategy

Scopus is the largest abstract and citation database of peer-reviewed literature: scientific journals, books and conference proceedings. Delivering a comprehensive overview of the world's research output in the fields of science, technology, medicine, social sciences, and arts and humanities. Scopus includes 53million records from 5000 publishers and covers 21 915 titles.

Keywords were determined by investigating MeSH terms in literature and databases. The final keywords to be used are firstly conditions, then intervention and lastly type of study: neuromuscular diseases OR neuromuscular disorders OR NMD OR muscular dystrophy OR Duchenne* OR DMD OR spinal muscular atrophy OR central core disease OR congenital myopathy OR restrictive lung dis* OR respiratory muscle condition OR diaphragm* weakness combined with respirat* mus* training AND respirat* mus* strength* OR respiratory mus* endurance OR inspirat* mus* training OR inspirat* mus* strength* OR inspirit* mus* endurance OR IMT OR diaphragm* strength*. These keywords will then be combined with random* OR trial* OR clinical trial OR placebo OR comparative stud* OR controlled trial OR CCT OR RCT OR double-blind* OR single-blind*.

To note: The search strategy was adapted accordingly (refer to table below):

Date of search	
Years covered	1966 to present
Complete strategy	First search: ALL neuromuscular diseases OR neuromuscular disorders OR NMD OR muscular dystrophy OR Duchenne* OR DMD OR spinal muscular atrophy OR central core disease OR congenital myopathy OR restrictive lung dis* OR respiratory muscle condition OR diaphragm* weakness Second search: ALL respirat* mus* training AND respirat* mus* strength* OR respiratory mus* endurance OR inspirat* mus* training OR inspirat* mus* strength* OR inspirit* mus* endurance OR IMT OR diaphragm* strength* Third search: ALL neuromuscular diseases OR neuromuscular disorders OR NMD OR muscular dystrophy OR Duchenne* OR DMD OR spinal muscular atrophy OR central core disease OR congenital myopathy OR restrictive lung dis* OR respiratory muscle condition OR diaphragm* weakness AND ALL random* OR trial* OR clinical trial OR placebo OR comparative stud* OR controlled trial OR CCT OR RCT OR double-blind* OR single-blind*. Fourth search: ALL respirat* mus* training AND respirat* mus* strength* OR respiratory mus* endurance OR inspirat* mus* training OR inspirat* mus* strength* OR inspirit* mus* endurance OR IMT OR diaphragm* strength AND ALL random* OR trial* OR clinical trial OR placebo OR comparative stud* OR controlled trial OR CCT OR RCT OR double-blind* OR single-blind*. Then lastly all three will be combined namely condition, intervention and type of study/design:

	Fifth search: ALL neuromuscular diseases OR neuromuscular disorders OR NMD OR muscular dystrophy OR Duchenne* OR DMD OR spinal muscular atrophy OR central core disease OR congenital myopathy OR restrictive lung dis* OR respiratory muscle condition OR diaphragm* weakness AND ALL respirat* mus* training AND respirat* mus* strength* OR respiratory mus* endurance OR inspirat* mus* training OR inspirat* mus* strength* OR inspirit* mus* endurance OR IMT OR diaphragm* strength AND ALL random* OR trial* OR clinical trial OR placebo OR comparative stud* OR controlled trial OR CCT OR RCT OR double-blind* OR single-blind*.
Summary of strategy	An <u>advanced search</u> will be done. Operators “OR” are already included, Code <u>ALL</u> is put prior to the list of conditions, interventions and types of studies (in order to ensure that all possible options are included). Firstly condition(s) will be searched then interventions and then types of studies will be combined with the abovementioned. Lastly condition, intervention and type of study will be combined.
Language restrictions	None

WHO International Clinical Trials Registry Platform search strategy

<http://apps.who.int/trialsearch/> (Through ICTRP search portal)

The mission of the WHO International Clinical Trials Registry Platform is to ensure that a complete view of research is accessible to all those involved in health care decision making. This will improve research transparency and will ultimately strengthen the validity and value of the scientific evidence base. Keywords were determined by investigating MeSH terms in literature and databases. The final keywords to be used are firstly conditions, then intervention and lastly type of study: neuromuscular diseases OR neuromuscular disorders OR NMD OR muscular dystrophy OR Duchenne* OR DMD OR spinal muscular atrophy OR central core disease OR congenital myopathy OR restrictive lung dis* OR respiratory muscle condition OR diaphragm* weakness combined with respirat* mus* training OR respirat* mus* strength* OR respiratory mus* endurance OR inspirat* mus* training OR inspirat* mus* strength* OR inspirit* mus* endurance OR IMT OR diaphragm* strength*. These keywords will then be combined with random* OR trial* OR clinical trial OR placebo OR comparative stud* OR controlled trial OR CCT OR RCT OR double-blind* OR single-blind*.

To note: The search strategy was adapted accordingly (refer to table below):

Date of search	
Years covered	Inception (?2004/2005) to present
Complete strategy	Title line: left open Conditions line: neuromuscular diseases OR neuromuscular disorders OR NMD OR muscular dystrophy OR Duchenne* OR DMD OR spinal muscular atrophy OR central core disease OR congenital myopathy OR restrictive lung dis* OR respiratory muscle condition OR diaphragm* weakness Combined with (AND): Interventions line: respirat* mus* training AND respirat* mus* strength* OR respiratory mus* endurance OR inspirat* mus* training OR inspirat* mus* strength* OR inspirit* mus* endurance OR IMT OR diaphragm* strength* Study type: no specification of study type is given in the advanced search option, therefore type of study design keywords will not be used in this database.
Summary of strategy	An <u>advanced search</u> will be done. The title line will be left open. Under conditions all the relevant Keywords will be entered, separated by "OR". This will be combined with adding all the relevant keywords for intervention to the line dedicated for that, keywords being separated by

	"OR". No other limitations on year or country will be added. Under recruitment status ALL will be chosen. Clinical trials in children will also be searched with the same combinations as used above.
Language restrictions	None (The database is mainly in English)

Appendix Bii: Data extraction form

Data extraction form (IMT)

STUDY ID _____

REVIEWER ID _____

Authors: _____

Title: _____

Method	YES / NO
Randomisation and allocation concealment	
<i>Adequate</i>	
Central randomisation by telephone; randomisation schemes controlled by third party; allocations in locked, unreadable file; and in sequentially numbered, opaque sealed envelopes.	
<i>Inadequate</i>	
Any allocation procedure transparent before assignment (e.g. open list of random numbers, alternation, date of birth, case record number)	
<i>Unclear</i>	
Sealed envelopes but not sequentially numbered or opaque; a trial in which the description suggests concealment but other features are suspicious (i.e. noticeably unequal control and trial groups, randomisation stated but no details available)	
<i>Not reported</i>	

Blinding	YES	NO
Patient		
Clinician		
Evaluator		

Description of trial
<i>Primary outcome measures</i>
<i>Secondary outcome measures</i>
<i>Adverse events reported</i>

INTERVENTION and comparison

IMT for	Tick applicable
Acute use (hospital/clinic)	
Chronic use (home/school)	
Compared to	
Placebo/sham	
Control	
No treatment	
Other	

	n	%
Number of patients		
Number randomised (if applicable)		
Number of patients completing treatment		
Number available for follow-up		

	Intervention 1	Intervention 2	Intervention 3	Intervention 4	Total
Total number					
Male					
Female					
Age range					
Diagnoses & clinical picture					
Dx test(s)					
Stage of disease/severity/fx level					
Comorbid conditions					

	Intervention 1	Intervention 2	Intervention 3	Intervention 4
Description				
Ventilated/Non-ventilated				
Flow/Resistance/Threshold (device: make and model)				
Intensity/Parameters used (cmH ₂ O)				
Duration of IMT (minutes)				
Duration of IMT (weeks/months)				
Frequency of IMT				
Rest periods during IMT				
Delivered by healthcare professionals/patient/caregiver				
Interface (trachea/face mask/mouthpiece, ETT)				
Duration of follow-up				
Other (specify)				

OUTCOMES

Outcomes measure (primary/secondary)	Total sample	Data presentation (M, MDN, SD, 95% CI etc.)	Intervention 1	Intervention 2	Intervention 3	Intervention 4	n (%) not reported

Risk of bias

Grade	Selection bias	Performance bias	Detection	Attrition	Others
Low risk					
High risk					
Unclear					

Appendix Biii: Excluded studies

The following studies (n=25) were excluded from the IMT systematic review based on full-text.

Authors, date	Title	Reason(s) for exclusion
Aldrich, Karpel, Uhrlass, Sparapani, Eramo & Ferranti (1989)	Weaning from mechanical ventilation: adjunctive use of inspiratory muscle adjunctive training.	Observational study, no control/comparison group (Methodology)
Angelini , Comi, Comola, Guastella, Intino & Lanzi (1985)	Clinical trials in Duchenne dystrophy.	Abstract and no respiratory muscle training/IMT was included (Methodology)
Angelini, Baron & Bej ato (1986)	Italian multicenter trials in Duchenne dystrophy	No IMT (natural history and diet of patients) (Condition)
Budweiser, Moertl, Jorres, Windisch, Heinemann & Pfeifer (2006)	Respiratory muscle training in restrictive thoracic disease: a randomized controlled trial	No NMDs included; adult population (> 18 years) (Condition and age range)
Bustamante, Galdiz, Ruiz, Cabriada, Serrano & Sobradillo (1997)	Benefits evolution of inspiratory muscle training after 6 months discontinuation [abstract]	Conference abstract: not specific NMDs and no age range given. (Condition and age range)
Condessa, Brauner, Saul, Baptista, Silva & Vieira (2013)	Inspiratory muscle training did not accelerate weaning from mechanical ventilation but did improve tidal volume and maximal respiratory pressures: a randomised trial.	No NMDs included; adult population (> 18 years) (Condition and age range)
DiMarco, Kelling, DiMarco, Jacobs, Shields & Altose (1985)	The effects of inspiratory resistive training on respiratory muscle function in patients with muscular dystrophy.	Observational study, no control/comparison group (Methodology)
Gething, Davies & Williams (2002)	Decreased ventilation and perceived respiratory exertion after inspiratory muscle training	Abstract: Healthy subjects included (no NMDs) (Participants)
Gigliotti, Pizzi, Duranti, Gorini, Iandelli & Scano (1995)	Control of breathing in patients with limb girdle dystrophy: a controlled study.	Adult population (20-74 years of age) (Age range)
Hoberty, Hastwell, Rittinger, Clanton & Diaz (2001)	Inspiratory muscle training and the outcomes of pulmonary rehabilitation	Abstract: COPD patients using IMT (Participants)
Houser & Johnson (1971)	Breathing exercises for children with Pseudohypertrophic Muscular Dystrophy	This study evaluated breathing exercises by making use of a positive pressure device (Bennett IPPB), this was not IMT. (Intervention)
Kagaya, Takahashi, Sugawara, Kasai, Kiyokawa & Shioya (2009)	Effective home-based pulmonary rehabilitation in patients with restrictive lung diseases.	No NMDs included; adult population (> 18 years) (Condition and age range)
Koessler, Wanke, Winkler, Nader, Toifl, Kurz & Zwick (2001)	2 Years' Experience With Inspiratory Muscle Training in Patients With Neuromuscular Disorders	Observational study, no control/comparison group (methodology), patients were

		allocated to groups based on their VC results (Methodology).
Martin, Davenport, Gonzalez-Rothi , Baz , Banner, Caruso, Layon & Gabrielli (2006)	Inspiratory muscle strength training improves outcome in failure to wean patients	This was only an abstract (no full text). The data was published as a full article in 2011; however the age range of this study was > 18 years (Publication and age range)
Merkle , Wanke, Formanek, Lahrmann, Toifl & Zwick (1993)	Inspiratory muscle training in patients with neuromuscular disease [abstract]	This abstract/conference presentation was published as an article (Wanke et al. 1994: previously included)
Ohkura , Kai, Kawagoshi, Sugawara, Takahashi & Satake (2013)	The effectiveness of new inspiratory muscle training [Abstract]	Poster: healthy subjects included (Participants)
Pinto, Swash & deCarvalho (2012)	Respiratory exercise in amyotrophic lateral sclerosis.	Although early onset ALS, age range was 18-75 years (Age range)
Rous, Lobato, Trigo, Vélez, Miguel, Cejudo, Ruiz, Muñoz, Galdiz Iturri, García, & Servera (2014)	Pulmonary rehabilitation	Guideline based on systematic reviews and meta-analyses (no intervention/experimental study)(Methodology)
Smith, Coakley & Edwards (1988)	Respiratory muscle training in Duchenne muscular dystrophy.	Not a full-text article but a letter to the editor (Methodology).
Takaso, Nakazawa, Imura Fukushima, Saito, Shintani, Miyajima, Itoman, Takahashi, Yamazaki, Ohtori, Oka & Sasaki (2010)	Preoperative inspiratory muscle training for patients with severe scoliosis and high-risk pulmonary dysfunction in duchenne muscular dystrophy	Observational study, no control/comparison group (Methodology).
Ungar, Gössler, Toifl & Wanke (1996)	Innovatives atemmuskeltraining für patienten mit Duchenne-muskeldystrophie eine psychische bewertung(German)	A psychological evaluation (patient's perspective on using IMT), not experimental (Methodology)
Vilozni, Bar-Yishay, Gur, Shapira, Meyer & Godfrey (1994)	Computerized respiratory muscle training in children with Duchenne Muscular Dystrophy.	Observational study, no control/comparison group (Methodology.)
Wild, Wanke, Lahrmann, Merkle, Toifl & Zwick (1995)	Training of the respiratory musculature in muscle dystrophy Duchenne	Abstract (complete data could not be obtained, no full-text article found) (Methodology).
Winkler, Zifko, Nader, Frank, Zwick, Toifl & Wanke (2000)	Dose-dependent effects of inspiratory muscle training in neuromuscular disorders	Observational study, no control/comparison group (Methodology).
Zupan , Praznikar & Sardoc (2002)	Inspiratory versus expiratory muscle training in children with neuromuscular diseases	Abstract (contacted authors for more information, no response)(complete data could therefore not be obtained, no full-text article found) (Methodology)

Appendix Ci: Types of neuromuscular disease included in the study and confirmation of diagnosis

- Muscular dystrophies such as Duchenne (DMD), Becker (BMD), Emery-Dreifuss (EDMD), Limb-girdle (LGMD) (DiMarco et al., 1985), congenital myotonic muscular dystrophy (MMD), distal muscular dystrophy (DD), facio-scapulohumeral (FSHD) and congenital muscular dystrophy (CMD) (Boyer et al., 2006; Gozal, 2000; Ho et al., 2015; Jensen et al., 2005).
- Motor neuron diseases including spinal muscular atrophies (SMA I, SMA II, SMA III) (Boyer et al., 2006; Gozal, 2000; Jensen et al., 2005).
- Congenital and metabolic myopathies such as Central core disease (CCD), Minicore disease, Centronuclear myopathy and Nemaline rod myopathy (Gozal, 2000).

