Analysis of The Demographics, Pathways to Diagnosis, Burden of Disease and Long-term Outcomes of Patients with Spinal Muscular Atrophy Managed at Red Cross War Memorial Children's Hospital

By

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LIST OF ABBREVIATIONS

AR	**Autosomal recessive**
DNA	**Deoxyribonucleic acid**
PEG	**Percutaneous endoscopic gastrostomy**
RCWCH	**Red Cross War Memorial Children's Hospital**
SA	**South African**
SMA	**Spinal muscular atrophy**
SMN	**Survival motor neuron**

Analysis of The Demographics, Pathways to Diagnosis, Burden of Disease and Long-term Outcomes of Patients with Spinal Muscular Atrophy Managed at Red Cross War Memorial Children's Hospital

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Abstract

Spinal muscular atrophy (SMA) is an autosomal recessive disorder of anterior horn cell degeneration which results in symmetrical muscle weakness that affects multiple systems. This study was conducted to determine the burden of disease of SMA on children under the neuromuscular service at Red Cross War Memorial Children's Hospital. A quantitative retrospective audit identified 86 DNA confirmed patients with SMA who attended the service from 2000 to August 2023. Thirty-six medical folders were accessible, 6 were excluded and 50 had been destroyed. An in-depth analysis of 30 folders showed a median age of diagnosis of 3.5 months for SMA1 (4 patients), 19 months for SMA2 (17 patients) and 34 months for SMA3 (9 patients). Five patients had demised and 4 were transferred to adult services. Over the study period, 172 chest infections were reported among the 30 children with SMA. Forty-three percent required home ventilation, 70% had scoliosis, 70% had contractures, 33% received feeding support via a percutaneous endoscopic gastrostomy tube and 44% of SMA3 patients had lost ambulation. Our SMA numbers are less than expected and delays in diagnosis were common. Strategies to improve diagnosis and minimize delays are needed and retaining medical records will provide more comprehensive insights on the long-term outcomes.

Keywords: spinal muscular atrophy, burden of disease, neuromuscular database, children, South Africa

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1. Introduction

The earliest academic record of Spinal muscular atrophy (SMA) was described by Guido Werdnig in two infant brothers in the late 1800s.[1] SMA is now accepted as an autosomal recessive (AR) disorder of alpha motor neuron degeneration in the anterior horns of the spinal cord that results in symmetrical muscle weakness and atrophy, due to homozygous deletion or mutation of the survival motor neuron 1 (*SMN1*) gene on chromosome 5q13 accounting for 95% of SMA cases.[2] The SMA affected individual is dependent on a limited amount of functional SMN protein which is mainly determined by the varying copy numbers of *SMN2* genes: although not decisive, in most cases a higher copy number clinically correlates with milder SMA phenotypes.[3]

Affecting all population groups, SMA is the second most common AR disorder after cystic fibrosis with an estimated incidence of 1 in 6000 to 1 in 10 000 and a carrier rate of 1 in 35.[4,5] Globally, studies show that SMA is more common in population groups of European descent than those of African descent.[6,7] These findings have also been observed in the South African (SA) population. A study by Labrum *et. al* found that SMA is more common within the SA population than previously considered, with a carrier rate of 1 in 50 and a predicted birth incidence of 1 in 3574 in the African population, and a carrier rate of 1 in 23 and a predicted birth incidence of 1 in 1945 in the European ancestry population.[8]

SMA is a neurodegenerative disorder that is associated with multiple physical complications. Respiratory complications from muscle weakness are a significant cause of morbidity and mortality and non-ambulant patients are at increased risk of developing contractures (occurring frequently and more prevalent in the lower limbs than the upper limbs), hip subluxation or dislocation and scoliosis due to weakness of the axial muscles.[9] With scoliosis being present in 60-95% of patients, spinal surgery is the recommended therapy for non-ambulant patients with a Cobb angle (spinal curvature) greater than 20%.[9,10] Untreated, scoliosis exacerbates chest wall deformities which further restricts pulmonary function, compromises sitting and balance and increases the risk of gastrointestinal reflux.[10–12] Reflux together with bulbar dysfunction increases risk of aspiration further compromising respiratory function. This patient group is also at risk of both obesity and undernutrition. Regular feeding, swallowing and nutritional assessments reduce nutritional deterioration overtime which subsequently improves quality of life and survival.[13] Specialised enteral devices to optimize nutrition were reported in 28% of children with SMA in a retrospective study at Boston's Children hospital. In the same cohort, 37% of children were on mechanical ventilation.[13] Appropriate multidisciplinary management of all these interlinked complications begins with understanding the burden of disease in the population of children with SMA in our setting, which has not been previously studied.

Studies done in populations of European descent show that SMA1 is the most common phenotype (about 50% of patients),[14] however studies in populations of African descent confirming these findings are limited. A study done in Cuba found a lower incidence of SMA1 in populations of African ancestry compared to those of European ancestry.[15] No studies looking at this specific variable have been done in Sub-Saharan Africa. We suspect many SMA1 children in South Africa are not detected most likely due to demise from respiratory complications prior to diagnosis. We believe there is also a delay in the diagnosis of SMA2 and SMA3 as many patients in South Africa still have poor access to healthcare. It is also important to note that the presentation and

focus of care for these patients is often related to the complications of the disease rather than the underlying weakness: SMA patients are typically managed for respiratory infections and unless carefully assessed an underlying motor disorder can be missed, especially in the acute setting. This study explores the burden of disease of this multisystem disorder in our community─ by measuring mortality, morbidity and social impact─ with the intent to optimize patient management. Understanding the referral pathways that SMA affected patients take will be used to identify ways to reduce delays in diagnosis and enable timeous interventions. Understanding the long-term outcomes of this population will strengthen support for the ongoing needs of these patients.

2. Methodology

Red Cross War Memorial Children's Hospital (RCWMCH) is the only tertiary hospital in sub-Saharan Africa dedicated to paediatric care. Patients from the public sector who cannot be managed at primary level care are referred to secondary level care and escalated to tertiary level care if further assessment and management is required. If critically ill, patients are referred or present directly to tertiary level care. The neuromuscular service is run by specialists in the Paediatric Neurology department. Patients are referred to the services from public and private hospitals in the Western Cape, the rest of South Africa and neighbouring countries. Definitive diagnosis of SMA is possible via genetic analysis available both in tertiary state centres and via private resources. The neurology clinicians coordinating the neuromuscular service operate a multidisciplinary service including rehabilitation, ancillary, pulmonology, orthopaedic and counselling support for genetics via the non-government organization social workers of the Muscular Dystrophy Foundation of South Africa. The service is unique through its support from a donor-funded specialist nurse-led tracheostomy initiative called Breatheasy. This programme empowers parents to care for children with tracheostomies or children utilising non-invasive ventilation at home. For patients with severe SMA (or those needing 24-hour care) who meet specific requirements stipulated by the government, the South African Department of Social development offers a care dependency grant that amounts to R2190 per month.[16]

A quantitative retrospective audit of patients with SMA registered in the RCWMCH database/ neuromuscular service from 2000 to August 2023 was conducted. Folders with insufficient information (inadequate medical records or lost records) were excluded from the study. Data collected from medical files was imported to REDCap (a Research Electronic Data Capture tool hosted at the University of Cape Town [REDCap, Vanderbilt University, Nashville, TN, USA]), and exported to a password protected Microsoft Excel spreadsheet for analysis. The proportions and measures of spread were reported. Data collection focused on patient demographics, referral patterns, disease burden and outcome. Red Cross Children's Hospital neuromuscular clinic follows international standard of care for management of patients with SMA, however unable to offer gene therapy as it is not available. The following terminology was adopted for the report: type 1 SMA equated to SMA1, type 2 SMA to SMA2 and type 3 SMA to SMA3. Diagnostic delay is defined as the mean age of onset/symptom recognition subtracted from the mean age of diagnosis. Ethical approval was obtained from the Human Research Ethics Committee of the University of Cape Town (HREC REF: 097/2023).