Diagnoses of NMD was confirmed with the following standardised tests (Bushby et al., 2005; Guglieri & Bushby, 2011; Bendixen et al., 2012):

- Blood tests (serum creatine kinase (CK)): > 1000IU/L and up to 30 000 IU/L is an indication of DMD; CK levels of <200 IU/L exclude DMD.
- Electromyography: EMG findings consistent with myopathy.
- Muscle biopsy: (absence of dystrophin). Skeletal muscle biopsy and immunohistochemical staining⁸⁰
- Molecular genetic testing/DNA analysis: This should be mandatory even with absence of dystrophin on muscle biopsy. Genetic confirmation of NMD can be done demonstrating absence, reduced dystrophin or abnormal dystrophin or sarcoglycan on immunohistochemical and/or immunobiochemical analysis (Grootenhuys et al., 2007)
- Imaging studies

⁸⁰ EMG and biopsy confirmation was not required if a brother had a biopsy proven DMD

Appendix Cii: Research personnel and colleagues involved in the inspiratory muscle training study

Name	Involvement	Institution
Brenda Morrow (BM)	Supervisor Assist with systematic review, data collection instruments, data analysis, correction of chapters/manuscripts	RCWMCH
Jennifer Jelsma	Co-supervisor (recently retired)	UCT
Lieselotte Corten (LC)	Co-investigator (recruitment and assessment) Assisted with systematic review, data collection instruments, input (chapters, manuscripts)	RCWMCH
Eleonora Lozano (EL)	Co-investigator (recruitment and assessment)	RCWMCH
Prof. Jo Wilmshurst (JW)	Co-investigator (Paediatric neurologist: NMD clinics and hospital admissions)	RCWMCH
Clinicians/physiotherapists	Referrals/recruitment; assistance with IMT programme development	RCWMH & DGMAH
Specialists (Neurologists, pulmonologists, paediatricians) and medical doctors	Referral of patients. monitoring of patients.	RCWMH & DGMAH
Rencia Gillespie	Opaque randomised envelopes	RCWMCH
Sannie Manale	Opaque randomised envelopes	DGMAH
Anri Human (AH)	Primary researcher (Recruitment and Assessment)	DGMAH (Gauteng)
Representative of Powerbreathe [®] (in SA)	Advisory capacity, referral of eligible patients	Powerbreathe representative (Gauteng)
Frida Kotsokoane (Physiotherapist) Greg Lebona (Medical doctor)	Monitoring patient safety, evaluating clinical picture if there should be a concern, assess interim analysis, and decide if patient should continue or should be withdrawn from the study.	Safety committee: DGMAH
Sameer Rahim (Physiotherapist) Liesel Andrag (Paediatrician)		Safety committee: RCWMCH

**Appendix Ciii: Information leaflets to be distributed at the NMD clinics
(IMT cross-over study)**

Leaflet was created in “publisher”

*“To know even one life has
breathed easier because you have
lived.
This is to have succeeded.”*
Ralph Waldo Emerson



**“Breathing exercises (inspiratory
muscle training) for children
with neuromuscular diseases.”**



Information leaflet for NMD clinics
IMT intervention



Dear patient and parents,

This information leaflet is to inform you
about research that is currently taking
place at Red Cross War Memorial
Children’s Hospital (RCWMCH) in Cape
Town and Dr. George Mukhari Academic
Hospital (DGMHAH) in Pretoria.



Who are we?

My name is Anri Human and I am a physiotherapist studying at the University of Cape Town. I am doing research in children with diseases that affect their muscles and this information leaflet has been given to you because your child has a condition which makes them eligible to be part of this study. Various members of the medical team are involved in this study such as neurologists, pulmonologists, paediatricians, physiotherapists and nurses. At RCWMCH the data will be collected by Lieselotte Corten and the physiotherapists. At DGMMAH the data will be collected by Anri Human and the physiotherapists.

Who can take part?

All children with a diagnosed NMD, between the ages of 5 and 18 years old, can be included. The physiotherapists will determine if you can be included, and if so, they will ask you and your parents' permission first. Children with weak breathing muscles will be included. Participation in this study is voluntary and you do not have to agree to be part of this study.

Who can I ask?

You can ask any questions to the physiotherapist that is helping you (Lieselotte, Anri or any of the other) or you can ask your mommy/daddy to phone us if you would like us to explain anything: Lieselotte Corten (071 588 3729), Anri Human (074 362 4055/(012) 521-4047) or A/Prof Brenda Morrow ((021) 658-5074).

Why are we doing this research?

This study aims to determine the effect of breathing muscle (inspiratory muscles) strengthening amongst children and adolescents with NMDs. This involves using a special device (Powerbreathe) to train the breathing muscles for three months. We want to determine if training the inspiratory muscles can assist patients in breathing easier and staying healthy for longer. Patients attending the neurology clinic as out-patients at both RCWMCH in Cape Town as well as DGMMAH in Pretoria will be asked to participate. This study has been approved by the University of Cape Town's Faculty of Health Sciences' Human Research Ethics Committee (HREC) (513/2015).

What is in it for you?

If you say "yes" to be part of this study you will not receive anything extra. We will give mommy/daddy/your caregiver some money to bring you to the hospital every two weeks/every month. We hope that by helping you to strengthen your breathing muscles you will feel better, breathe easier and stay healthier for longer. What we learn from this study can be used for other children with the same condition as you also.

What will happen?

Every child that comes to the NMD clinic will be screened for eligibility for this study. You will still receive your physiotherapy home exercises and advice as always. This study will look at adding the exercise to strengthen your breathing muscles. If you say "yes" to take part in this study, the group you are in will be decided by chance, like the chance of getting "heads" when you flip a coin. Group 1 will start training with the machine (Powerbreathe device) every day for three months. You will come and visit the physiotherapist at the hospital/clinic every two weeks whilst you are training with the device so that we can see how you are doing and do a few lung tests. This will be done for three months, after that we will still ask you to visit the hospital/clinic once a month for another three months to see if the changes of exercising are maintained. If you are in Group 2, you will come and visit the physiotherapist at the hospital every month, for three months, before you can start training with the Powerbreathe device. The rest will be as for Group 1. You will only be part of this study for either 6 months or a maximum of 9 months (depending if you are in Group 1 or 2), after that you will not be in the study anymore. When you have to start with the breathing exercise programme your physiotherapist will explain to you and your mommy/daddy/caregiver how the device works. You will get a programme of exercises that you will have to do every day. Mommy/daddy/your caregiver will help you train and write down how much you have exercised every day and how tired you felt. If you get tired when exercising you can take a rest. After three months of training when you return to the clinic, you will bring the device back and give it to the physiotherapist. If you are included in the research, you and your parents will receive a more detailed information leaflet (available in English, Afrikaans, Tswana and Xhosa).

[FINAL IMT pamphlet for NMD clinics.pub](#)

Appendix Civ: Inspiratory muscle training data collection sheet

THE EFFECT OF IMT ON CLINICAL OUTCOMES IN PAEDIATRIC AND ADOLESCENT PATIENTS WITH NMD [SECTION A: BASELINE]

Hospital: RCWMCH (✖) ☐	DGMAH (✖) ☐
Clinician's name: _____	Date: _____
Patient file number: _____	Coding (administrative purposes): _____
Included in MI-E study? (✖) Y ☐	N ☐
Flu shot received? (✖) Y ☐	N ☐

Patient file information

Date of birth

.....

Date of recruitment

.....

Age at recruitment

.....

Gender (Sex)

Male ☐

Female ☐

Mobility

Ambulatory ☐

Non-ambulatory ☐

Brooke scale:.....Vignos scale:.....

Weight (kg)

.....

Waist circumference (cm)

.....

Height (cm)

Stadiometer:

Length ulna:

BMI (kg/m²)

.....

Diagnosis

.....

Suspected ☐

Confirmed ☐

Tests:

- Blood tests

Specify (e.g. CK, IU/L)

Date 1:

.....

Date 2:	
Date 3:	

Biopsy mm

Date:

Genetic testing	Results:
Date:	

- Co-morbidities Reflux ☐ Seizures ☐ Cardiac ☐ Other ☐

Specify:

Surgery	Yes ☐ No ☐
Date 1:	Procedure:
Date 2:	Procedure:

Home ventilation (day) Yes ☐ No ☐

Device

Frequency

Home ventilation (night)	Yes ☐ No ☐
Device	
Frequency	

Chronic Medication (e.g. Captopril)⁸¹:

- Name:	- Dosage:
- Name:	- Dosage:
- Name:	- Dosage:
- Name:	- Dosage:

Any acute medication at the moment?	- Dosage:
Name:	- Dosage:

Baseline home programme:	Frequency:
Technique	
- ROM	

⁸¹ Please note that if a patient presents with clinical cardiac failure (as confirmed by the cardiologist) or are taking inotropes to support their cardiac function they have to be excluded from IMT. ACE inhibitors given prophylactically for cardiac protection is not an exclusion.

-
- **Strengthening/endurance**
 - **Stretches**
 - **CPT:**
 -
 - **MI-E**
 - **Breath-stacking:**
- Independent ☐ Assisted ☐

Others:

Deformities (spine)	Description	Cobb angle
Date:		
Chest X-ray findings (if available):		

Recruitment/baseline assessment

Lung function tests recruitment	Results:
- Peak expiratory cough flow (PECF)	l/min
- Vital capacity (VC)	l
- Forced vital capacity (FVC)	l
- Forced expiratory volume in one second (FEV₁)	l/min

Inspiratory mm testing:

	Pimax/MIP	SNIP (cmH ₂ O)
- Baseline		
- 1st month (pre-training) control group		
- 2nd month (pre-training) control group		
- 3rd month (pre-training) control group		
Mobility assessment		

Upper limb function (Brooke scale) ⁸²		
Grade	Description	Patient ability
1	Starting with arms at the sides, the patient can abduct the arms in a full circle. until they touch above the head	
2	Can raise arms above head only by flexing the elbow (shortening the circumference of the movement) or using accessory muscles.	
3	Cannot raise hands above head, but can raise an 8-oz glass of water to the mouth.	
4	Can raise hands to the mouth, but cannot raise an 8-oz glass of water to the mouth.	
5	Cannot raise hands to the mouth, but can use hands to hold a pen or pick up pennies from the table.	
6	Cannot raise hands to the mouth and has no useful function of hands.	
Lower limb function (Vignos scale) ⁸³		
Grade	Description	Patient ability
1	Walks and climbs stairs without assistance.	
2	Walks and climbs stair with aid of railing.	
3	Walks and climbs stairs slowly with aid of railing.	
4	Walks unassisted and rises from chair but cannot climb stairs.	
5	Walks unassisted but cannot rise from chair or climb stairs.	
6	Walks only with assistance or walks independently with long leg braces.	
7	Walks in long leg braces but requires assistance for balance.	
8	Stands in long leg braces but unable to walk even with assistance.	
9	Is in a wheelchair.	
10	Is confined to a bed.	

Any other relevant information

⁸² (Lu & Lue n.d.)

⁸³ (Lu & Lue n.d.)

FOLLOW-UP ASSESSMENT (EITHER 2 OR 4 WEEKS DURING IMT; 3 MONTHLY POST-IMT)
[SECTION B]

Please note any changes in medication with every follow-up:

Change to medication

Date:	Chron/Acute:	Name:	Dosage:
.....			
.....			
.....			
.....			
.....			

Current IMT training programme (please revise/adapt with each visit as needed)

IMT training programme:

Week	BORG/OMNI average over past 2 weeks	Intensity (cmH ₂ O)	Repetitions	Sets	Rest-interval
- Baseline	N/A				
- Week 2					
- Week 4					
- Week 6					
- Week 8					
- Week 10					
- Week 12					

Inspiratory mm testing: Pimax/MIP¹ ☐ SNIP² ☐ (3 best values)

Visit	Pimax/MIP (cmH ₂ O) ⁸⁴	SNIP(cmH ₂ O) ⁸⁵
1 st month pre-training (control group)		
2 nd month pre-training (control group)		
3 rd month pre-training (control group)		
Week 2 (experimental group)		
Week 4 (experimental group)		
Week 6 (experimental group)		
Week 8 (experimental group)		
Week 10 (experimental group)		
Week 12 (experimental group)		
1 month F/U		
2 months F/U		
3 months F/U (end)		

CXR (if available) at baseline⁸⁶:

CXR (if available) after 3 months of IMT:

CXR (if available) after 3 months of follow-up:

HRQoL (attach completed PedsQL questionnaire):

PedsQL (child) ☐

PedsQL (proxy) ☐

After 3 months of follow-up:

PedsQL (child) ☐

PedsQL (proxy) ☐

⁸⁴ From RV

⁸⁵ From FRC

⁸⁶ Lung volume, infiltrates, atelectasis, scoliosis, other abnormalities

	Hospitalisations? (Indicate dates)	Antibiotic usage? (Indicate dates)	Adverse events? If yes, indicate date and type ¹ :
1.			
2.			
3.			
4.			
5.			
6.			
7.			
8.			
9.			
10.			

Adverse events: If yes, please specify:

Mild/moderate: Nausea/vomiting; Pain/discomfort; Gastric distension

Severe: Bradycardia; Desaturation; Barotrauma/pneumothorax

Other (please specify):

After 3 months of IMT

Lung function tests admission

- Peak expiratory cough flow (PECF)
- Vital capacity (VC)
- Forced vital capacity (FVC)
- Forced expiratory volume in one second
(FEV₁)
- Peak expiratory flow (PEF)

Results:

.....l/min

.....l

.....l

.....l

.....l/min

Mobility/function:

Brooke scale:

Vignos scale:

MFM:

Satisfaction with IMT (after 3 months of training):

Please rate your satisfaction with the use of IMT on a scale of 0-10

0 1 2 3 4 5 6 7 8 9 10



("Not satisfied at all" to "Extremely satisfied")

After 3 months of follow-up (No IMT/monitoring period)

Lung function tests admission

Results:

- Peak expiratory cough flow (PECF) l/min
- Vital capacity (VC)
- Forced vital capacity (FVC)
- Forced expiratory volume in one second (FEV₁)
- Peak expiratory flow (PEF) l/min

Mobility/function:

MFM:

Brooke scale:

Vignos scale:

<u>Patient</u> preference of IMT (*)	
If given the opportunity to choose, would you like to continue with IMT?	Yes ☐ No ☐
Please motivate your answer:	
<u>Parental</u> preference of IMT (*)	
If given the opportunity to choose, what would you prefer your child to use?	Yes ☐ No ☐
Please motivate your answer:	

Appendix Cv: PedsQL (self/child-reported)

Health-related quality of life was measured by making use of the age-appropriate child and proxy version of PedsQL (5-7 years; 8-12 years; 13-18 years). These forms were available in English, Afrikaans and translated into isiXhosa and Setswana.

ID#	_____
Date:	_____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0 - English (South Africa)

YOUNG CHILD REPORT (ages 5-7)

Instructions for interviewer:

I am going to ask you some questions about things that might be a problem for some children. I want to know how much of a problem any of these things might be for you.

Show the child the template and point to the responses as you read.

If it is not at all a problem for you, point to the smiling face

If it is sometimes a problem for you, point to the middle face

If it is a problem for you a lot, point to the frowning face

I will read each question. Point to the pictures to show me how much of a problem it is for you. Let's try a practice one first.

	Not at all	Sometimes	A lot
Is it hard for you to snap your fingers			

Ask the child to demonstrate snapping his or her fingers to determine whether or not the question was answered correctly. Repeat the question if the child demonstrates a response that is different from his or her action.

Think about how you have been doing for the last few weeks. Please listen carefully to each sentence and tell me how much of a problem this is for you.

After reading the item, gesture to the template. If the child hesitates or does not seem to understand how to answer, read the response options while pointing at the faces.

PHYSICAL FUNCTIONING (problems with...)	Not at all	Sometime s	A lot
1. Is it hard for you to walk	0	2	4
2. Is it hard for you to run	0	2	4
3. Is it hard for you to play sports or exercise	0	2	4
4. Is it hard for you to pick up big things	0	2	4
5. Is it hard for you to take a bath or shower	0	2	4
6. Is it hard for you to do chores (like pick up your toys)	0	2	4
7. Do you have pains or aches (<i>Where?</i> _____)	0	2	4
8. Do you ever feel too tired to play	0	2	4

Remember, tell me how much of a problem this has been for you for the last few weeks.

EMOTIONAL FUNCTIONING (problems with...)	Not at all	Sometime s	A lot
1. Do you feel scared	0	2	4
2. Do you feel sad	0	2	4
3. Do you feel mad	0	2	4
4. Do you have trouble sleeping	0	2	4
5. Do you worry about what will happen to you	0	2	4

SOCIAL FUNCTIONING (problems with...)	Not at all	Sometime s	A lot
1. Is it hard for you to get along with other kids	0	2	4
2. Do other kids say they do not want to play with you	0	2	4
3. Do other kids tease you	0	2	4
4. Can other kids do things that you cannot do	0	2	4
5. Is it hard for you to keep up when you play with other kids	0	2	4

SCHOOL FUNCTIONING (problems with...)	Not at all	Sometime s	A lot
1. Is it hard for you to pay attention in school	0	2	4
2. Do you forget things	0	2	4
3. Is it hard to keep up with schoolwork	0	2	4
4. Do you miss school because of not feeling well	0	2	4
5. Do you miss school because you have to go to the doctor's or hospital	0	2	4

How much of a problem is this for you?

Not at all



Sometimes



A lot



PedsQL 4.0 - (5-7)

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PedsQL-4.0-Core - South Africa/English - Version of 11 Feb 16 - Mapi.
ID043653 / PedsQL-4.0-Core-VC_AU4.0_eng-ZA.doc

[PedsQL translations\ZA English versions\PedsQL ZA English young child 5 to 7 years.pdf](#)

[PedsQL translations\ZA English versions\PedsQLZA English child report 8 to 12 years.pdf](#)

[PedsQL translations\ZA English versions\PedsQL ZA English teenager report 13 to 18 years.pdf](#)

Appendix Cvi: PedsQL (proxy/parent report)

[PedsQL translations\ZA English versions\PedsQL PROXY young child 5 to 7 years.pdf](#)

Study ID no. _____
Date: _____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0 - English (South Africa)

PARENT REPORT for CHILDREN (ages 8-12)

DIRECTIONS

On the following page is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past ONE month** by circling:

- 0 if it is **never** a problem
- 1 if it is **almost never** a problem
- 2 if it is **sometimes** a problem
- 3 if it is **often** a problem
- 4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

During the past **ONE month**, how much of a **problem** has your child had with ...

PHYSICAL FUNCTIONING (problems with...)	Never	Almost Never	Some- times	Often	Almost Always
1. Walking more than 100 metres	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in sports activities or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Having a bath or shower by him or herself	0	1	2	3	4
6. Doing chores around the house	0	1	2	3	4
7. Having pain or aches	0	1	2	3	4
8. Low energy level	0	1	2	3	4

EMOTIONAL FUNCTIONING (problems with...)	Never	Almost Never	Some- times	Often	Almost Always
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad or down	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Worrying about what will happen to him or her	0	1	2	3	4

SOCIAL FUNCTIONING (problems with...)	Never	Almost Never	Some- times	Often	Almost Always
1. Getting along with other children	0	1	2	3	4
2. Other kids not wanting to be his or her friend	0	1	2	3	4
3. Getting teased by other children	0	1	2	3	4
4. Not able to do things that other children his or her age can do	0	1	2	3	4
5. Keeping up when playing with other children	0	1	2	3	4

SCHOOL FUNCTIONING (problems with...)	Never	Almost Never	Some- times	Often	Almost Always
1. Paying attention in class	0	1	2	3	4
2. Forgetting things	0	1	2	3	4
3. Keeping up with schoolwork	0	1	2	3	4
4. Missing school because of not feeling well	0	1	2	3	4
5. Missing school to go to the doctor or hospital	0	1	2	3	4

Appendix Cvii: Information leaflet and informed consent for parent(s)/caregiver(s)/legal guardians

“The effect of inspiratory muscle training on clinical outcomes and health-related quality of life in paediatric and adolescent patients with neuromuscular diseases attending out-patient clinics”

Section A: an information leaflet that will explain what this study is about

(you will receive a copy also).

Section B: an informed consent form to be signed should you agree for your child to participate in this study.

Section A: Information leaflet

Dear Sir/madam

My name is Anri Human and I am a registered PhD student in Physiotherapy at the University of Cape Town. We are doing a research study on the physiotherapy methods used on children and adolescents with neuromuscular diseases (NMDs) including Duchenne’s muscular dystrophy (DMD), myopathy, and spinal muscular atrophy (SMA). This study aims to determine the effect of breathing muscle (inspiratory muscles) strengthening amongst children and adolescents with NMDs. This involves using a special device (Powerbreathe K3 ®) to train the breathing muscles for three months. Patients attending the neurology clinic as out-patients at both Red Cross War Memorial Children’s Hospital (RCWMCH) in Cape Town as well as Doctor George Mukhari Academic Hospital (DGMAH) in Pretoria will be asked to participate.

We would kindly request that your child participates in this study and your cooperation will be greatly appreciated. This study has been approved by the University of Cape Town’s Faculty of Health Sciences’ Human Research Ethics Committee (HREC). The HREC number is 513/2015.

Before you decide if your child should participate in this research project or not, please read the following information about the study:

Background

Many adults and children with NMDs have weak breathing muscles which makes it difficult for them to have a good cough and get rid of mucus/secretions/phlegm in the lungs. If mucus stays in the lungs, patients can get chest infections and become very ill.

Due to their disease, children with NMDs may experience that their breathing muscles become weaker as they grow older. Strengthening the breathing muscles that helps to breathe in (inspiratory muscles), could help him/her to take deeper breaths. When breathing deeper, the lung tissue and chest muscles are kept from becoming tight and the cough effort can also improve. Stronger breathing muscles can make breathing easier in children with NMDs which can improve their quality of life as they might not get ill or need medication as often.

We do not yet know if inspiratory muscle training (IMT) is better or safer for children with NMDs compared to what they currently follow as their home programme. That is why we want to do this study.

Why do we want to do this study?

The study wants to see if there is a difference in the number of hospital admissions, lung infections that need medication (antibiotics) and health-related quality of life between the usual home programmes that children follow and the added IMT during a three month period.

Why is it necessary that we do this study?

Inspiratory muscle training (IMT) devices are used for children and adults with NMDs, to help them to keep their breathing muscles strong for as long as possible. Improved strength may improve their breathing and ability to cough. Currently, only a few people in South Africa are using IMT. We need to know if this strengthening can help to make breathing easier for patients and/or slow down the process of the muscles becoming weaker. If so, this might decrease the amount of times children have to be hospitalised or have to take antibiotics due to chest infections. We need to know if IMT is as effective, worse or better than the home programmes children currently follow so that we can offer the best and safest possible treatment to children with NMDs.

How long will this study take?

Should you agree for your child to participate in this study, he/she will be in one of two groups: The first group will start with IMT (using the Powerbreathe K3 ® device) for three months, thereafter they will stop training for three months but still be monitored/followed-up for another three months. The second group will not have any IMT training for the first three months, but will then train with the IMT device for the second three months, after which the training will be stopped and they will be followed up for another three months as well. Therefore your child might either be involved in the study for six or nine months, depending on which group they were in.

For the whole period of the study (either six/nine months), you will be asked to bring your child to the hospital either every two weeks (whilst training) or every month (not training) for monitoring. You will be re-imbursed for your travelling on these days, as this falls outside the framework of standard care and follow-up of the hospital.

Once this research study is completed, you will be informed about the results of this study through an information leaflet.

What does this study mean for you and your child?

Should you agree for your child to participate in this study they will be put in one of two groups: either the experimental group, who will receive the IMT training devices first or the control group, who will receive the IMT training devices only after three months. Both groups will also receive normal medical management and follow-up during this time. The group that your child will be in will be decided by chance, which is like tossing a coin – your child has an equal chance of being assigned to either group. In both groups patients will be assessed and treated by the doctors and physiotherapists in the same way, it will only be the timing of using IMT that is different (first three months or second three months)

During the IMT your child will receive a K3 handheld electronic IMT training device to use for the three months that they have to strengthen their breathing muscles. You and your child will also receive a training programme to follow twice a day. The physiotherapist will explain to you and your child exactly how to use the device and answer any questions you might have. Your child will be allowed to practise a few times in the presence of the physiotherapist so that he/she can correct where needed. When training with the IMT device your child should be in a sitting position. We do not want them to become too tired, so if they get extremely tired (based on an exhaustion scale we will give you) they can take a rest for a few seconds (20-60 seconds). Furthermore, your child will receive a diary in which they will be asked to record their daily training: the number of breaths they completed and how they experience the training (for example how tired they feel). Younger children might need your assistance

to complete their diaries. The diaries will be given to the clinician or researcher at the end of the three months training period. The K3 devices also have an electronic diary that keeps a record of how, when and how much your child has exercised per day, up to 30 sessions at a time. Whilst training you will be asked to bring your child to the hospital for monitoring every two weeks and then the data from the device will be written down. At the end of the three months when you come for your visit to the hospital, the device has to be returned to the researcher/clinician. After the training, you will be requested to continue to come to the hospital once a month for monitoring, for another three months. After this, your child will not be part of the study anymore.

Who will know that my child is taking part in this study?

Only the physiotherapists working with your child will know in which group your child is. The research assistant/clinician measuring your child's lung function or breathing muscle strength during follow-up visits to the hospital is not aware -please do not tell her if your child is training with the IMT device or not.

Researchers need to be as objective as possible during the study.

Which tests will be done?

During your child's participation in this study, certain tests will be done on the first day, on a two-weekly/monthly basis and the last follow-up visit, to monitor their progress.

At the first visit your child's weight (kilograms), height (cm), and function of the arms and legs will be written down. His/her body and limbs will be inspected for any deformities, and medical information from their file about his/her diagnosis, medication and medical management (including X-ray results) will be recorded. You and your child will also be asked about the physiotherapy home programme that he/she follows, the medications that he/she currently takes and if they have been hospitalised or been to the doctor since the previous visit to the hospital/clinic. At every two-weekly visit your child will be asked about their exhaustion (tiredness) level whilst doing IMT over the two weeks (on a scale of 0-10). Then they will be asked to do some lung function tests to determine how well their lungs are doing and tests to evaluate their breathing muscle strength. For these tests they will do certain breathing exercises into a mask and tube that are connected to a machine that will give us measurements. Another device that will be used has a small probe that goes in one nostril, this will measure your child's breathing muscle strength when taking a deep breath. The lung function tests and muscle strength tests will take approximately 20 minutes. This is not painful at all and will only last a few minutes.

You and possibly your child (if they are old enough) will be asked to complete a questionnaire at the beginning of the study and after three, six/nine months, on how you and they view their health-related quality of life. Also at the end of three months, we will ask you and your child about your satisfaction/comfort with the IMT programme (on a scale of 0-10).

No test is invasive or involves needles, therefore there will be no discomfort to your child during observations or testing.

Can anything good or bad happen to my child?

If you do agree for your child to be part of this study, you and your child will not necessarily gain anything. However, we hope that the results from this study can help/improve the physiotherapy treatment and long-term management of children and adolescents with neuromuscular diseases at Red Cross Children's Hospital, Doctor George Mukhari Academic Hospital and other hospitals throughout the country, in the near future.

IMT is hoped to improve your child's lung function, breathing and cough as well as slow down the weakening of their breathing muscles. Although some studies have found IMT to be successful, others found the opposite. Patients with Duchenne's muscular dystrophy might not have the same protective mechanism in their muscles as people without the disease. For this reason, your child's exercise programme will be guided by the latest evidence and research and adapted to his/her reactions and experience to the training programme.

The main risk during this research is exhaustion. For this reason, you and/or your child will be asked to write down his/her level of tiredness (Borg/OMNI scale) before and after their IMT exercise so that the researchers can monitor this. Furthermore, we would request that your child takes a break/rest (20-60 seconds) if they get too tired during the exercising. The time needed to rest before continuing the exercises will have to be written down in the diary also. All this information will be used for monitoring your child's performance, to make sure that they train effectively without becoming too tired. The recorded tiredness level as well as other lung functions will be monitored by the physiotherapists and researchers every two weeks so that the exercise programme can be changed if needed.

If your child experiences any symptoms such as pain/discomfort in the chest or any other symptoms that might seem to be caused by IMT, please inform the researchers immediately. If any of these symptoms appear to be caused by the IMT treatment, the muscle strengthening exercise programme (IMT) will be stopped and we will inform the safety committee.

Lung function and inspiratory muscle strength tests will be done at the beginning of your child's training period, end of training (after 3 months) and three months after the training has stopped (6 months). These tests could cause some fatigue, dizziness and shortness of breath, but these tests are not harmful.

Voluntary participation and right to withdrawal (Your choice)

Participation in this study is voluntary and you do not have to agree for your child to participate. It is up to you to decide if you would like your child to participate. You can therefore say "yes" to participate or decline by saying "no". Should you say "no" to participate in this study, your child will still receive the best care possible and the medical services delivered to your child will be not be influenced in any way.