3. Results

The RCWMCH neuromuscular database had a total of 7732 patients, who attended the service from 2000, by August 2023. Figure 1 details the flow diagram of the patients recruited in the SMA audit. Seven hundred and twelve patients (9%) had neuromuscular disease of which 86 had DNA confirmed SMA. Twenty had SMA1, 51 SMA2 and 15 SMA3. Forty-three percent of patients were female with a male to female ratio of 1.3:1. Out of 86 DNA confirmed patients, 36 patient folders were available for detailed review. Thirty patients had complete records and in-depth data analysis (including 6 patients of European ancestry, 13 indigenous African patients and 11 patients of mixed-race ancestry) and 6 had inadequate records as they were loss to follow-up (two patients from neighbouring countries, 1 out of province and 3 out of town[1]). The remaining 50 folders had been destroyed (patients over the age of 21years and patients who have not attended clinic/hospital within 5 years of last visit). Twenty-one patients from the 30 complete folder reviews are actively attending the neuromuscular clinic (age range of 3- 20 years with a median age of 11 years); 5 had demised (4 SMA1 and 1 SMA2) and 4 transferred to adult services (3 SMA2 and 1 SMA3). Eight of these 30 patients had a positive family history of SMA with one affected sibling. There were three deaths from the partially reviewed folders (2 SMA1 and 1 SMA2) and our electronic records system documented 19 deaths from the destroyed folders (9 SMA1 and 10 SMA2). This is likely an underestimation. We suspect that the remaining SMA1 patients, all born before 2010, would have demised: natural history studies of SMA1 show that the median age of death is < 1year.[17] Even with limited information regarding the outcomes of the unaccounted SMA2 and SMA3 patients, the mortality was still high at 37% (20 SMA1 and 12 SMA2/ 86).

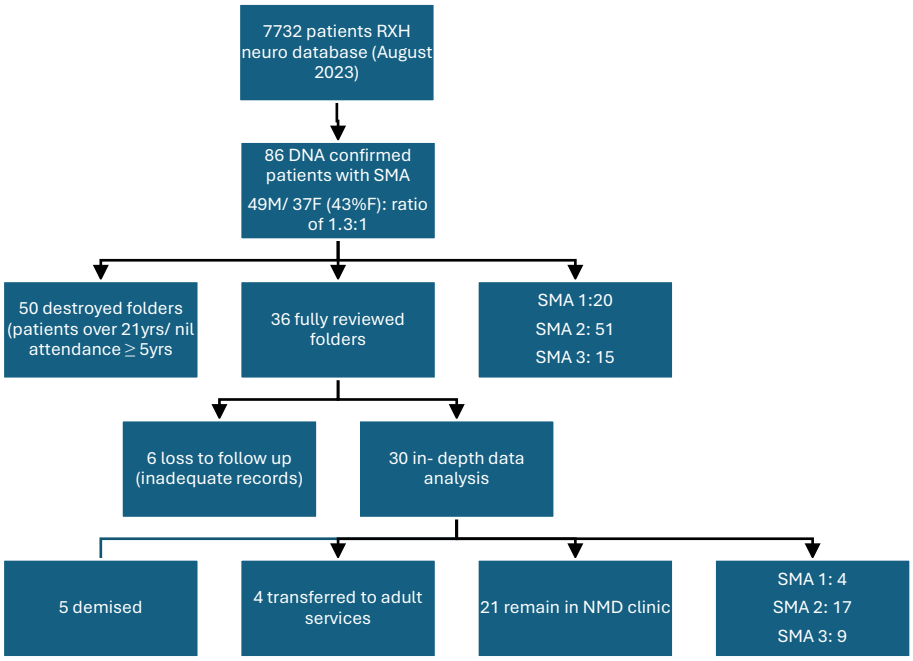


Fig. 1. Flow diagram showing a breakdown of patients with SMA in the RCWMCH neuromuscular database.

[1] Atlantis: 40 kilometers north of Cape Town, Paarl: 60 kilometers northeast of Cape Town, Oudtshoorn: in the Klein karoo 420 kilometers east of Cape Town.

In-depth analysis of 30 folders found a median age of diagnosis of 3.5 months for SMA1, 19 months for SMA2 and 34 months for SMA3. There was a 3.25 month diagnostic delay for SMA1, 10.7 months for SMA2 and 18 months for SMA3. Diagnostic delays are compared with other studies in table 3 in the discussion. Half of the patients were referred from tertiary (n=11, 37%) and regional centres (n=4, 13%). The rest were equally referred (n=5, 17%) from the orthopaedic clinic, private practice and level 1 health care institution. The primary presenting complaint was delayed milestones (mainly gross motor), and those patients initially referred to the orthopaedic clinic (those with SMA3) had complaints of frequent falls or abnormal gait. Most patients were of low socioeconomic status as represented by the graph below.

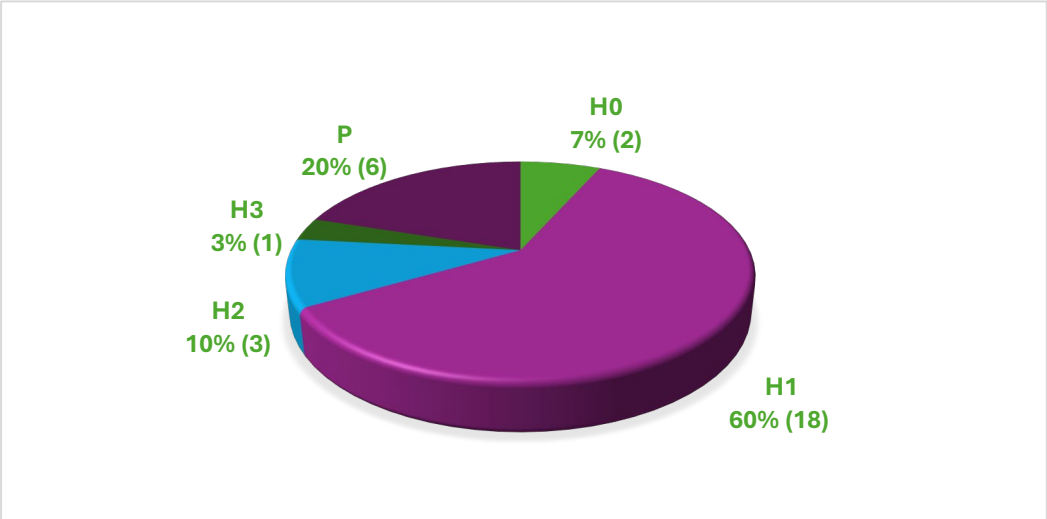


Fig. 2. Socioeconomic status of children with SMA. Facility fees are adjusted according to income, ranging from the most marginalized patients who pay no facility fees (H0) to patients who are privately funded by medical schemes. H0: no facility fees/ a family unit receiving social grants, H1: +/- 40% of facility fee/ a family unit with an income of < R8333 a month, H2: +/- 60% of facility fee/ a family unit with an income between R8333- R29166, H3: full facility fee/ a family unit with an income >R29166, Private: a family unit funded by private medical schemes.