If you agree for your child to participate we will ask you to sign an informed consent form. We will also ask your child if they are willing to participate (verbally if <7 years), or if your child is seven years and older we will ask his/her permission to participate by also signing a form (written assent). If your child's hands are too weak to hold a pen to sign the form, we will get witnessed assent from him/her.

If you change your mind during the study, you can withdraw your child from this study at any time if you wish to do so. This decision will in no way influence the medical services your child will receive at the hospital/clinic.

Privacy and confidentiality (What will happen to the data)?

All information collected will be used for research purposes only. To protect the privacy of your child and to ensure objectivity, your child's name will be replaced by a code on all our study forms. The key to the codes will be kept in a safe place and all measures will be taken to ensure your child's privacy and protect their identity. The only people who will have access to the data are the researchers and clinicians involved in the study. There is however a small risk that someone who should not have your information could learn something about you. We have however taken all possible precautions to ensure that your information is kept safe. This will be done by making sure that forms are kept in a cabinet that locks in the researcher's office, any computer document related to the study will be password protected.

Lastly, your child's name will never be used in any information related to this study, hence your anonymity and privacy will be respected at all times.

Insurance and safety committee (What if something goes wrong?)

If you should agree for your child to be part of this study and even though your child followed all instructions of clinicians, researchers and staff, if he/she gets injured or ill due to the research your child might need medical treatment. In the unlikely event of this happening, this research project is covered by the No Fault insurance policy of the University of Cape Town (<http://www.health.uct.ac.za>):

The University of Cape Town (UCT) has insurance cover for the event that research-related injury or harm results from your participation in the trial. The insurer will pay all reasonable medical expenses in accordance with the South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI) in the event of an injury or side effect resulting directly from your participation in the trial. You will not be required to prove fault on the part of the University.

The University will not be liable for any loss, injuries and/or harm that you may sustain where the loss is caused by

- The incorrect use of study intervention devices during the study
- Any injury that results from you not following the protocol requirements or the instructions that the study doctor/clinician/physiotherapist/nursing staff/may give you
- Any injury that arises from inadequate action or lack of action to deal adequately with a side effect or reaction to the study intervention
- An injury that results from negligence on your part

“By agreeing to participate in this study, you do not give up your right to claim compensation for injury where you can prove negligence, in separate litigation. In particular, your right to pursue such a claim in a South African court in terms of South African law must be ensured. Note, however, that you will usually be requested to accept that payment made by the University under the SA GCP guideline 4.11 is in full settlement of the claim relating to the medical expenses. “

An injury is considered trial-related if, and to the extent that, it is caused by study activities. You must notify the study doctor/clinician/physiotherapist/nursing staff/researcher immediately of any side effects and/or injuries during the trial, whether they are research-related or other related complications.

UCT reserves the right not to provide compensation if, and to the extent that, your injury came about because you chose not to follow the instructions that you were given while you were taking part in the study. Your right in law to claim compensation for injury where you prove negligence is not affected. Copies of these guidelines are available on request.

You are not giving up any of either your own or that of your child's legal rights by participating in this study. When signing the informed consent form, you indicate that you agree for your child to participate based on the information supplied to you.

If your child participates in this study they will be monitored by the physiotherapists and researchers on a regular basis. If any unwanted symptom such as chest pain/discomfort or severe exhaustion should arise either directly or indirectly because of participation in this study, please contact the physiotherapist immediately.

Research assistants/clinicians:

Lieselotte Corten (RCWMCH) 071 588 3729

Christelle Barnard (DGMH) 082 789 5680

What will happen after the research is done (post-trial care)?

If the use of IMT, as an adjunct to standard management, is found to be more effective than no training at all; participants (you/your child) that were involved in this study will be offered an alternative, more cost-effective IMT device (Powerbreathe Classic ® device) which should have the same clinical effect as the K3 that you used. Furthermore the Powerbreathe Classic ® can be used at home for you/your child's long-term management.

Contact details

If you have any questions or concerns regarding your child's participation or anything related to this study either before, during or after the study, please do not hesitate to contact the primary researchers. You are welcome to ask any questions about any aspect of the study that you might not understand, or if you would like more information, we will gladly supply it.

Anri Human

074 362 4055/(012) 521-4047; anrihuman@gmail.com

Brenda Morrow

(021) 658-5074; Brenda.Morrow@uct.ac.za

You can also contact the University of Cape Town Faculty of Health Sciences Human Ethics Committee (HREC) if you have any questions or concerns regarding your child's health, welfare and rights as a research participant:

Human Research Ethic Committee (HREC)

Prof Marc Blockman (Chairperson)

Old Main Building, Groote Schuur Hospital

(021) 406-6338

Marc.Blockman@uct.ac.za

Section B: Informed consent

If you give consent for your child to participate we would kindly request you to sign this consent statement.

PARENTAL/PATIENT (18 YEARS OLD) CONSENT FORM (ENGLISH)

Name of study: **The effect of inspiratory muscle training on clinical outcomes and health-related quality of life in paediatric and adolescent patients with neuromuscular diseases.**

I have read the information leaflet pertaining to the abovementioned study, and understand the aims and objectives of the proposed study. I have been provided the opportunity to ask questions, and all the questions I have asked were answered to my satisfaction.

I understand that participation in this study is completely voluntary and that I/my child may withdraw from participating in this study at any time and without supplying reasons. My child or I will not be prejudiced in any way if I choose not to participate. I have not been coerced in any way to let my child participate in this study.

I understand that if we decide to participate and I/another caregiver have to bring my child to the hospital every two weeks for tests and follow-up, I will receive transport money for these visits.

I am aware of the fact that this study has been approved by the Human Research Ethics Committee (HREC) of the University of Cape Town; HREC: 513/2015. I am fully aware that the results of this study will be used for scientific purposes and may be published. I agree to participation, provided my child's privacy is guaranteed.

I hereby give consent for my child to participate in this study.

.....

Name of parent/caregiver of participant/patient Signature of parent/caregiver of participant/patient

Place.....

Date.....

Witness.....

Statement by the Researcher

I have provided written information regarding this study to the parents/caregivers/patient.

I agree to answer any future questions concerning the study to the best of my ability.

I will adhere to the approved protocol.

Name of researcher: Anri Human/Lieselotte Corten/Eleonora Lozano

Signature of researcher:.....

Signed on this day of (month) 2015 at(place).

Appendix Cviii: Information leaflet for patients and assent form (11-17 years)



The effect of inspiratory muscle training on clinical outcomes and health-related quality of life in paediatric and adolescent patients with neuromuscular diseases.

This document consists of two parts:

Section A: Information to explain what this study is about (you will receive a copy also)

Section B: an assent form for you to sign if you agree to take part in this study

Section A: Information leaflet

My name is Anri Human and I am a physiotherapist studying at the University of Cape Town. I am doing research on children with neuromuscular disorders, like you have, and how physiotherapists can help children when they are at home (home programme) to make their breathing muscles stronger so they can breathe better and cough easier.

We will be using a machine (Powerbreathe K3[®]) that you can hold in your hand that will help you make your “breathing in” muscles stronger. This study will be done at Red Cross War Memorial Children’s Hospital (RCWMCH) in Cape Town as well as Doctor George Mukhari Academic Hospital (DGMAH) in Pretoria. Hopefully, this study can help children with neuromuscular disease have stronger breathing muscles for longer and not get lung infections so often.

We would like to ask you if you would take part in this study. You are being asked because you have a neuromuscular disease and visit the neuro/out-patient’s clinic, at the hospital, a few times per year. If you agree to take part in this study you will either be in Group 1 or 2. The first group will immediately start with the breathing exercise programme for three months. Group 2 will only start with the breathing exercise programme after three months. The group you are in will be decided by chance, like the chance of getting “heads” when you flip a coin.

Both groups will still be cared for by the doctors and nurses as they would have done normally. Both groups will be coming to the hospital either every two weeks (whilst exercising) or once a month to do a few lung function tests and for monitoring (this can be for either 6 or 9 months, depending if you are in Group 1 or 2). When you have to start with the breathing exercise programme your physiotherapist will explain to you and your parents how the machine (Powerbreathe K3[®]) works, and you will receive an exercise programme specifically for you. We will also give you a diary to write in how many times you exercised with the device per day, and how tired you felt before and afterwards. Your mother and/or father can help and motivate you, but you have to take the responsibility to exercise as the physiotherapist explained, otherwise the programme cannot be effective.

When you do your training at home you will be in an upright position. Before you start you will write down your tiredness level on a scale of 0-10 (not tired at all to very tired). You will then do the exercises as your physiotherapist has explained, resting in-between sets. If you feel dizzy, nauseous or become extremely tired during the exercise you should tell your parents, stop the exercise and write it in your diary. The following day you can try to exercise again. If you complete your number of sets you should also write down how tired you felt afterwards on a scale of 0-10. After three months you will return to the hospital and bring back the machine. Then you will come and visit the hospital again once a month for three more months so that we can monitor you and see how your lungs are doing.



If you are to be in the second group you will also be cared for by the doctors and nurses as they would have done normally. You will come in every month so that we can do tests to monitor you and see how your lungs are doing. The physiotherapist will then only give you a Powerbreathe K3[®] to exercise with after three months.

Training with the K3 should not hurt and may only feel a bit strange if you have not experienced it before. You will be expected to take a deep breath against some resistance (to exercise your breathing muscle). You will repeat this a few times before you have a rest. Then you will complete your sets of exercises. This will probably be done twice a day and should take no longer than 20 minutes.



During your visit to the hospital every month we will have to do some tests to see how you are doing.

Some tests will be done when you start with the training programme:

- When you come to the hospital for your first clinic visit your weight, height and/or length of your forearm will be measured. Your arms, legs and trunk will be investigated to look for any abnormalities. We will also get some information from your file about your condition.
- You and your parents will be asked about your current physiotherapy home programme that you follow.
- You will be asked what you can do with your arms (for example put your hand on your head) and your legs (for example if you can climb stairs, use a wheelchair), you will be asked to do certain activities to see how well you can perform them (MFM).
- You and/or your parents will be asked to complete a list of questions to tell us how you feel about your life (quality of life). We will also ask your parent/caregiver to tell us how they think your life is (quality of life). This will be done at the beginning and end of training as well as three months after your training.

At the end of the training, we will also ask you and your parents about how you experienced the IMT machine (Powerbreathe K3[®]) during the three months of training.

Some tests will be done every time you visit the clinic/hospital (every two weeks/once a month):

- You will be asked about how many times you had to use certain medications (antibiotics) over the past two weeks/month, as well as any change in your regular medications and if you have been admitted to hospital within that two weeks/month.
- You will be asked about your training programme and your level of tiredness before and after training every day (on a scale of 0-10).

- You will be asked to do certain lung tests to see how your lungs are doing. This will mean that we will ask you to do breathing exercises into a mask and tube that is connected to a machine that will give us numbers to tell us about your lungs. We will also put a small device in your one nostril that is connected to a machine and ask you to take a few deep breaths while we measure the strength of your breathing muscles.

These tests are not painful and will last about 20 minutes. You will be asked to do certain tests three times, if you get tired the physiotherapist will give you a chance to rest.

None of the tests that we will do to see how you are doing will be painful. We will not need to take blood at all for this study.



What is in it for me?

If you agree to be part of this study you will not receive anything extra for your participation. We will give mommy/daddy/your caregiver some money to bring you to the hospital every two weeks/month. We hope that by helping you to strengthen your breathing muscles you will feel better, breathe easier and stay healthier for longer. What we learn from this study can be used for other children with the same condition as you also.

You will only be part of this study for either 6 months or a maximum of 9 months (depending if you are in Group 1 or 2), after that you will not be in the study anymore.

Can anything go wrong?

We would like to tell you about some things that might happen if you are part of the study:

We are not currently sure of the best way to use the strengthening machine (Powerbreathe K3 ®) in children and adolescents with your condition. To make sure that you are safe we have written guidelines that will help the physiotherapists to give you a specific training programme.

Although using the machine for training should not be painful, you might find it uncomfortable in the beginning. You might also find that the training can make you feel tired or feel short of breath, and you might experience chest discomfort or nausea. If this should happen, please write it down in your diary and tell your parents/caregivers as well as your physiotherapist when you see him/her. If these things happen when using the K3 device, your training will be changed by the physiotherapist. If these symptoms should continue, then in consultation with the doctor, your training might be stopped. That is why the physiotherapists will ask questions about your tiredness when training and look at your daily diary when you visit the hospital on a two-weekly/monthly basis.

The lung function and breathing muscle tests are done when you come to the hospital can make you feel dizzy or light-headed, maybe even short of breath and tired, but the tests will not cause you pain or harm you in any way.

What if I say no?

To take part or not to take part in this study is your choice. You are allowed to say that you do not want to be in this study, even if your mother/father/caregiver said you could. No one will be upset if you say no. You can ask us questions or talk to your mother and/or father about this before you decide.

If you decide to be part of the study we will ask you to sign an assent form.

Should you change your mind later and do not want to continue taking part in the study you can tell us. You do not have to give any reasons why you don't want to be part of the study anymore. The doctors, nurses and physiotherapists will continue to help and look after you every time you come to the hospital.

Who will know that I am part of this study?

As soon as we are done we will write a report about what we have learned and will share it with other doctors and therapists that also work with children with your condition. Your name will be safe and no one will be able to recognise you because we will not use your name in the report. Only the physiotherapists involved in the study will know who you are.

What will happen when the study is done?

If we find that the use of the strengthening machine is more effective than no training, then you will be offered another, more cost-effective training device (Powerbreathe Classic ®device) that you can use at home as part of your exercise programme.

Who do I ask if I have any questions?

You are welcome to ask any questions to the physiotherapists that treat you or you can contact us, we will gladly explain anything you might want to know:

Anri Human

074 362 4055/ (012) 521-4047; anrihuman@gmail.com

Brenda Morrow

(021) 658-5074; Brenda.Morrow@uct.ac.za



Section B: Assent form

If you agree to participate in this study we would kindly request you to sign this assent form:

PATIENT ASSENT FORM (ENGLISH) (11-17 years)

Name of study: **“The effect of inspiratory muscle training in children and adolescents with neuromuscular diseases”**

The study to be done has been explained to me and I understand why this is important. The researchers/physiotherapists gave me a chance to ask questions if I was uncertain about anything or did not understand. I now understand, as they answered my questions well.

I understand that taking part in this study is my own choice and that I can stop at any time without having to explain why. I have not been forced in any way to be part of this study.

I was told that the physiotherapist has received permission to do this study at my hospital from the Human Research Ethics Committee of the University of Cape Town; HREC: 513/2015). I have been told that what is found from this study might be shared with others. I agree to be in this study on the condition that no one will be able to recognise me and that my name will be kept safe.

Based on your decision, please choose your answer:

I would **like to** be in this study.

☐

I **do not** want to be in this study.

☐

If you agree, please sign your name below

.....

Name of patient/participant

.....

Signature of participant/patient

Place.....

Date.....

Witness.....(obtaining assent)

Statement by the Researcher

I have provided written/oral information regarding this study to the patient.

I agree to answer any future questions concerning the study to the best of my ability.

I will adhere to the approved protocol.

Name of researcher: Anri Human/Lieselotte Corten/Eleonora Lozano

Signature of researcher:

Signed on this day of (month) 2015 at(place).

Appendix Cix: Information leaflet for patients and assent form (Intervention II) (7-10 years⁸⁷)



Breathing exercises for children with neuromuscular disease.

This document consists of two parts:

Section A: Information to explain what this study is about (you will receive a copy also)

Section B: an assent form for you to sign if you agree to take part in this study

As most patients in this age range might not be able to read well, the parents/clinicians can assist in explaining the aims and purposes of the study and obtaining assent to participate. The information leaflet serves as a guideline.

Section A: Information leaflet

My name is Anri Human and I am a physiotherapist studying at the University of Cape Town. I am doing research in children with neuromuscular disorders, like you have, and how physiotherapists can help them. We want to see if using a machine (Powerbreathe K3[®]) that makes your “breathing in” muscles stronger can help you breathe easier and stay healthy for longer.

We would like to ask you if you want to take part in this study because your “breathing in” muscles are a bit weak. If you say “yes” then we will put you in Group 1 or 2. The group you are in will be decided by chance, like the chance of getting “heads” when you flip a coin. Both groups will still be cared for by the doctors and nurses as they would have done normally. Group 1 will start training with the machine (Powerbreathe K3[®]) every day for three months. You will also come and visit the physiotherapist in the hospital every two weeks/month so that we can see how you are doing and do a few lung tests.

⁸⁷ Children <7 years received a verbal explanation based on this information leaflet (7-10 years)

Patients younger than seven were asked for verbal assent. If a patient older than seven years of age was too weak to hold a pen to sign, then witnessed verbal assent were sought.

These visits will take place for 6 months if you are in Group 1. If you are in Group 2, you will come and visit the physiotherapist at the hospital every month, for three months, before you can start training with the machine. The visits every two weeks whilst you are exercising and every month after exercising will continue for 9 months if you are in Group 2.

When you have to start with the breathing exercise programme your physiotherapist will explain to you and your mommy/daddy/caregiver how the machine (Powerbreathe K3[®]) works. You will get a programme of exercises that you will have to do every day. Mommy/daddy/caregiver will help you train and to write down how much you have exercised every day and how tired you felt. If you get tired when exercising you can take a rest.

If you don't feel well (feel dizzy, or you feel like throwing up) or become extremely tired during the exercise you should tell your mommy/daddy. After three months of training when you return to the hospital, you will bring back the machine. You will come and visit the hospital again once a month for three more months so that we can monitor you and see how your lungs are doing.



Training with the K3 should not hurt and may only feel a bit strange if you have not experienced it before. You will be expected to take a deep breath, which might seem a bit hard at first. You will breathe against the machine a few times before you take a rest. Your exercises should take no longer than 20 minutes per day.



During your visit to the hospital every two weeks/month we will have to do some tests to see how you are doing.

Some tests will be done when you start with the training programme:

- When you come to the hospital for your first clinic visit your weight, height and/or length of your forearm will be measured.
- We will look at the shape of your arms, legs and body. We will also get some information from your file about your condition.
- Mommy/daddy/your caregiver will be asked about the physiotherapy exercises you do at home.
- You will be asked about what you can do with your arms and legs (for example put your hand on your head).
- You will be asked to do certain activities to see how well you can perform them (MFM).
- You and/or mommy/daddy/caregiver will be asked some questions about if you enjoy life (quality of life).

At the end of the training, we will also ask you and mommy/daddy if you liked using the Powerbreathe K3[®] during the three months of training.

Some tests will be done every two weeks/month when you visit your physiotherapist at the clinic/hospital:

- You and your mommy/daddy will be asked about how many times you had to use certain medications (antibiotics).
- You will be asked about how much you have trained and how tired you felt.
- You will be asked to do certain lung tests to see how your lungs are doing. This will mean that we will ask you to do breathing exercises into a mask and tube that is connected to a machine that will give us numbers to tell us about your lungs. We will also put a small device in your nose, that is connected to a machine and ask you to take a few deep breaths so we can see how strong your “breathing in” muscles are.

These tests are not painful and will last about 20 minutes. You will be asked to do certain tests three times, if you get tired the physiotherapist will give you a chance to rest.

None of the tests that we will do to see how you are doing will be painful. We will not need to take blood at all for this study.



What is in it for me?

If you say “yes” to be part of this study you will not receive anything extra. We will give mommy/daddy/your caregiver some money to bring you to the hospital every two weeks/month. We hope that by helping you to strengthen your breathing muscles you will feel better, breathe easier and stay healthier for longer. What we learn from this study can be used for other children with the same condition as you also.

You will only be part of this study for either 6 months or a maximum of 9 months (depending if you are in Group 1 or 2), after that you will not be in the study anymore.

Can anything go wrong?

We would like to tell you about some things that might happen if you are part of this study:

To make sure that you are safe we will give you a very specific training programme. Training with the K3 is not painful, but you may feel a bit uncomfortable in the beginning.

When training you might feel tired, short of breath, feel discomfort in your chest or feel like throwing up-if this happens, please tell mommy/daddy and your physiotherapist. If these things happen when using the K3 device, your training will be changed by the physiotherapist. If these symptoms should carry on, then we might stop your training with the K3.

The lung function and breathing muscle tests that you will do when coming to the hospital can make you feel dizzy or light-headed, maybe even short of breath and tired, but the tests will not cause you pain or harm you in any way.

What if I say no?

To take part or not to take part in this study is your choice. You are allowed to say that you do not want to be in this study, even if your mother/father/caregiver said you could. No one will be upset if you say no. You can ask us questions or talk to your mother and/or father about this before you decide.

If you decide to be part of the study we will ask you to sign an assent form.

Should you change your mind later and do not want to continue taking part in the study you can tell us. You do not have to give any reasons why you don't want to be part of the study anymore. The doctors, nurses and physiotherapists will continue to help and look after you every time you come to the hospital.

Who will know that I am part of this study?

As soon as we are done we will write a report about what we have learned and will share it with other doctors and physiotherapists that also work with children with your condition. Your name will be safe because we will not use your name in the report. Only the physiotherapists that see you will know who you are.

What will happen when the study is done?

If we find that the use of this strengthening machine is working well, then you will be given a training device (Powerbreathe Classic® device) that you can use at home.

Who do I ask if I have any questions?

You can ask any questions to the physiotherapist that is helping you or you can ask your mommy/daddy to phone us if you would like us to explain anything:

Anri Human

074 362 4055/ (012) 521-4047

anrihuman@gmail.com

Or

Brenda Morrow

(021) 658-5074

Brenda.Morrow@uct.ac.za

Section B: Assent form (7-10 years)

PATIENT ASSENT (ENGLISH) (7-10 years)⁸⁸

If you decide “yes” we will ask you to sign this form.

Name of study: **“The effect of breathing exercises in children with neuromuscular disease”**

The study to be done has been explained to me and I understand why this is important. The researchers/physiotherapists gave me a chance to ask questions if I was uncertain about anything or did not understand. I now understand, as they answered my questions well.

I understand that taking part in this study is my own choice and that I can stop at any time without having to explain why. I have not been forced in any way to be part of this study.

I was told that the physiotherapist has received permission to do this study at my hospital from the Human Research Ethics Committee of the University of Cape Town; HREC: 513/2015). I have been told that what is found from this study might be shared with others. I agree to be in this study on the condition that no one will be able to recognise me and that my name will be kept safe.

Based on your decision, please choose your answer:

I would **like to** be in this study.

☐

I **do not** want to be in this study.

☐

If you agree, please sign your name below

.....

Name of patient/participant

Signature of participant/patient

Place.....

Date.....

Witness.....(obtaining assent)

⁸⁸ Patients younger than seven were asked for verbal assent. If a patient older than seven years of age was too weak to hold a pen to sign, then witnessed verbal assent were sought.

Statement by the Researcher

I have provided written/oral information regarding this study to the patient.

I agree to answer any future questions concerning the study to the best of my ability.

I will adhere to the approved protocol.

Name of researcher: Anri Human/Lieselotte Corten

Signature of researcher:

Signed on this Day of(month) 2015 at(place).

Appendix Di: Ethical clearance certificate⁸⁹



UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee



Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • Facsimile [021] 406 5411
Email: sumayah.ariefdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

01 December 2015

HREC REF: 513/2015

Prof B Morrow

Department of Paediatrics & Child Health
c/o 5th Floor ICH Building
Red Cross War Memorial Children's Hospital
Rondebosch

Dear Prof Morrow

PROJECT TITLE: THE EFFECT OF MECHANICAL INSUFFLATION -EXSUFFLATION AND INSPIRATORY MUSCLE TRAINING ON THE CLINICAL OUTCOMES AND HEALTH-RELATED QUALITY OF LIFE IN PAEDIATRIC AND ADOLESCENT PATIENTS WITH NEUROMUSCULAR DISEASES PRESENTING WITH RESPIRATORY MUSCLE WEAKNESS: A MULTI-CENTRE TRIAL (PhD candidate- A Human)

Thank you for your response letter, addressing the issues raised by the Human Research Ethics Committee (HREC).

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30th December 2016.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC reference no in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

Signature Removed

PROFESSOR M BLOCKMAN

CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.

Institutional Review Board (IRB) number: IRB00001938

Hrec/ref:513/2015

⁸⁹ HREC renewal was received from 2016-2021. The thesis title was changed from the original inclusion of both MI-E and IMT, because the MI-E was not deemed feasible after initial enrolment and the scope of the thesis would have been too broad. The final thesis therefore only described IMT.

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☒ Approved	Annual progress report	Approved until/next renewal date	30.01.2022
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Signature Removed	Date Signed 16/1/2021

Comments to PI from the HREC
<i>Study deviation noted. Thank you</i>

Principal Investigator to complete the following:

1. Protocol Information

Date (when submitting this form)	12/01/2021		
HREC REF Number	513/2015	Current Ethics Approval was granted until	30 November 2019
Protocol title	The effect of mechanical insufflation-exsufflation and inspiratory muscle training on clinical outcomes and health-related quality of life in paediatric and adolescent patients with neuromuscular diseases presenting with respiratory muscle weakness: a multi-centre trial.		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?		☐ Yes ☒ No	
If yes, could you please provide the HREC Ref's for all sub-studies? Note: A separate FHS016 must be submitted for each sub-study.			
Principal Investigator	Prof. Brenda May Morrow		
Department / Office Internal Mail Address	5 th Floor ICH Building, Red Cross Hospital		

1.1 Does this protocol receive US Federal funding?	☐ Yes	☒ No
1.2 If the study receives US Federal Funding, does the annual report require full committee approval?	☐ Yes	☐ No N/A
1.3 Has sponsorship of this study changed? If yes, please attach a revised summary of the budget.	☐ Yes	☒ No

Appendix Dii: Mapi Trust translation agreement and permission to use PedsQL



User agreement Special Terms

Mapi Research Trust, a non-for-profit organisation subject to the terms of the French law of 1st July 1901, registered in Carpentras under number 453 979 346, whose business address is 27 rue de la Villette, 69003 Lyon, France, hereafter referred to as "MRT" and the User, as defined herein, (each referred to singularly as a "Party" and/or collectively as the "Parties"), do hereby agree to the following User Agreement Special and General Terms:

MRT Contact:

Mapi Research Trust
PROVIDE
Address: 27 rue de la Villette, 69003 LYON, France
Telephone: +33 4 72 13 65 75
Fax: +334 72 13 66 82

RECITALS

The User acknowledges that it is subject to these Special Terms and to the General Terms of the Agreement, which are included in Appendix 1 to these Special Terms and fully incorporated herein by reference. Under the Agreement, the Questionnaire referenced herein is licensed, not sold, to the User by MRT for use only in accordance with the terms and conditions defined herein. MRT reserves all rights not expressly granted to the User.

The Parties, in these Special Terms, intend to detail the special conditions of their partnership.

The Parties intend that all capitalized terms in the Special Terms have the same definitions as those given in article 1 of the General Terms included in Appendix 1.
In this respect, the Parties have agreed as follows:

Article 1. CONDITIONS SPECIFIC TO THE USER

Section 1.01 Identification of the User

User Name : **Anri Human (lecturer: Sefako Makgatho Health Sciences University; Garankuwa; South Africa)**

Legal form : **[individual or company's legal form]**

Address : Sefako Makgatho Health Sciences University, Molotlegi Street, Garankuwa 0208

PO Box 239, MEDUNSA, 0204

Country : South Africa

Name of the contact in charge of the Agreement: Ms. Anri Human

Telephone number: (012) 521-4047, Fax number: -

Email address: anrihuman@gmail.com/anri.human@smu.ac.za

If different: N/A

Legal form : **[individual or company's legal form]**

Address : **[personal address or address of registered office]**

Country :

Billing address:

VAT number (if applicable):

Addressee:

PO number or internal reference (if applicable):

Section 1.02 Identification of the Questionnaire

Title of the Questionnaire: PedsQL™ (Pediatric Quality of Life Inventory™)

Author: James W. Varni

Owner: James W. Varni

Copyright notice: Copyright © 1998 JW Varni, Ph.D. All rights reserved.

References: See Appendix 2

Article 2. RIGHTS TO USE

Section 2.01 Context of the Use of the Questionnaire

The User undertakes to only use the Questionnaire in the context of the Study as defined hereafter.
[Tick the box and complete the corresponding fields]

☐ individual clinical practice (please go directly to section 2.02)

Planned term of use:

Number of patients expected:

☒ clinical project or study

Title: The effect of mechanical insufflation-exsufflation and inspiratory muscle training on clinical outcomes and health-related quality of life in paediatric and adolescent patients with neuromuscular diseases presenting with respiratory muscle weakness: a multi-centre trial.

Study/protocol reference: 513/2015 (HREC at UCT)

Disease or condition: Neuromuscular diseases (5-18 year olds)

Type of research: ☒ clinical trial : ☐ Phase II / ☐ Phase III (Inspiratory muscle training: chr of the study)

☐ epidemiologic/observational

☐ other:

Questionnaire used as primary end point: ☐ yes

☒ no (secondary outcome measure)

Number of patients expected: 44 (22 per group: cross-over study)

Number of submissions to the Questionnaire for each patient: Baseline, post-intervention and after 3 months of follow-up

Term of clinical follow-up for each patient: 3 month follow-up (post-intervention)

Planned term for project: start (month/year): September 2016

end (month/year): November 2017

Mode of Administration: ☒ paper

☐ electronic

If electronic administration, please indicate mode of data collection:

☐ Hand held device – specify device:

☐ Interactive Voice Response (IVR) – specify:

☐ Web - specify website:

☐ Digital Pen - specify device:

☐ Tablet - specify device:

☐ other - specify:

Use of IT Company (e-vendor): ☐ no
☐ yes – names of IT Company and contact:.....