Mortalities: All SMA1 patients from the fully reviewed folders died from respiratory failure (n=4, 13%). Without intervention, two of these patients died within the expected median age of < 1 year. The other two patients who were on home non-invasive ventilation had a varied life-expectancy of 3 and 6 years. The fifth death from the fully reviewed folders was a patient with SMA2 who died at 14 years of age, shortly after receiving corrective scoliosis surgery. From the partially reviewed folders, 1 SMA2 patient (from the neighbouring country of Namibia) died at the age of 10 in his sleep at home. There was no history of preceding illness. We presume the 2 SMA1 patients from the partially reviewed folders died from respiratory failure within the expected median age. One patient was referred from Paarl and the second patient was last seen at the RCWMCH neuromuscular clinic at 10 months of age. This patient resided in Angola and was referred to the service via clinicians in Namibia. Some of the mortality data from the destroyed folders was extracted from isolated electronic documents and from the clinical staff directly involved in patient care. This includes a patient with SMA2 from Kenya who entered the RCWMCH service at the age of 2 years. She returned to Kenya with a percutaneous endoscopic gastrostomy (PEG), tracheostomy and non-invasive ventilation and died at home at 7 years of age from respiratory failure. There were two untimely deaths of SMA2 children who died at the age of 5 years on the school bus at different times, presumably from an obstructed airway on route to school.

Respiratory: There was a total of 172 chest infections recorded among children with SMA within the study period: 21 chest infections (12,2%) amongst SMA1 patients; 142 chest infections (83%) amongst SMA2 patients and 9 (5,2%) amongst SMA3 patients. Fifty-eight percent (n=101) required hospital admission of which 5.8% (n=10, 4 SMA1 and 6 SMA2) required ICU admission. Fifty-two percent (n=89) of chest infections were within the first 5 years of life. For SMA2 patients, there was an average of 10 infections per year between 0-5 years (n=61), 10 infections per year between 6-10 years (n=50), and 4 infections per year between 11-18 years (n=31). Thirteen (43%) patients were on home ventilation of which one required ventilation for more than 16 hours a day.

Table 1a
Number of chest infections per patient according to type of SMA age 0-5yrs.
Two-thirds of <1 chest infections are from patients with the severe SMA1 phenotype. Due to early demise, SMA1 patients are not represented in the later years.

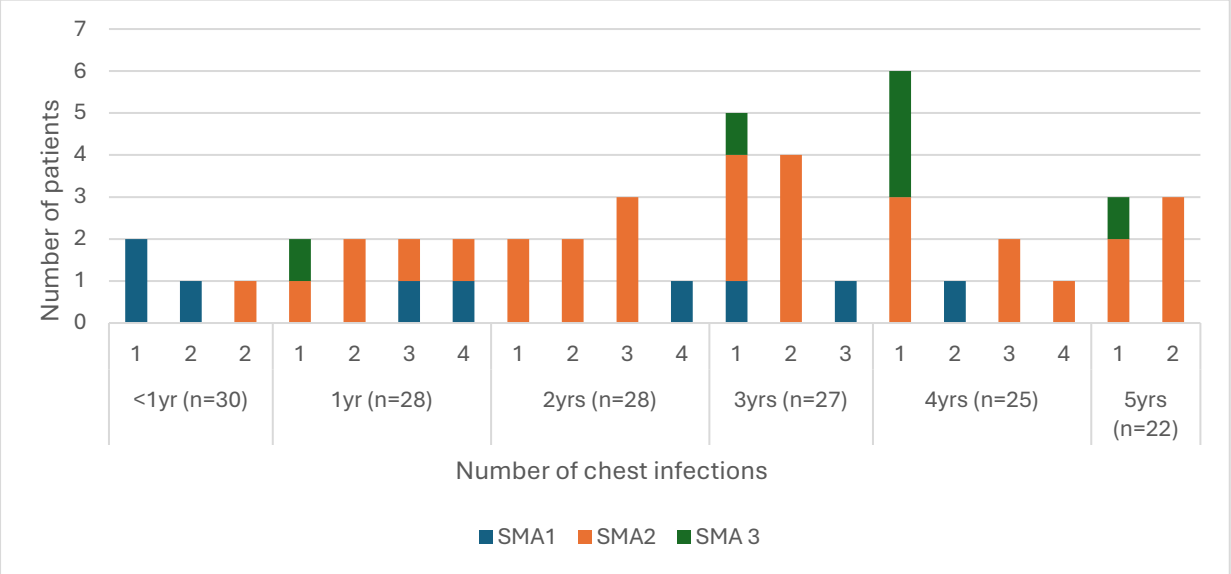


Table 1b
Number of chest infections per patient according to type of SMA age 6-10yrs.

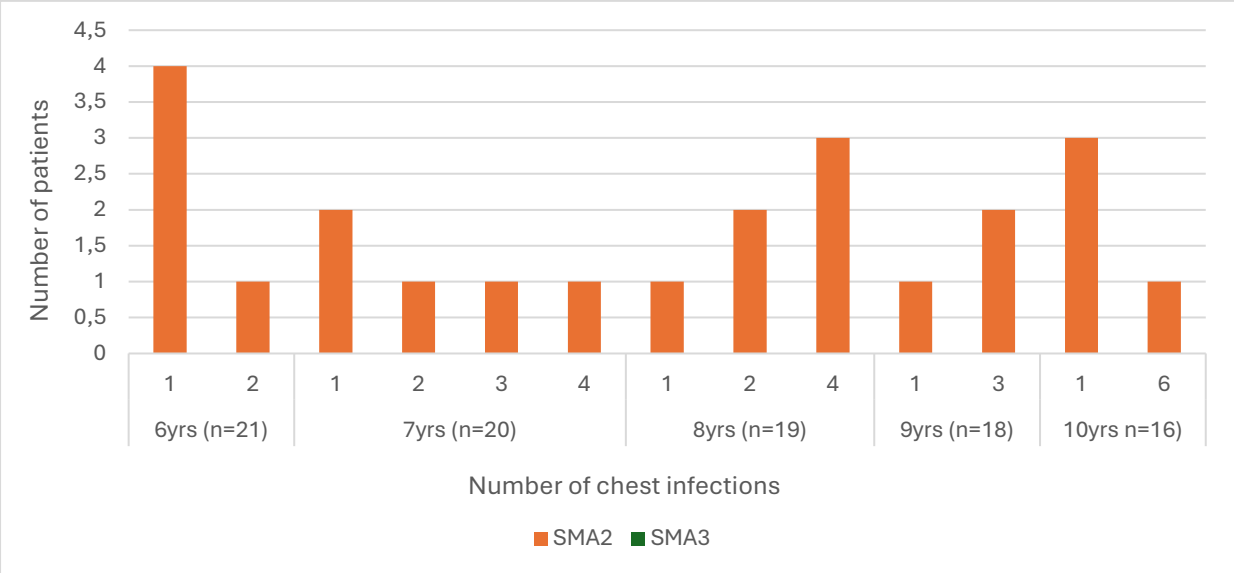
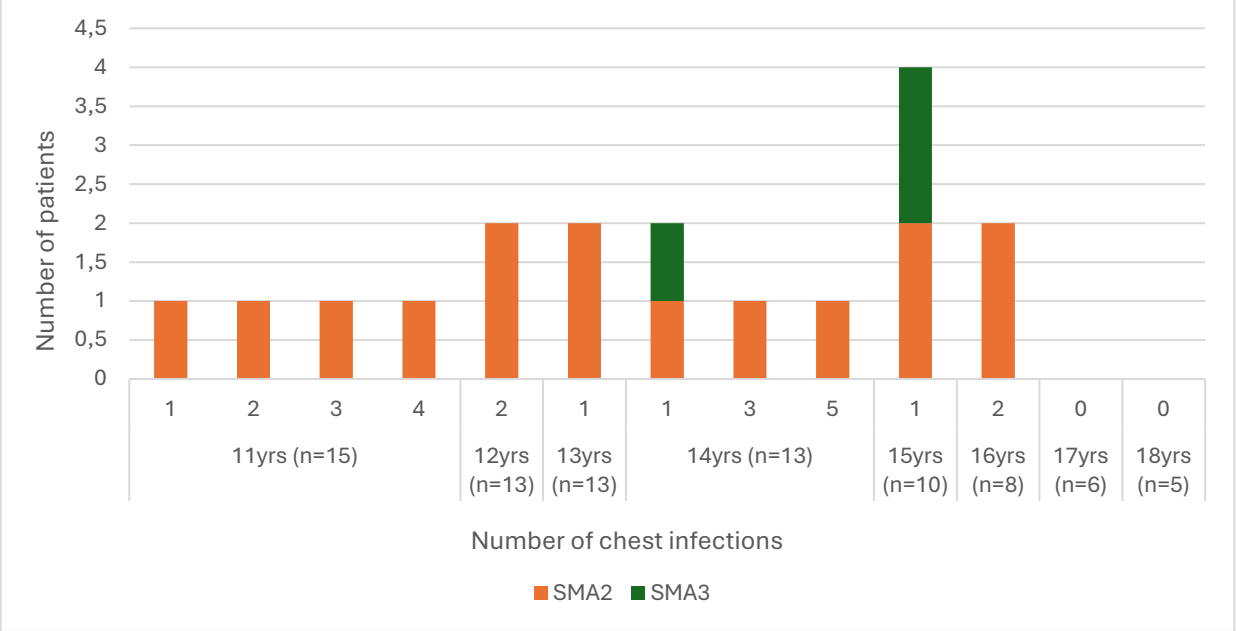


Table 1c
Number of chest infections per patient according to type of SMA age 11-18yrs.



Musculoskeletal complications: 21 (70%) patients (15 SMA2 [71%] and 6 SMA3[29%]) had scoliosis at the time of analysis of which 6 (29%) underwent corrective surgery. Other associated musculoskeletal complications included contractures predominantly affecting the lower limbs in 70% (n=21) of patients (15 SMA2 [71%], 5 SMA3 [24%] and 1 SMA1 [5%]). There was an 86% (n=18) overlap between patients with scoliosis and contractures. One patient with SMA2 had had previous bilateral hip dislocations. At the time of review 4/9 (44%) patients with SMA3 had lost ambulation of which 3 (33%) were using a wheelchair and 1 (11%) a scooter. The median age of loss of ambulation was 10.5 years.

Nutrition: A notable proportion (n=12, 40%) of patients with SMA were failing to thrive including those who were severely wasted (1 SMA1, 7 SMA2, 4 SMA3), 10% were overweight (n=3, 2 SMA2 and 1 SMA3) and the remainder (n=15, 50%) had a normal weight for age. One third of patients (n=10, 33%) were receiving feeding support via a PEG.

Social: 19 (63%) SMA patients received a care dependency grant. Two patients had applied and were awaiting approval, 6 patients did not meet the financial qualifying criteria (patients with access to medical aid), 1 patient was not a South African citizen and 2 patients with SMA3 did not meet the physical criteria as they were independent for activities of daily living and ambulant. Most patients (21/22, 95%) of school going age were placed. The patient not attending school at the time of analysis was awaiting special needs school placement. Fourteen (67%) patients attended special needs school (1 SMA1, 11 SMA2 and 2 SMA3), 6 (29%) patients (all SMA3) attended mainstream school and 1 (5%) SMA2 child was home-schooled. With regard to activities of daily living, all SMA2 patients (n=17) required assistance in all areas, except for feeding where 12 (71%) patients were feeding independently. Four (44%) SMA3 patients were independent in toileting, 3 (33%) in bathing and dressing and 2 (22%) in transferring. All SMA3 (n=9) patients were feeding independently.

Table 2: Transitioned patients: 4 SMA patients (3 SMA2 and 1 SMA3) were transitioned to adult services.

SMA Type	Age of Transition	Burden of disease	Social outcome
2	14yrs	Home ventilation/ severe scoliosis (pre-surgery)/ contractures/ PEG	Private patient studying computer science
2	15yrs	Scoliosis surgery at 13yrs/ contractures	Private patient, social outcome unknown, however still attending adult services.
2	18yrs	Scoliosis surgery at 11yrs/ contractures	H1 patient who won a disability National pageant in 2021
3	15yrs	Scoliosis (pre-surgery)/ contractures/ lost ambulation at 10yrs. Mobilizing with a wheelchair	H1 patient who became a mother

4. Discussion

This is the first comprehensive SA long-term follow-up review analysing the demographics, referral pathways and burden of disease of children with SMA. A systematic review published in 2015 found that delays in the diagnosis of SMA are common and that there is a direct correlation between severity of disease (type of SMA) and time to diagnosis: the more severe the disease, the shorter the diagnostic delay [18] which is also true for our study. A more serious and life-threatening phenotype demands a more urgent diagnosis. However, despite SMA1 being the most common and severe paediatric phenotype, the proportion in our patient group was far less (20/86=23%). We speculate that the major proportion of SMA1 affected infants in our setting are not recognized or referred and presumedly die from respiratory infections before a diagnosis is considered. The absence of patients with type 0 SMA in our database is likely due to its rarity and early demise of patients in the neonatal period prior to diagnosis or prior to a neurology consultation. Table 3 compares our study's diagnostic delays with two different studies.[18,19]

Table 3: A comparison of symptom onset, SMA diagnosis and diagnostic delay between our population group and two previous studies.

	SMA1	SMA2	SMA3
Our study: mean age of onset in months (range)	0.5 (0-1)	10.3 (6-15)	25 (14-6 years)
Mean age of diagnosis in months (range)	3.75 (0-8)	21 (9-42)	43 (16-8 years)
Diagnostic delay	3.25	10.7	18
2015 Review: mean age of onset in months (range)	2.5 (1-11)	8.3 (2-18)	39 (5-16 years)
Mean age of diagnosis in months (range)	6.3 (0.6-9)	20.7 (1.2-6 years)	50.3 (3.0-6.8 years)
Diagnostic delay	3.6	12.4	11.3
2020 Review: mean age of onset in months (range)	2.75 (0-10)	10 (3-24)	32 (9-15 years)
Mean age of diagnosis in months (range)	4.7 (10 days- 13.2)	15.6 (5- 4.41years)	4,34yrs (10-18 years)
Diagnostic delay	1.95	5.6	20

A factor that might influence diagnostic delays in our population group is our referral pathways. The local clinic is the first point of medical contact for most of our patients. Sometimes this pathway is bypassed, and diagnosis potentially made earlier, when patients present in crisis (usually with a severe lower respiratory tract infection) directly to a tertiary institution where there is access to paediatricians who are more equipped in identifying muscle weakness and quick to refer to the appropriate discipline for further assessment. Improving developmental milestone screening at the local clinic (and all levels of care) is one of the strategies that would allow for earlier identification of symptoms and earlier referral to institutions that have access to genetic testing. However, this does not guarantee an expedited diagnosis since SMA might not be considered by medical professionals who lack experience in paediatric diseases. This is evident in the inappropriate referrals to orthopaedic clinics for a presumed orthopaedic diagnosis and missed opportunities in the acute setting when patients present with other medical conditions which may or may not be related to the neuromuscular disease. As most of our patients are of low socioeconomic status, financial constraints are an additional contributor to delayed health seeking behaviours which further delay diagnosis, especially for health conditions that may not appear to be life-threatening. Patients wait to receive a grant at the end of the month to afford travel to both clinics and hospitals during the process of investigation and diagnosis. A way to minimize the travel burden and reduce diagnostic delays (including eliminating the wait for the next available neurology clinic date at a tertiary centre) is to empower the local setting with clinicians who have the training experience to identify pathology quickly and expedite genetic testing. Earlier diagnosis would be of great benefit as it enables earlier implementation of supportive measures that decrease the rates of respiratory complications and slow down musculoskeletal deterioration. Newborn screening avoids many of these diagnosis delaying steps, however the expense of implementing such is difficult to justify when disease modifying therapies are not yet available in a health system that already has limited resources.