☐ other project

Title:

Disease or condition:

Planned term of use: start (month/year):
end (month/year):.....

Description of the project:

Presentation format of project:

Requested module(s): (please tick the appropriate box(es))

PedsQL™ Generic Core Scales										
Please specify: Standard ☐ Acute ☐ Both ☐										
Adult (over 26)		Young Adult (18-25)		Adolescent (13-18)		Child (8-12)		Young Child (5-7)		Toddler (2-4)
Self-report	Parent proxy-report	Self-report	Parent proxy-report	Child self-report	Parent proxy-report	Child self-report	Parent proxy-report	Child self-report	Parent proxy-report	Parent proxy-report
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

PedsQL™ Infant Scales	
Please specify: Standard ☐ Acute ☐ Both ☐	
☐ Parent-report form (1-12 months)	☐ Parent-report form (13-24 months)

PedsQL™ Short Form 15 Generic Core Scales										
Please specify: Standard ☐ Acute ☐ Both ☐										
Adult (over 26)		Young Adult (18-25)		Adolescent (13-18)		Child (8-12)		Young Child (5-7)		Toddler (2-4)
Self-report	Parent proxy-report	Self-report	Parent proxy-report	Child self-report	Parent proxy-report	Child self-report	Parent proxy-report	Child self-report	Parent proxy-report	Parent proxy-report
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

PedsQL™ Arthritis Module						
Adolescent (13-18)		Child (8-12)		Young Child (5-7)		Toddler (2-4)
Child self-report	Parent proxy-report	Child self-report	Parent proxy-report	Child self-report	Parent proxy-report	Parent proxy-report
☐	☐	☐	☐	☐	☐	☐

PedsQL™ Asthma Module						
Please specify: Standard ☐ Acute ☐ Both ☐						
Adolescent (13-18)		Child (8-12)		Young Child (5-7)		Toddler (2-4)
Child self-report	Parent proxy-report	Child self-report	Parent proxy-report	Child self-report	Parent proxy-report	Parent proxy-report
☐	☐	☐	☐	☐	☐	☐

Financing of the Project:

☒ Not funded academic research/project, individual medical practice	<i>Projects not explicitly funded, but funding comes from overall departmental funds or from the University or individual funds. (primarily from university research funds)</i>
☐ Funded academic research/project	<i>Projects receiving funding from commerce, government, EU or registered charity. Funded academic research- sponsored by industry- fits the "commercial study/project" category.</i>
☐ Large non-commercial organization Research and Evaluation (per-study license)	<i>Large non-commercial organization Research and Evaluation; e.g. states, nations, hospitals, healthcare systems (includes an important number of patients and/or centres)</i>
☐ Large non-commercial organization Unlimited Research and Evaluation and clinical use (annual license, unlimited use)	<i>Large non-commercial organization Research and Evaluation; e.g. states, nations, hospitals, healthcare systems (includes an important number of patients and/or centres)</i> Please specify number of centres-----
☐ Large non-commercial organization Unlimited Research and Evaluation and clinical use (Patient Registry)	<i>Large non-commercial organization Research and Evaluation; e.g. states, nations, hospitals, healthcare systems</i> <i>Patient Registry: an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves a predetermined scientific, clinical, or policy purposes</i> Please specify number of patients-----
☐ Commercial study	<i>Commercial studies (industry, CRO, any for-profit companies)</i> Please specify number of centres-----
☐ Commercial Patient Registry	<i>Commercial studies (industry, CRO, any for-profit companies)</i> <i>Patient Registry: see above</i> Please specify number of patients-----
Grants / Sponsoring from (if any) (name of the governmental/ foundation/company or other funding/sponsoring source):	Consumables for the Nippy Clearway are sponsored by Bakoni Medical..

Section 2.02 Conditions for use

The User undertakes to use the Questionnaire in accordance with the conditions for use defined hereafter.

(a) Rights transferred

Acting in the Owner's name, MRT transfers the following limited, non-exclusive rights, to the User (the "Limited Rights")

(i) to use the Questionnaire, only as part of the Study; this right is made up exclusively of the right to communicate it to the Beneficiaries only, by any means of communication and by any means of remote distribution known or unknown to date, subject to respecting the conditions for use described hereafter; and

(ii) to reproduce the Questionnaire, only as part of the Study; this right is made up exclusively of the right to physically establish the Questionnaire or to have it physically established, on any paper, electronic, analog or digital medium, and in particular documents, articles, studies, observations, publications, websites whether or not protected by restricted access, CD, DVD, CD-ROM, hard disk, USB flash drive, for the Beneficiaries only and subject to respecting the conditions for use described hereafter; and

(iii) Should the Questionnaire not already have been translated into the language requested, the User is entitled to translate the Questionnaire or have it translated in this language, subject to informing MRT of the same beforehand by the signature of a Translation Agreement indicating the terms of it and to providing a copy of the translation thus obtained as soon as possible to MRT.

(iii) In the context of commercial studies or any project funded by the pharmaceutical industry, the User undertakes to have the Questionnaire translated in this language by Mapi Language Services. Mapi Language Services is the only organization authorized by the Owner to perform linguistic validation/translation work on the Questionnaire.

PedsQLTM_UserAgreement_March2016_22.0_protected.docx

© 2013 Mapi Research Trust. The unauthorized modification and use of any portion of this document is prohibited.

The User acknowledges and accepts that it is not entitled to amend, modify, condense, adapt, reorganise the Questionnaire on any medium whatsoever, in any way whatsoever, even minor, without MRT's prior specific written consent.

(b) Specific conditions for the Owner

The Owner has intended to transfer a part of the copyright on the Questionnaire and/or the Documentation to MRT in order to enable MRT to make it available to the User for the purpose of the Study, subject to the User respecting the following conditions:

User shall not modify, abridge, condense, translate, adapt, recast or transform the Questionnaire in any manner or form, including but not limited to any minor or significant change in wordings or organisation in the Questionnaire, without the prior written agreement of the Owner. If permission is granted, any improvements, modifications, or enhancements to the Questionnaire which may be conceived or developed, including translations and modules, shall become the property of the Owner.

The User therefore undertakes to respect these special terms.

(c) Specific conditions for the Questionnaire

- Use in Individual clinical practice or Research study / project

The User undertakes never to duplicate, transfer or publish the Questionnaire without indicating the Copyright Notice.

In the case of use of an electronic version of the Questionnaire in academic studies, the User undertakes to respect the following special obligations:

- In case of use of an IT Company (e-vendor), User shall check with Mapi Research Trust that IT Company has signed the necessary License Agreement with Mapi Research Trust before developing the electronic version of the Questionnaire
- Not modify the questionnaire (items and response scales, including the response scale numbers from 0-4)
- Cite the reference publications
- Insert the Owner's copyright notice on all pages/screens on which the Questionnaire will be presented and insert the Trademark information: PedsQL™, Copyright © 1998 JW Varni, Ph.D. All rights reserved.
- Mention the following information: "PedsQL™ contact information and permission to use: Mapi Research Trust, Lyon, France – Internet: <https://eprovide.mapi-trust.org> and www.pedsq.org/index.html "
- Submit the screenshots of all the Pages where the Questionnaire appears to Dr James W. Varni before release for approval and to check that the above-mentioned requirements have been respected.

In the case of use of an electronic version of the Questionnaire in commercial studies / projects, the User undertakes to respect the following special obligations:

User shall:

- In case of use of an IT Company (e-vendor), User shall check with Mapi Research Trust that IT Company has signed the necessary License Agreement with Mapi Research Trust before developing the electronic version of the Questionnaire
- Not modify the questionnaire (items and response scales, including the response scale numbers from 0-4)
- Cite the reference publications
- Insert the Owner's copyright notice on all pages/screens on which the Questionnaire will be presented and insert the Trademark information: PedsQL™, Copyright © 1998 JW Varni, Ph.D. All rights reserved.
- Mention the following information: "PedsQL™ contact information and permission to use: Mapi Research Trust, Lyon, France – Internet: <https://eprovide.mapi-trust.org> and www.pedsq.org/index.html "

- For the first migration of the Questionnaire (generally the original version) into a specific electronic device
 - o Review of screenshots:

After implementation of the Questionnaire into the device, the user/IT Company will generate screen captures (screenshots) of the original questionnaire as displayed in the device. These will be reviewed by Mapi to check that they are consistent with the original paper version in terms of presentation, content and completion except for specific instructions related to the electronic administration. Corrections that may be needed will be reported to the user/IT Company. In this case, screenshots after correction will be generated for another round of review by Mapi until all screenshots are approved.

Dr James W. Varni will review all approved screenshots for a final validation.

- o Usability testing:

Usability testing is a methodology which aims to examine whether respondents are able to use a device and associated software as intended. Major issues of concern in usability testing typically include device complexity, navigation and response selection for example.

The objective of this investigation is to ensure that the electronic version of the questionnaire as included in the device meets usability criteria, focusing on functional aspects and respondents' understanding of instructions. Usability testing consists in interviews with patients where patients will complete the electronic version of the Questionnaire on the device and comment on their understanding of the instructions, ease of use and handiness of the device. A Usability testing report presenting results will be produced. If any changes are recommended, these will be implemented by the user/IT Company. If issues raised by respondents are rated as major, the user/IT Company may need to perform additional developments and another round of interviews may be needed.

Dr James W. Varni will review the changes suggested, if any, following the interviews.

The review of screenshots is mandatory. The usability testing is highly recommended by Mapi, however should the User and/or IT Company decide not to perform this step, Mapi Research Trust shall not be held responsible

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for any consequence and expense associated with this decision which shall remain the User and/or IT Company's sole liability.

The review of screenshots and usability testing, when and if performed, shall be performed exclusively by Mapi and shall be sponsored by the User.

The performance of the review of screenshots and usability testing will result in a certification of the electronic device original version of the Questionnaires by Mapi for future licenses.

- For the migration of other language versions of the Questionnaire on an existing certified specific electronic device

- o Update version

After the electronic device original version of the Questionnaire is fully ready, the Questionnaire's language versions developed for paper administration will be updated to reflect the changes in wording of instructions implemented in the electronic device original version of the questionnaire.

Native speakers of the languages will reflect the changes made to the electronic device original version of the Questionnaire and will provide English equivalents of all changes made for Mapi's quality control.

- o Review of screenshots:

After implementation of the Questionnaire into the device, the user/IT Company will generate screen captures (screenshots) of the original questionnaire as displayed in the device. These will be reviewed by Mapi to check that they are consistent with the original paper version in terms of presentation, content and completion except for specific instructions related to the electronic administration. Corrections that may be needed will be reported to the user/IT Company. In this case, screenshots after correction will be generated for another round of review by Mapi until all screenshots are approved.

The update of version and review of screenshots are mandatory. These steps shall be performed exclusively by Mapi and shall be sponsored by the User.

The performance of the update of version and review of screenshots will result in a certification of the electronic device language version of the Questionnaires by Mapi for future licenses.

- Use in a publication:

In the case of a publication, article, study or observation on paper or electronic format of the Questionnaire, the User undertakes to respect the following special obligations:

- not to include any full copy of the Questionnaire, but a version with the indication "sample copy, do not use without permission"
- to indicate the name and copyright notice of the Owner (PedsQL™, Copyright © 1998 JW Varni, Ph.D. All rights reserved)
- to include the reference publications of the Questionnaire
- to indicate the details of MRT for any information on the Questionnaire as follows: PedsQL™contact information and permission to use: Mapi Research Trust, Lyon, France. Internet: <https://eprovide.mapi-trust.org> and www.pedsq.org
- to provide MRT, as soon as possible, with a copy of any publication regarding the Questionnaire, for information purposes
- to submit the screenshots of all the Pages where the Questionnaire appears to MRT before release to check that the above-mentioned requirements have been respected.

- Use for dissemination or marketing:

In the case of use in a dissemination/marketing context:

- On a website with unrestricted access:

The publication of a copy of the PedsQL™ on a website with unrestricted access is not permitted.

- On a website with restricted access:

In the case of publication on a website with restricted access, the User may include a version of the Questionnaire that may be amended, subject to this version being protected by a sufficiently secure access to only allow the Beneficiaries to access it.

Article 3. TERM

MRT transfers the Limited Rights to use the Questionnaire as from the date of delivery of the Questionnaire to the User and for the whole period of the Study.

Article 4. BENEFICIARIES

The Parties agree that the User may communicate the Questionnaire in accordance with the conditions defined above to the Beneficiaries involved in the Study only, in relation to the Study defined in section 2.01.

Article 5. TERRITORIES AND LANGUAGES

MRT transfers the Limited Rights to use the Questionnaire on the following territories and in the languages indicated in the table below:

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<i>Language:</i>	<i>For use in the following country</i>	<i>Language:</i>	<i>For use in the following country</i>	<i>Language:</i>	<i>For use in the following country</i>
Afrikaans	South Africa				
isiXhosa	South Africa				
English	South Africa				
Setswana	South Africa				

Article 6. PRICE AND PAYMENT TERMS

The User undertakes in relation to MRT to pay the price owed in return for the availability of the Questionnaire, according to the prices set out in Appendix 3, depending on the languages requested and the costs of using the Questionnaire, in accordance with the terms and conditions described in section 6.02 of the General Terms included in Appendix 1.

Agreed and acknowledged by:

User's Name: Anri Human

User's Title: Ms.

Date: 31/08/2016

User's Signature:

MRT transfers the Limited Rights to use the Questionnaire on the following territories and in the languages indicated in the table below:

<i>Language:</i>	<i>For use in the following country</i>	<i>Language:</i>	<i>For use in the following country</i>	<i>Language:</i>	<i>For use in the following country</i>
<i>Afrikaans</i>	<i>South Africa</i>				
<i>isiXhosa</i>	<i>South Africa</i>				
English	South Africa				
Setswana	South Africa				

Price and payment terms

The User undertakes in relation to MRT to pay the price owed in return for the availability of the Questionnaire, according to the prices set out in Appendix 3, depending on the languages requested and the costs of using the Questionnaire, in accordance with the terms and conditions described in section 6.02 of the General Terms included in Appendix 1.

Agreed and acknowledged by:

User's Name: Anri Human

User's Signature:

User's Title: Ms.

Date: 31/08/2016



Sonia Bothorel
Managing Director
27 rue de la Villette
69003 Lyon, France

Date: 08/31/20

Re: Letter to certify Mr Anri Human's rights to translate the PedsQL

This letter is to certify that Mr Anri Human, South Africa, has signed a Translation Agreement with Mapi Research Trust, dated October 2, 2016, in order to gain access to translate the Adolescent version (parent/proxy report) of the Standard version of the Generic Core Scales of the PedsQL in Xhosa. The author and copyright owner, Prof. James W. Varni has granted Mapi Research Trust the official exclusive right to distribute the PedsQL questionnaire, acting on his behalf.

Mapi Research Trust hereby confirms that Mr Anri Human translated the original US English Adolescent version (parent/proxy report) of the Standard version of the Generic Core Scales of the PedsQL into Xhosa. The backward translation was reviewed and approved by Prof. James W. Varni in January 16th, 2020.

Sonia Bothorel Sonia Bothorel
31 Aug 2020 13:40:056+0000

REASON: I approve this document
35c1b998-025e-494e-a2ba-d19efb49f8f2

Mapi Research Trust • 27 rue de la Villette • 69003 Lyon • France
Tel: +33 (0) 4 72 13 66 66 • www.mapi-trust.org • www.eprovide.mapi-trust.org
eprove@mapi-trust.org

Association de loi 1901 enregistrée à Lyon • N° Siret 453 979 346 00021 • T.V.A. FR 44 453 979 346

DocUID : bb3e7a47-e1c2-445b-a7f5-f2d2050e0

Appendix Diii: Permission to conduct a pre-experimental, six-week pilot study



GAUTENG PROVINCE
EDUCATION
REPUBLIC OF SOUTH AFRICA

For administrative use only:
Reference no: D2017/286
Enquiries: Diane Bunting 011 843 6503

GDE RESEARCH APPROVAL LETTER

Date:	14 November 2016
Validity of Research Approval:	06 February 2017 29 th September 2017
Name of Researcher:	Ms Anri Human
Address of Researcher:	15 Takbok Street
	South Africa
	Theresa Park
Telephone / Fax Number/s:	Tel: 012 5214047 Cell: 074 3624055
Email address:	anrihuman@gmail.com
Research Topic:	The effects of mechanical insufflation-exsufflation and inspiratory muscles training on clinical outcomes and health related quality of life paediatric and adolescent patients with neuro-muscular diseases presenting with respiratory muscle weakness: a multi-centre trial
Number and type of schools:	One Primary school and one Secondary school
District/s/HO	Gauteng East and Gauteng North

Re: Approval in Respect of Request to Conduct Research

This letter serves to indicate that approval is hereby granted to the above-mentioned researcher to proceed with research in respect of the study indicated above. The onus rests with the researcher to negotiate appropriate and relevant time schedules with the school/s and/or offices involved. A separate copy of this letter must be presented to the Principal, SGB and the relevant District/Head Office Senior Manager confirming that permission has been granted for the research to be conducted. However participation is VOLUNTARY.

Signature Removed

2016/11/14

Making education a societal priority

Office of the Director: Knowledge Management and Research

9th Floor, 111 Commissioner Street, Johannesburg, 2001
P.O. Box 7710, Johannesburg, 2000 Tel: (011) 355 0506
Email: David.Makhado@gauteng.gov.za
Website: www.education.gpg.gov.za

The following conditions apply to GDE research. The researcher has agreed to and may proceed with the above study subject to the conditions listed below being met. Approval may be withdrawn should any of the conditions listed below be flouted:

1. The District/Head Office Senior Manager/s concerned, the Principal/s and the chairperson/s of the School Governing Body (SGB,) must be presented with a copy of this letter.
2. **Kindly note that approval may be granted on condition that the safety of the learners and feedback on training can be ensured by qualified physiotherapists that can correct their breathing pattern.**
3. The Researcher will make every effort to obtain the goodwill and co-operation of the GDE District officials, principals, SGBs, teachers, parents and learners involved. Participation is voluntary and additional remuneration will not be paid;
4. Research may only be conducted after school hours so that the normal school programme is not interrupted. The Principal and/or Director must be consulted about an appropriate time when the researcher/s may carry out their research at the sites that they manage.
5. Research may only commence from the second week of February and must be concluded by the end of the THIRD quarter of the academic year. If incomplete, an amended Research Approval letter may be requested to conduct research in the following year.
6. Items 6 and 7 will not apply to any research effort being undertaken on behalf of the GDE. Such research will have been commissioned and be paid for by the Gauteng Department of Education.
7. It is the researcher's responsibility to obtain written principal, educator, parental and learner consent before commencing with research;
8. The researcher is responsible for supplying and utilizing his/her own research resources, such as stationery, photocopies, transport, faxes and telephones and should not depend on the goodwill of the institutions and/or the offices visited for supplying such resources.
9. The names of the GDE officials, schools, principals, parents, teachers and learners that participate in the study may not appear in the research title or research report.
10. On completion of the study the researcher must supply the Director: Education Research and Knowledge Management, with electronic copies of the Research Report, Thesis, Dissertation as well as a Research Summary (on the GDE Summary template).
11. The researcher may be expected to provide short presentations on the purpose, findings and recommendations of his/her research to both GDE officials and the schools concerned;
12. Should the researcher have been involved with research at a school and/or a district/head office level, the Director/s and school/s concerned must also be supplied with a brief summary of the purpose, findings and recommendations of the research study.

The Gauteng Department of Education wishes you well in this important undertaking and looks forward to examining the findings of your research study.

Kind regards

Signature Removed

David Makhado

Director: Education Research and Knowledge Management

Date: 2016/11/14

Making education a societal priority

Office of the Director: Knowledge Management and Research

9th Floor, 111 Commissioner Street, Johannesburg, 2001
P.O. Box 7710, Johannesburg, 2000 Tel: (011) 355 0506
Email: David.Makhado@gauteng.gov.za
Website: www.education.gpg.gov.za

Appendix Div: Permission for cross-over randomised controlled trial (Western Cape)



Directorate: Research

Audrey.wyngaard@westerncape.gov.za

tel: +27 021 467 9272

Fax: 0865902282

Private Bag x9114, Cape Town, 8000
wced.wcape.gov.za

REFERENCE: 20170303 –8815

ENQUIRIES: Dr A T Wyngaard

Ms Anri Human
PO Box 43052
Theresa Park
0155

Dear Ms Anri Human

RESEARCH PROPOSAL: THE EFFECT OF MECHANICAL INSUFFLATION-EXSUFFLATION (MI-E) AND INSPIRATORY MUSCLE TRAINING (IMT) ON THE CLINICAL OUTCOMES AND HEALTH-RELATED QUALITY OF LIFE (HRQOL) IN PAEDIATRIC AND ADOLESCENT NEUROMUSCULAR DISEASE (NMD) PATIENTS PRESENTING WITH RESPIRATORY MUSCLE WEAKNESS: A MULTI-CENTRE TRIAL

Your application to conduct the above-mentioned research in schools in the Western Cape has been approved subject to the following conditions:

1. Principals, educators and learners are under no obligation to assist you in your investigation.
2. Principals, educators, learners and schools should not be identifiable in any way from the results of the investigation.
3. You make all the arrangements concerning your investigation.
4. Educators' programmes are not to be interrupted.
5. The Study is to be conducted from **23 January 2018 till 29 September 2018**
6. No research can be conducted during the fourth term as schools are preparing and finalizing syllabi for examinations (October to December).
7. Should you wish to extend the period of your survey, please contact Dr A.T Wyngaard at the contact numbers above quoting the reference number?
8. A photocopy of this letter is submitted to the principal where the intended research is to be conducted.
9. Your research will be limited to the list of schools as forwarded to the Western Cape Education Department.
10. A brief summary of the content, findings and recommendations is provided to the Director: Research Services.
11. The Department receives a copy of the completed report/dissertation/thesis addressed to:

**The Director: Research Services
Western Cape Education Department
Private Bag X9114
CAPE TOWN
8000**

We wish you success in your research.

Kind regards.

Signed: Dr Audrey T Wyngaard

Directorate: Research

DATE: 05 January 2018

Lower Parliament Street, Cape Town, 8001
tel: +27 21 467 9272 fax: 0865902282
Safe Schools: 0800 45 46 47

Private Bag X9114, Cape Town, 8000
Employment and salary enquiries: 0861 92 33 22
www.westerncape.gov.za



Molotlegi Street, Ga-Rankuwa, Gauteng, 0208
Physiotherapy Department, Health Sciences Building
Office N219, 2nd Floor, PO Box 239, MEDUNSA, 0204
Email: anri.human@smu.ac.za; Telephone: 012 521-4047/5828

Dr. Blake

CEO of Red Cross War Memorial Children's Hospital

Re: Permission to conduct research at RCWMCH

Dear dr,

I am currently a registered PhD student at the University of Cape Town, Division of Physiotherapy. I would like to apply for permission to conduct my research at RCWMH. The topic of my study is: **The effect of mechanical insufflation-exsufflation and inspiratory muscle training on clinical outcomes and health-related quality of life in paediatric and adolescent patients with neuromuscular diseases presenting with respiratory muscle weakness: a multi-centre trial.**

This study will consist of two interventions which will take place simultaneously: Mechanical insufflation-exsufflation study (acute, hospital setting) and inspiratory muscle training (chronic, out-patient/clinic setting). Ethical clearance have been obtained from the Human Research and Ethics Committee of the University of Cape Town (HREC: 513/2015). Staff members of the Physiotherapy department at RCWMH are willing to assist with this study. Informed consent and assent from the parents and the patient will be required and they may withdraw from the study at any time without any consequences. All information will be treated with the utmost of confidentiality. I hereby attach a copy of the proposal for your perusal.

The results will be disseminated in the form of a written report to RCWMCH at the conclusion of the study.

Your positive consideration will be highly appreciated.

If you have any questions, or would like more information, please do not hesitate to contact me.

Sincerely,

Ms. A. Human (researcher)

Date



**Western Cape
Government**

Health

Dr AS Booysen
Manager: Medical Services
Email: Tony.Booyesen@Westerncape.gov.za
Tel: +27 21 658 5788 fax: +27 21 658 5166

**Dr A Human
Red Cross War Memorial Children's Hospital**

Dear Dr A Human

APPROVAL OF RESEARCH

PROJECT TITLE: THE EFFECT OF MECHANICAL INSUFFLATION-EXSUFFLATION AND INSPIRATORY MUSCLE TRAINING ON CLINICAL OUTCOMES AND HEALTH-RELATED QUALITY OF LIFE IN PAEDIATRIC AND ADOLESCENT PATIENTS WITH NEUROMUSCULAR DISEASES PRESENTING WITH RESPIRATORY MUSCLE WEAKNESS: A MULTI-CENTRE TRIAL.

It is a pleasure to inform you that approval is hereby granted to conduct the above-mentioned study at Red Cross War Memorial Children's Hospital.

Yours sincerely,

Signature Removed

Dr AS Booysen
Manager: Medical Services
Date: 18.03.16

Appendix Dv: Permission for cross-over randomised controlled trial (Gauteng)



Molotlegi Street, Ga-Rankuwa, Gauteng, 0208
Physiotherapy Department, Health Sciences Building
Office N219, 2nd Floor, PO Box 239, MEDUNSA, 0204
Email: anri.human@smu.ac.za; Telephone: 012 521-4047/5828

CEO: Dr. George Mukhari Academic Hospital
3111 Setlogelo Drive
Ga-Rankuwa
0208

Dear dr. F. Kgongwane and colleagues,

RE: Permission to conduct research at DGMAH

My name is Anri Human, I am a physiotherapist working at Sefako Makgatho Health Sciences University and am currently registered for my PhD at UCT under the supervision of profs. Brenda Morrow and Jennifer Jelsma. Hereby I would like to ask for permission to conduct research on physiotherapy management of children and adolescents with neuromuscular diseases (NMDs) at Dr. George Mukhari Academic Hospital (DGMAH). This study is a multi-centre trial, therefore we aim to collect data at both Red Cross War Memorial Children's hospital (RCWMCH) and Dr. George Mukhari Hospital in order to obtain a larger sample size, variety of patients and conditions in order for us to be able apply the findings to a broader NMD population in South Africa.

The title of the study is: The effect of mechanical insufflation-exsufflation and inspiratory muscle training on clinical outcomes and health-related quality of life in paediatric and adolescent patients with neuromuscular diseases presenting with respiratory muscle weakness: a multi-centre trial.

An effective cough is essential for secretion clearance and a weak cough is usually a strong contributor of respiratory morbidity in patients with NMDs. The aim of this study would be to identify effective, safe and cost-effective measures to optimise cough efficacy and respiratory muscle strength/function of the above mentioned patients in order to prevent morbidity and improve their overall quality of life. The study will consist of two phases: The acute/hospital phase investigates the effect of manual and mechanical cough assist techniques in NMD patients admitted to hospital due to respiratory infections, retention of secretions and a weak cough.

The second phase assesses the effect of a three month inspiratory muscle training programme as part of their home programme on children and adolescents attending the neuromuscular disease clinics at DGMAH.

For the acute phase patients with a diagnosis of NMD admitted to hospital will be recruited for the study. For phase two patients with NMDs that attend the neuromuscular disease outpatient clinic on a regular basis, as part of their follow-up management, will be recruited for the inspiratory muscle training home programme. The areas involved in the research (wards and clinic) will be informed once permission from the hospital has been granted and data collection can commence. The patient recruitment and primary data collection will be done by the primary researcher (Anri Human). The information collected by clinicians will be minimal and pertain to the daily assessment and treatment parameters of the patients. Review of patient files will be done in the wards or at the clinic respectively. The clinicians of DGMAH involved in Paediatric physiotherapy supports this research initiative, as it potentially stands to inform practice and possibly reduce treatment times, as well as improve patients' health-related quality of life.

To ensure confidentiality and privacy of patient information the various identifiable documents, including data sheets and questionnaires, will be de-identified and coded. The primary researcher will only be unblinded to allocation after completion of data analysis. Hard copies of data will be safely stored in a locked cabinet in the primary researcher's (Anri Human). Electronic information will be kept in a password protected database. The key to the data code will be kept in a separate location than the coded data collection sheets/questionnaires and access to these records will be limited to only investigators involved in the study. No identifiers will appear in any information relating to this research.

Results will be shared by means of a workshop with clinicians and specialists, presentations at local and/or international congresses as well as through publications in peer-reviewed international and national journals. A copy of the final PhD thesis will also be submitted to the CEO's office.

If you have any questions, please do not hesitate to contact either myself or my supervisors.