Non-invasive ventilatory methods are an effective supportive intervention that improve survival and quality of life.[20,21] However this adds a significant economic burden, as living longer means ongoing access to health care facilities and care-giver dependency. A study conducted in Germany in 2016, which looked at SMA patients between the age of 0-73 years, found the mean direct cost of illness per patient per year to be 14 times more than the average health costs per patient.[22] Patients with SMA1 have the highest total cost of illness per patient per year compared to patients with SMA2 and SMA3. This includes medical costs (such as inpatient and outpatient medical costs, respiratory management and rehabilitation) and non-medical costs such as travel expenses and caregiver costs. The indirect medical costs are also significant, leading to loss of economic productivity when clinical deterioration ensues in patients with SMA3, and limited careers and productivity in parents who have children with SMA1 and SMA2. As most of our patients are of low socio-economic status, those who are employed are working in low paying jobs that provide little to no benefits and often unaccommodating to regular absenteeism. This further limits employment options and perpetuates the cycle of poverty as parents leave their jobs and rely on a meagre care-dependency grant to look after an entire household. In our study, we have a small number of patients with SMA1 surviving up to the age of 6 years with respiratory support. Patients with SMA2, who are weaker than patients with SMA3, are those who present the overall largest burden of respiratory chest infections, musculoskeletal complications and nutritional abnormalities.

The life expectancy of SMA inversely correlates with disease type. Without respiratory support, patients with SMA1 rarely live beyond 2 years.[23] Those with milder phenotypes survive into school years and adulthood requiring transitioning from paediatric to adult services. Some of the challenges facing transition include anxiety concerning unfamiliar health professionals, unfamiliar hospital environments, and adult services being ill-equipped to support home ventilation programs. Placement options for patients desiring to move out of home are also limited. For patients surviving into school years, education is an important part of development and social integration. Children with SMA in general have no cognitive impairment, therefore preservation of cognition via education is encouraged to improve independence and quality of life. The SA Schools Act encourages children with disabilities to enroll in ordinary public schools,[24] however admission criteria in these schools is often discriminatory or exclusionary.[25] Alternatively, special school placement for children with physical disabilities is limited and waiting lists can be long. Although our constitution advocates for inclusive, quality and free primary and secondary education for people with disabilities, this is not always the reality.[25] It is encouraging to see that most children with SMA in our study were placed at schools. It would be interesting to see how many of these patients (if they survive into adulthood) are able to find employment in their adult years.

Life expectancy for some of the SMA2 patients in our population group however has been dramatically shortened, including the unexpected death of the patient who had scoliosis surgery. Although identified as an anaesthetic related death, it is important to consider the *SMN2* mis-splicing effects of stresses (such as starvation, temperature changes and hypoxia) which further reduce functional SMN protein and exacerbate disease pathology in an already vulnerable peri-operative period.[26] On a background of mitochondrial dysfunction and therefore abnormal fatty acid oxidation leading to inefficient energy generation,[27] optimal nutritional management is especially important during catabolic states to prevent fatigue which worsens muscle weakness and negatively impacts recovery. The burden of scoliosis is high (70% in our population group) and inevitable with progressive axial muscle weakness. The more severe phenotypes of SMA are associated with earlier, more severe, and rapidly progressive scoliosis with an earlier age of surgical intervention.[10] Non-surgical management options (such as physiotherapy) can delay the inevitable progression of spinal curvature and allow the skeleton to mature for surgical treatment.[9,28] Studies support the benefits of corrective surgery, but a better understanding and management of the metabolic disorders associated with SMA will aid in minimizing peri-operative risks and assist in providing better care during other catabolism inducing states.

Tracheostomy and long-term mechanical ventilation remains a contentious issue and often discouraged (especially for patients with SMA1 and considered on an individual basis for patients with SMA2) in both high income countries and particularly in resource limited settings like SA, due to ethical considerations of cost, health care capacity, family burden and quality of life.[29] The Breatheasy tracheostomy program has made tracheostomies accessible for under-privileged children by equipping the caregiver with the necessary skills to manage a child with a tracheostomy at home.[30] As evidenced by the premature deaths of the two 5 year old

children on the school bus, the reality is that some SMA patients in our population group (those of low socioeconomic status) fail to consistently receive the support which might be regarded as standard in more resource equipped settings. This has an impact on their projected life expectancy. The burden of care is especially demanding for patients with proximal muscle weakness and a tracheostomy. Weak intercostal muscles impair the ability to cough making bronchial secretion clearance difficult.[31] Coupled with severe head lag, the risk of airway obstruction is high. Patients require constant supervision and are completely dependent on carers who are trained in airway management to help them with head positioning and to clear secretions. Patients are also dependent on carers for physical movement. Despite physiotherapy attendance, the high percentage of contractures reflects inadequate support in physical movement. Limits to comfortable and appropriate seating make the progression of scoliosis more rapid and with limited household finances, modifications to housing and vehicles to accommodate physical incapacity are often not possible. Although 43% of SMA patients at the time of analysis were on home ventilation, 20% had received corrective scoliosis surgery, 33% were on PEG feeds and 45% of SMA3 patients were no longer ambulant, more studies (to include patients transitioned to adult services) are required to determine a more comprehensive picture of the long-term outcomes.

Limitations: With an estimated incidence of 1 in 6000-10 000 and a predicted SMA birth incidence that is higher in the South African population than previously anticipated, 86 patients in 23 years is 3-4 times lower than the 230-368 expected cases (the Western Cape captured almost 100 000 birth registrations in 2022).[32] Considering our current health system and the country's previous social construct of segregation, the demographic of the RCWMCH population group does not accurately reflect the overall SMA demographic in South Africa. Our registry predominantly includes patients in the public sector which is mainly represented by patients of African and mixed-race ancestry. With SMA being more prevalent amongst patients of European ancestry, we suspect there may be additional children in the private sector.
Due to many folders being destroyed, our sample size was reduced and this has impacted data collection for statistically reliable analysis. An upgrade from a paper system to an electronic system is a manner in which patient information can be retained for future studies. A national registry for SMA would address the selection bias of our database of predominantly public patients of lower socioeconomic status. This limitation could be resolved in the future when the public/private health system becomes the National Health Insurance that aims to provide universal health coverage.