Kind regards

Ms. A. Human

Lecturer: Physiotherapy department

25 April 2016

Dr. George Mukhari Academic Hospital

Office of the Director Clinical Services
Enquiries : Dr. PMT Mabusela
Tel : (012) 529 3880
Fax : (012) 560 0099
Philly.Mabusela@gauteng.gov.za

To : Ms. Anri Human
: Department of Paediatrics & Child Health
: University of Cape Town
: Cape Town
: 7925

Date : 03rd June 2016

PERMISSION TO CONDUCT RESEARCH

The Dr. George Mukhari Academic Hospital hereby grants you permission to conduct research on "The effect of mechanical insufflations –Exsufflation and inspiratory muscle training on the clinical outcomes and health-related quality of life in paediatric and Adolescent patients with neuromuscular diseases presenting with respiratory muscle weakness: A multi-centre trial (PhD candidate- A Human) at Dr. George Mukhari Academic Hospital."

The hospital is aware that you have already obtained Clearance from the University of Cape Town

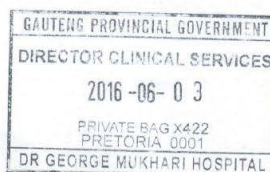
We note that you have already obtained ethical Clearance from the Human Research Ethics Committee.

- ☒ This permission is granted subject to the following conditions:
That the Hospital incurs no cost in the course of your research.
- ☒ That access to the staff and patients at the Dr George Mukhari Academic Hospital will not interrupt the daily provision of services.
- ☒ That prior to conducting the research you will liaise with the supervisors of the relevant sections to introduce yourself (with this letter) and to make arrangements with them in a manner that is convenient to the sections.

Yours sincerely

Signature Removed

DR. PMT MABUSELA
DIRECTOR CLINICAL SERVICES



Appendix Ei: Additional results from the pre-experimental, pilot (Chapter 5) and cross-over randomised controlled trial (Chapter 6)

Pre-post intervention inspiratory muscle strength (Pimax) for individual participants in pre-experimental study (n=8)

<i>Participant</i>	<i>Sex (M/F)</i>	<i>Age (years)</i>	<i>Pimax baseline (cmH₂O)</i>	<i>Pimax baseline (% pred.)</i>	<i>Pimax post-intervention (6 weeks)</i>	<i>Pimax post-intervention (6 weeks) (% pred.)</i>
1	f	17.58	33	53.22	33	53.22
2	m	11.25	37	49.07	55	72.94
3	f	9.83	23	47.37	29	59.73
4	f	9.42	40	64.63	37	59.79
5	m	15.42	51	79.13	67	103.96
6	m	16.67	20	27.06	41	55.48
7	f	13.17	34	61.07	48	86.21
8	m	8.33	65	103.75	75	119.71

Pre-post intervention inspiratory muscle strength (SNIP, PIF and S-index) for individual participants (n=8)

<i>Participant</i>	<i>Sex (M/F)</i>	<i>Age (years)</i>	<i>SNIP baseline (cmH₂O)</i>	<i>SNIP post-intervention (6 weeks)</i>	<i>PIF baseline (L/s)</i>	<i>PIF post-intervention (6 weeks)</i>	<i>S-index baseline (cmH₂O)</i>	<i>S-index post-intervention (6 weeks)</i>
1	f	17.58	14	31	1	1.8	21	34
2	m	11.25	71	40	2.1	2.6	38	47
3	f	9.83	22	27	0.7	1.1	15	23
4	f	9.42	15	15	0.6	1.5	15	31
5	m	15.42	43	67	1.5	3.4	28	62
6	m	16.67	32	35	0.6	3.8	14	67
7	f	13.17	40	34	1.1	1.4	22	27
8	m	8.33	60	74	2	2.3	38	44

**Pulmonary function: pre-intervention data based on recruitment site and group allocation for RCT
(n=23)**

Variable	All participants (n=23)	DGMAH (Gauteng) (n=12)	RCWMCH (Western Cape) (n=11)	Study cite (p- value)	Group 1 (ce) (n=10)	Group 2 (ec) (n=13)	Allocation (p-value)
VC (absolute value) (n=19)	1.42 (±0.40)	1.57 (0.38)	1.16 (0.31)	0.03	1.60 (±0.32) (n=8)	1.28 (±0.41) (n=11)	0.09
FVC (absolute value)	1.55 (±0.46)	1.62 (±0.46)	1.47(±0.48)	0.47	1.56 (±0.28)	1.54 (±0.58)	0.95
FVC Z-score	-4.03 (-5.19 to - 2.94)	-3.93 (-4.91 to - 2.86) [#]	-4.03 (-5.19 to - 3.30)	0.74*	-3.39 (-4.53 to -2.94)	-4.38 (- 5.29 to - 3.30)	0.28*
FEV₁ (absolute value)	1.34 (±0.42)	1.43 (±0.36)	1.23 (±0.47)	0.25	1.33 (±0.40)	1.34 (±0.45)	0.93
FEV₁ Z-score	-3.47 (±1.56)	-3.26 (±1.30)	-3.69 (±1.84)	0.52	-3.10 (±1.62)	-3.78 (±1.50)	0.29
PEF	189.09 (±78.50)	217.50 (±80.96)	158.09 (±65.73)	0.07	197.00 (±68.63)	183.00 (±87.59)	0.68
Pimax (absolute value)	40.57 (±24.46)	51.67 (±27.68)	28.45 (±12.80)	0.02	47.50 (±24.51)	35.23 (±23.98)	0.24
Pimax predicted values (%)	60.40 (±35.59)	75.54 (±40.55)	43.89 (±20.06)	0.03	70.62 (±34.47)	52.55 (±35.74)	0.24
SNIP (absolute value)	47.09 (±24.49)	57.83 (±25.48)	35.36 (±17.76)	0.02	57.10 (±25.56)	39.38 (±21.48)	0.09
PECF (n=23)	200.87 (±94.18)	243.33 (±92.28)	154.55 (±74.98)	0.02	200.50 (±94.89)	201.15 (±97.51)	0.99

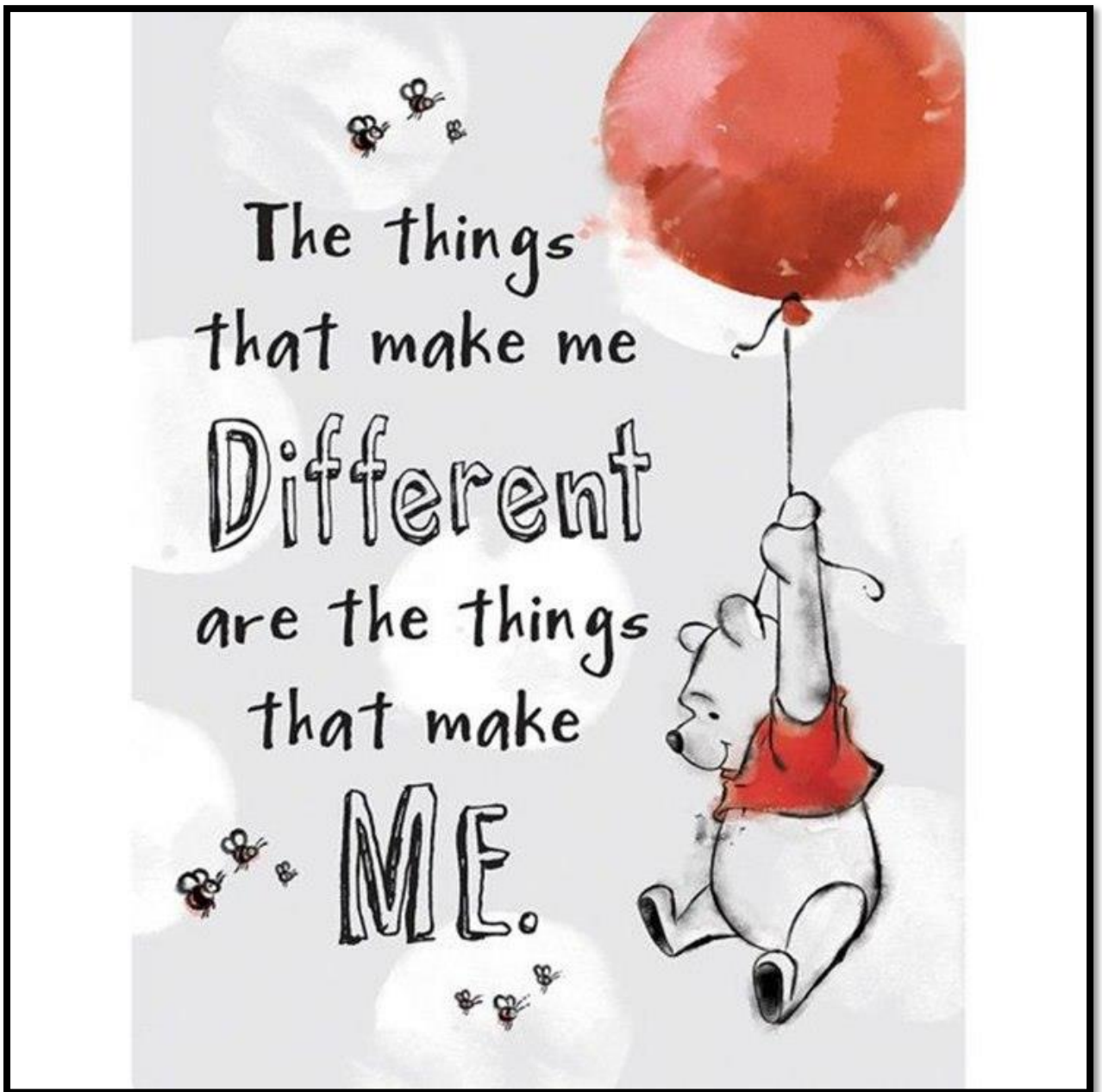
Values are expressed as mean (±SD); [#]=median (IQR); *Mann Whitney U.

Spirometry values from recruitment to post monitoring based on group allocation

	Baseline (recruitment)	Pre-intervention (IMT)	Post-intervention	Post three-month monitoring
Group 1 (ce)				
VC (n=8)	1.53 (±0.26)	1.60 (±0.32)	1.47 (±0.39)	1.47 (±0.82) (n=9)
FVC (n=10)	1.65 (±0.48)	1.56 (±0.28)	1.45 (±0.41)	1.53 (1.34-1.85)
FEV ₁ (n=10)	1.44 (±0.33)	1.33 (±0.40)	1.33 (±0.35)	1.39 (±0.37)
PEF (n=10)	197.100 (±51.00)	197.00 (±68.63)	169.90 (±49.16)	189.70 (±50.49)
PECF (n=9-10)	195.56 (±106.55)	200.50 (±94.88)	240.00 (±111.83)	221.50 (±122.70)
Pimax (n=10)	41.90 (±21.43)	47.50 (±24.51)	61.50 (±23.97)	60.40 (21.64)
SNIP (n=10)	45.10 (±22.06)	57.10 (±25.56)	55.60 (±24.74)	50.30 (±17.57)
Group 2 (ec)				
VC (n=11)	1.28 (±0.41)	1.28 (±0.41)	1.32 (±0.38)	1.42 (±0.53)
FVC (n=13)	1.54 (±0.58)	1.54 (±0.58)	1.54 (±0.46)	1.60 (1.28-1.64)
FEV ₁ (n=13)	1.34 (±0.45)	1.34 (±0.45)	1.41 (±0.39)	1.40 (±0.38)
PEF (n=13)	183.00 (±87.59)	183.00 (±87.59)	202.38 (±73.26)	193.92 (±68.50)
PECF (n=13)	201.12 (±97.51)	201.15 (±97.51)	236.92 (±88.47)	207.69 (±104.99)
Pimax (n=13)	35.23 (±23.98)	35.23 (±23.98)	50.23 (±31.05)	51.31 (±25.64)
SNIP (n=13)	39.38 (±21.48)	39.38 (±21.48)	55.69 (±23.47)	51.54 (±21.93)

Summary of pulmonary function and child reported HRQoL based on the different periods (baseline, pre-intervention, training (indicated in yellow) and non-training (indicated in green)) to be used for meta-analysis in systematic reviews.

Group 1 (ce) (n=10)									Group 2 (ec) (n=13)							
Timeframe	VC (n=8)	FVC	FEV ₁	PEF	PECF (n=9;10)	Pimax	SNIP	Child PedsQL total (n=9;10)	VC (n=11)	FVC	FEV ₁	PEF	PECF	Pimax	SNIP	Child PedsQL total
Baseline (recruitment)	1.53 (±0.26)	1.65 (±0.48)	1.44 (±0.33)	197.100 (±51.00)	195.56 (±106.55)	41.90 (±21.43)	45.10 (±22.06)	58.76 (17.54)	1.28 (±0.41)	1.54 (±0.58)	1.34 (±0.45)	183.00 (±87.59)	201.12 (±97.51)	35.23 (±23.98)	39.38 (±21.48)	64.05 (±18.10)
Pre-intervention	1.60 (±0.32)	1.56 (±0.28)	1.33 (±0.40)	197.00 (±68.63)	200.50 (±94.88)	47.50 (±24.51)	57.10 (±25.56)	65.96 (±16.46)	1.28 (±0.42)	1.54 (±0.58)	1.34 (±0.45)	183.00 (±87.59)	201.15 (±97.51)	35.23 (±23.98)	39.38 (±21.48)	64.05 (±18.10)
Period 1 (End of first arm/12 weeks (3 months) of study)	1.60 (±0.32)	1.56 (±0.28)	1.33 (±0.40)	197.00 (±68.63)	200.50 (±94.89)	46.70 (±25.15)	56.90 (±25.88)	65.96 (±16.46)	1.32 (±0.38)	1.55 (±0.46)	1.41 (±0.39)	202.38 (±73.26)	236.92 (±88.47)	50.23 (±31.05)	55.69 (±23.47)	70.78 (±17.69)
Period 2 (End of second arm/12 weeks (3 months) of the study)	1.47 (±0.39)	1.45 (±0.41)	1.33 (±0.35)	169.90 (±49.16)	240.00 (±111.83)	61.50 (±23.97)	55.60 (±24.74)	68.67 (±15.75)	1.42 (±0.53)	1.66 (±0.72)	1.40 (±0.38)	193.92 (±68.50)	207.69 (±104.99)	51.31 (±25.64)	51.54 (±21.93)	73.53 (±15.07)
Mean difference (95% CI)	-0.21 (0.24- 0.73)	-0.01 (0.53- 1.40)	0.11 (0.34- 0.90)	-27.00 (66.19- 175.68)	23.00 (39.55- 104.98)	8.40 (18.83- 49.97)	-13.5 (17.05- 45.26)	-2.38 (15.03- 39.89)	-0.06 (0.35- 0.87)	-0.11 (0.39- 0.89)	0.08 (0.15- 0.34)	27.84 (29.54- 68.00)	65.00 (50.75- 116.82)	13.92 (15.15- 34.87)	19.38 (19.62- 45.16)	4.01 (13.88- 31.96)



"No country can claim to have achieved universal healthcare if it has not adequately and equitably met the needs of those with rare diseases"

Rare Diseases SA.