5. Conclusion

Delays in diagnosis are common for all SMA types. The higher proportion of SMA2 patients could suggest that many SMA1 patients are missed and likely demise from respiratory failure prior to diagnosis. Newborn screening provides a solution but austerity measures in the public health sector provide no financial room for implementation. Presently, a more viable option to assist in detecting patients and minimizing diagnostic delays would be to implement better developmental milestone screening programs at all levels of care together with a decentralized specialist presence. To avoid data loss, an improvement in record keeping, such as electronic upgrades, would assist in the retention of patient information. Even with the noted limitations, this study has identified a high mortality in patients with SMA1 and SMA2 in our population group and a high burden of disease which translates to a high economic burden. Newborn screening together with affordable disease modifying therapy, which we hope will be available in the future, is positively life-altering for the patient and caregiver and would ultimately aid the economy by decreasing health care costs (especially when drug patent laws expire) and by increasing productivity for both patients and caregivers.

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Declaration of Competing Interest

The authors have no conflict of interest to declare.

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Appendix A

Table 1: Socio-demographic characteristics, burden of disease disaggregated by spinal muscular atrophy (total n=30).

Characteristic	**Total**	**Type 1 n=4**	**Type 2 n=17**	**Type 3 n=9**
Age at diagnosis (months), median (IQR)	24.0 (13.0-34.0)	3.5 (1.0-6.5)	19.0 (14.0-24.0)	34.0 (32.0-47)
Mean age of symptom recognition in months (range)		0.5 (0-1)	10.3 (6-15)	25 (14-72)
Mean age of diagnosis in months (range)		3.75 (0-8)	21 (9-42)	43 (16-96)
Diagnostic delay		3.25	10.7	18
Sex, n (%)				
Male	16 (53)	2 (50)	10 (59)	4 (44)
Female	14 (47)	2 (50)	7 (41)	5 (56)
Socioeconomic status, n (%)				
H0	2 (6)	0	1 (6)	1 (11)
H1	18 (60)	2 (50)	11 (65)	5 (56)
H2	3 (10)	0	2 (12)	1 (11)
H3	1 (3)	1 (25)	0	0
P	6 (20)	1 (25)	3 (18)	2 (22)
Referring facility, n (%)				
Local clinic	3 (10)	0	3 (18)	0
District hospital	2 (7)	1 (25)	0	1 (11)
Regional hospital	4 (13)	0	2 (12)	2 (22)
Tertiary hospital	11 (37)	2 (50)	7 (41)	2 (22)
Orthopedics clinic	5 (17)	0	2 (12)	3 (33)
Other	5 (17)	1 (25)	3 (18)	1 (11)
Diagnosis method (genetics)	30 (100)	4 (100)	17 (100)	9 (100)
Family history of SMA, n (%)	8 (27)	1 (25)	5 (29)	2 (22)
Members affected (one)	8 (100)	1 (100)	5 (100)	2 (100)
Members affected (sibling)	8 (27)	1 (25)	5 (29)	2 (22)
Respiratory: chest infections ***Age seen <1 year, Total n=30 (%)***				
# of chest infections/ annum				
Zero	26 (87)	1 (25)	16 (94)	9 (100)
One	2 (7)	2 (50)	0	0

Two	2 (7)	1 (25)	1 (6)	0
# of chest infections requiring ABx only				
Zero	29 (97)	4 (100)	16 (94)	9 (100)
One	1 (3)	0	1 (6)	0
# of adm for chest infections				
Zero	27 (90)	2 (50)	16 (94)	9 (100)
One	2 (7)	1 (25)	1 (6)	0
Two	1 (3)	1 (25)	0	0
# of chest infections requiring IV/ICU				
Zero	29 (97)	3 (75)	17 (100)	9 (100)
One	1 (3)	1 (25)	0	0
Age seen 1 year, Total n=28 (%)				
# of chest infections/ annum				
Zero	20 (71)	0	12 (71)	8 (89)
One	2 (7)	0	1 (6)	1 (11)
Two	2 (7)	0	2 (12)	0
Three	2 (7)	1 (50)	1 (6)	0
Four	2 (7)	1 (50)	1 (6)	0
# of chest infections requiring ABx only	24 (86)	1 (50)	15 (88)	8 (89)
Zero	2 (7)	1 (50)	0	1 (11)
One	2 (7)	0	2 (12)	0
Two				
# of adm for chest infections				
Zero	22 (79)	0	13 (76)	9 (100)
One	1 (4)	0	1 (6)	0
Two	2 (7)	0	2 (12)	0
Three	3 (11)	2 (100)	1 (6)	0
# of chest infections requiring IV/ICU				
Zero	28 (100)	2 (100)	17 (100)	9 (100)
Age seen 2 years, Total n=28 (%)				
# of chest infections/ annum				
Zero	20 (71)	1 (50)	10 (59)	9 (100)
One	2 (7)	0	2 (12)	0
Two	2 (7)	0	2 (12)	0
Three	3 (11)	0	3 (18)	0
Four	1 (4)	1 (50)	0	0
# of chest infections requiring ABx only	26 (93)	2 (100)	15 (88)	9 (100)

Zero	1 (4)	0	1 (6)	0
One	1 (4)	0	1 (6)	0
Three				
# of adm for chest infections				
Zero	21 (75)	1 (50)	11 (65)	9 (100)
One	4 (14)	1 (50)	3 (18)	0
Two	2 (7)	0	2 (12)	0
Three	1 (4)	0	1 (6)	0
# of chest infections requiring IV/ICU	26 (93)	1 (50)	16 (94)	9 (100)
Zero	1 (4)	0	1 (6)	0
One	1 (4)	1 (50)	0	0
Three				
Age seen 3 years, Total n= 27 (%)				
# of chest infections/ annum				
Zero	17 (63)	0	9 (56)	8 (89)
One	5 (19)	1 (50)	3 (19)	1 (11)
Two	4 (15)	0	4 (25)	0
Three	1 (4)	1 (50)	0	0
# of chest infections requiring ABx only	24 (89)	2 (100)	14 (88)	8 (89)
Zero	3 (11)	0	2 (12)	1 (11)
One				
# of adm for chest infections				
Zero	19 (70)	0	10 (63)	9 (100)
One	6 (22)	2 (100)	4 (25)	0
Two	2 (7)	0	2 (12)	0
# of chest infections requiring IV/ICU				
Zero	25 (93)	1 (50)	15 (94)	9 (100)
One	1 (4)	0	1 (6)	0
Two	1 (4)	1 (50)	0	0

Age seen 4 years, Total n=25 (%)				
# of chest infections/annum				
Zero	15 (60)	0	9 (60)	6 (67)
One	6 (24)	0	3 920)	3 (33)
Two	1 (4)	1 (100)	0	0
Three	2 (8)	0	2 (13)	0
Four	1 (4)	0	1 (7)	0
# of chest infections requiring ABx only	19 (76)	0	13 (87)	6 (67)

Zero	5 (20)	1 (100)	1 (7)	3 (33)
One	1 (4)	0	1 (7)	0
Two				
# of adm for chest infections				
Zero	18 (72)	0	9 (60)	9 (100)
One	4 (16)	1 (100)	3 (20)	0
Two	2 (8)	0	2 (13)	0
Three	1 (4)	0	1 (7)	0
# of chest infections requiring IV/ICU				
Zero	24 (96)	1 (100)	14 (93)	9 (100)
One	1 (4)	0	1 (7)	0
Age seen 5 years, Total n=22 (%)				
# of chest infections/ annum				
Zero	16 (73)	1 (100)	8 (62)	7 (88)
One	3 (14)	0	2 (15)	1 (12)
Two	3 (14)	0	3 (23)	0
# of chest infections requiring ABx only				
Zero	17 (77)	1 (100)	9 (69)	7 (88)
One	5 (23)	0	4 (31)	1 (12)
# of adm for chest infections				
Zero	20 (91)	1 (100)	11 (85)	8 (100)
One	2 (9)	0	2 (15)	0
# of chest infections requiring IV/ICU				
Zero	20 (91)	1 (100)	11 (85)	8 (100)
One	2 (9)	0	2 (15)	0
Age seen 6 years, Total n=21 (%)				
# of chest infections/ annum				
Zero	16 (76)	1 (100)	7 (58)	8 (100)
One	4 (19)	0	4 (33)	0
Two	1 (5)	0	1 (8)	0
# of chest infections requiring ABx only	19 (90)	1 (100)	10 (83)	8 (100)
Zero	2 (10)	0	2 (17)	0
One				
# of adm for chest infections				
Zero	17 (81)	1 (100)	8 (67)	8 (100)
One	4 (19)	0	4 (33)	0
# of chest infections requiring IV/ICU				

Zero	21 (100)	1 (100)	12 (100)	8 (100)
Age seen 7 years, Total n=20 (%)				
# of chest infections/ annum				
Zero	15 (75)	-	7 (58)	8 (100)
One	2 (10)	-	2 (17)	0
Two	1 (5)	-	1 (8)	0
Three	1 (5)	-	1 (8)	0
Four	1 (5)	-	1 (8)	0
# of chest infections requiring ABx only				
Zero	17 (85)	-	9 (75)	8 (100)
One	1 (5)	-	1 (8)	0
Two	2 (10)	-	2 (17)	0
# of adm for chest infections				
Zero	15 (75)	-	7 (58)	8 (100)
One	5 (25)	-	5 (42)	0
# of chest infections requiring IV/ICU				
Zero	19 (95)	-	11 (92)	8 (100)
One	1 (5)	-	1 (8)	0
Age seen 8 years, Total n=19 (%)				
# of chest infections/ annum				
Zero	13 (68)	-	5 (45)	8 (100)
One	1 (5)	-	1 (9)	0
Two	2 (11)	-	2 (18)	0
Four	3 (16)	-	3 (27)	0
# of chest infections requiring ABx only	13 (68)	-	5 (45)	8 (100)
Zero	3 (16)	-	3 (27)	0
One	2 (11)	-	2 (18)	0
Two	1 (5)	-	1 (9)	0
Three				
# of adm for chest infections				
Zero	15 (79)	-	7 (64)	8 (100)
One	2 (11)	-	2 (18)	0
Two	1 (5)	-	1 (9)	0
Three	1 (5)	-	1 (9)	0
# of chest infections requiring IV/ICU				
Zero	19 (100)	-	11 (100)	8 (100)
Age seen 9 years, Total n=18 (%)				
# of chest infections/ annum				

Zero	15 (83)	-	8 (73)	7 (100)
One	1 (6)	-	1 (9)	0
Three	2 (11)	-	2 (18)	0
# of chest infections requiring ABx only				
Zero	16 (89)	-	9 (82)	7 (100)
Three	2 (11)	-	2 (18)	0

# of adm for chest infections				
Zero	17 (94)	-	10 (91)	7 (100)
One	1 (6)	-	1 (9)	0
# of chest infections requiring IV/ICU				
Zero	18 (100)	-	11 (100)	7 (100)
Age seen 10 years, Total n=16 (%)				
# of chest infections/ annum				
Zero	12 (75)	-	6 (60)	6 (100)
One	3 (19)	-	3 (30)	0
Six or more	1 (6)	-	1 (10)	0
# of chest infections requiring ABx only				
Zero	14 (88)	-	8 (80)	6 (100)
One	1 (6)	-	1 (10)	0
Three	1 (6)	-	1 (10)	0
# of adm for chest infections				
Zero	13 (81)	-	7 (70)	6 (100)
One	2 (13)	-	2 (20)	0
Two	1 (6)	-	1 (10)	0
# of chest infections requiring IV/ICU				
Zero	15 (94)	-	9 (90)	6 (100)
One	1 (6)	-	1 (10)	0
Age seen 11 years, Total n=15 (%)				
# of chest infections/ annum				
Zero	11 (73)	-	5 (56)	6 (100)
One	1 (7)	-	1 (11)	0
Two	1 (7)	-	1 (11)	0
Three	1 (7)	-	1 (11)	0
Four	1 (7)	-	1 (11)	0
# of chest infections requiring ABx only	14 (93)	-	8 (89)	6 (100)
Zero	1 (7)	-	1 (11)	0

One				
# of adm for chest infections				
Zero	12 (80)	-	6 (67)	6 (100)
Two	1 (7)	-	1 (11)	0
Three	1 (7)	-	1 (11)	0
Four	1 (7)	-	1 (11)	0
# of chest infections requiring IV/ICU	15 (100)	-	9 (100)	6 (100)
Zero				
Age seen 12 years, Total n=13 (%)				
# of chest infections/ annum				
Zero	11 (85)	-	6 (75)	5 (100)
Two	2 (15)	-	2 (25)	0
# of chest infections requiring ABx only				
Zero	10 (77)	-	5 (63)	5 (100)
One	1 (8)	-	1 (13)	0
Two	1 (8)	-	1 (13)	0
Three	1 (8)	-	1 (13)	0
# of adm for chest infections				
Zero	11 (85)	-	6 (75)	5 (100)
One	2 (15)	-	2 (25)	0
# of chest infections requiring IV/ICU				
Zero	13 (100)	-	8 (100)	5 (100)
Age seen 13 years, Total =13 (%)				
# of chest infections/ annum				
Zero	11 (85)	-	6 (75)	5 (100)
One	2 (15)	-	2 (25)	0
# of chest infections requiring ABx only				
Zero	12 (92)	-	7 (88)	5 (100)
One	1 (8)	-	1 (12)	0
# of adm for chest infections				
Zero	11 (85)	-	6 (75)	5 (100)
One	2 (15)	-	2 (25)	0
# of chest infections requiring IV/ICU				
Zero	13 (100)	-	8 (100)	5 (100)
Age seen 14 years, Total=13 (%)				
# of chest infections/ annum				

Zero	9 (69)	-	5 (63)	4 (80)
One	2 (15)	-	1 (12)	1 (20)
Three	1 (8)	-	1 (12)	0
Five	1 (8)	-	1 (13)	0
# of chest infections requiring ABx only				
Zero	10 (77)	-	6 (75)	4 (80)
One	2 (15)	-	1 (13)	1 (20)
Two	1 (8)	-	1 (13)	0
# of adm for chest infections				
Zero	10 (77)	-	5 (62)	5 (100)
One	1 (8)	-	1 (13)	0
Three	2 (12)	-	2 (25)	0
# of chest infections requiring IV/ICU				
Zero	12 (100)	-	7 (100)	5 (100)
Age seen 15 years, Total n=10 (%)				
# of chest infections/ annum				
Zero	6 (60)	-	3 (60)	3 (60)
One	4 (40)	-	2 (40)	2 (40)
# of chest infections requiring ABx only				
Zero	9 (90)	-	5 (100)	4 (80)
One	1 (10)	-	0	1 (20)
# of adm for chest infections				
Zero	7 (70)	-	3 (60)	4 (80)
One	3 (30)	-	2 (40)	1 (20)
# of chest infections requiring IV/ICU				
Zero	10 (100)	-	5 (100)	5 (100)
Age seen 16 years, Total=8 (%)				
# of chest infections/ annum				
Zero	6 (75)	-	2 (50)	4 (100)
Two	2 (25)	-	2 (50)	0
# of chest infections requiring ABx only				
Zero	6 (75)	-	2 (50)	4 (100)
One	1 (12)	-	1 (25)	0
Two	1 (12)	-	1 (25)	0
# of adm for chest infections				
Zero	7 (88)	-	3 (75)	4 (100)
One	1 (12)	-	1 (25)	0

# of chest infections requiring IV/ICU Zero	8 (100)	-	4 (100)	4 (100)
Age seen 17 years, Total n=6 (%)				
# of chest infections/ annum Zero	6 (100)	-	3 (100)	3 (100)
# of chest infections requiring ABx only Zero	6 (100)	-	3 (100)	3 (100)
# of adm for chest infections Zero	6 (100)	-	3 (100)	3 (100)
# of chest infections requiring IV/ICU Zero	6 (100)	-	3 (100)	3 (100)
Age seen 18 years, Total n=5 (%)				
# of chest infections/ annum Zero	5 (100)	-	3 (100)	2 (100)
# of chest infections requiring ABx only Zero	5 (100)	-	3 (100)	2 (100)
# of adm for chest infections Zero	5 (100)	-	3 (100)	2 (100)
# of chest infections requiring IV/ICU Zero	4 (100)	-	2 (100)	2 (100)
Patient on home bipap, n (%)	13 (43)	2 (50)	9 (53)	2 (22)
Home bipap hours, n (%) <12 hours >16 hours	12 (92) 1 (8)	1 (50) 1 (50)	9 (100) 0	2 (100) 0
Musculoskeletal complications				
Scoliosis, n (%)	21 (70)	0	15 (88)	6 (67)
Scoliosis corrective surgery, n (%)	6 (29)	-	4 (27)	2 (33)
Other musculoskeletal complications, n (%) Contractures Dislocations	21 (70) 1 (3)	1 (25) 0	15 (88) 1 (6)	5 (56) 0
Mobilising independently, n (%)	5 (17)	0	0	5 (57)
Mobilising device, n (%) Wheelchair Mobdevice	19 (63) 6 (20)	1 (25) 3 (75)	15 (88) 2 (12)	3 (33) 1 (11)
Nutritional status, n (%)				

Normal	15 (50)	3 (75)	8 (47)	4 (44)
Overweight	3 (10)	0	2 (12)	1 (11)
FTT/UWFA	2 (7)	1 (25)	1 (6)	0
Moderately wasted	3 (10)	0	2 (12)	1 (11)
Severely wasted	7 (23)	0	4 (24)	3 (33)
Need for PEG support, n (%)	10 (33)	3 (75)	5 (29)	2 (22)
Social				
Care givers involved, n (%)				
One	10 (33)	2 (50)	6 (35)	2 (22)
Two	18 (60)	2 (50)	9 (53)	7 (78)
Three	2 (7)	0	2 (12)	0
Care dependency grant, n (%)	19 (63)	1 (25)	12 (70)	6 (67)
Reason for not having grant, n (%)				
Applied awaiting approval	2	2	0	0
Foreign national	1	0	1	0
Doesn't meet requirements	2	0	2	0
Other	6	1	2	3
Patient school going, n (%)				
No	1 (3)	0	1 (6)	0
Yes	21 (70)	1 (25)	12 (71)	8 (89)
Not applicable	8 (27)	3 (75)	4 (24)	1 (11)
Type of school, n (%)				
Mainstream	6	0	0	6
Special needs	14	1	11	2
Home-schooled	1	0	1	0
Independent activities, n (%)				
Bathing	3 (10)	0	0	3 (33)
Dressing	3 (10)	0	0	3 (33)
Toileting	4 (13)	0	0	4 (44)
Transferring	2 (7)	0	0	2 (22)
Continence	24 (80)	1 (25)	15 (88)	8 (89)
Feeding	21 (70)	0	12 (71)	9 (100)
N/A	5 (17)	3 (75)	2 (12)	0
Mortality				
Vital status (died – respiratory complications), n (%)	4 (13)	4 (100)	0	0
Vital status (died- sepsis), n (%)	1	0	1 (5.8)	0

Appendix B

UNIVERSITY OF CAPE TOWN
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FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

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	28.02.2025
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee	Signed by candidate	Date Signed	29/2/2024

Note: Please email this form and supporting do
hrec-enquiries@uct.ac.za.
Please clarify your plan for research-related activities during COVID-19 lockdown.
Please use the latest form found on our website:
http://www.health.uct.ac.za/fhs/research/humanethics/forms

If file to
HUMAN RESEARCH
ETHICS COMMITTEE
2 8 FEB 2024
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

Comments to PI from the HREC

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	28/02/2024		
HREC REF Number	097/2023	Current Ethics Approval was granted until	28/02/2024
Protocol title	Analysis of The Demographics, Pathways of Diagnosis, Burden of Disease And Long-term Outcomes of Patients With Spinal Muscular Atrophy Managed at Red Cross War Memorial Children's Hospital.		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?		☐ Yes	☑ No
If yes, could you please provide the HREC Reference number for all sub-studies? **Note:** A separate FHS016 must be submitted for each sub-study.			
Principal Investigator	Professor Jo Wilmshurst		
Department / Office Internal Mail Address	Paediatrics and Child Health, Division of Neurology		

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

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? **Note:** Any annual approvals for **Full Committee** review MUST be submitted on the monthly HREC submission dates. (Please send electronic copy for full committee review to hrec-submission@uct.ac.za)	☐ Yes	☐ No

If yes in 1.2 please complete section 1.3 below for invoicing purposes

1.3 Ethics Renewal Fee

Please **(tick ✓)**appropriate box for billing purposes:

Submission Type	***Description***	***New fee (Vat Incl.)***	***tick ✓***
Research funded solely from UCT departmental/ divisional/group budget	Annual evaluation of research progress report for re-certification	**R0,00**	☐√
Non-sponsored student research for degree purposes at UCT/Other Universities & Colleges	Annual evaluation of research progress report for re-certification	**R0,00**	☐
Annual re-certification / Progress report (FHS016 Form)	Clinical Trial & International Grant Funded Research - Annual evaluation of research progress report for re-certification for Full Committee Approval	**R7000,00**	☐
Annual re-certification / Progress report (FHS016 Form)	Clinical Trial & International Grant Funded Research - Annual evaluation of research progress report for re-certification for Expedited review	**R3 710.00**	☐
Annual re-certification / Progress report (FHS016 Form)	National grant funded research - Annual evaluation of research progress report for re-certification for Full Committee Approval	**R6000.00**	☐
Annual re-certification / Progress report (FHS016 Form)	National Grant funded research for Annual evaluation of research progress report for re-certification for Expedited review	**R1 500,00**	☐

NB: Protocols funded by UCT (e.g. departmental funding / student research) and by certain grant funding organizations (e.g. MRC, NRF, CANSA,) are exempt from these charges.

Please provide details for Invoicing, either complete section 1 or 2 :

1. Invoice billing – Directly to Sponsor

Sponsor's name	
Billing Address of Sponsor:	
Vat Number:	
Contact person	
Telephone number	

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

Email Address	
2. **Internal Journal Billing:**	
Fund Number:	
Cost Centre Number:	
Account Holder Name:	
Division of Account Holder:	

2. List of documentation for approval

3. Protocol status (tick ✓)

☐	Open Enrolment
☐	Closed to enrolment (tick ✓)
☐	Research-related activities are ongoing
☐	Research-related activities are complete, long-term follow-up only
☐√	Research-related activities are complete, data analysis only
☐	Main study is complete but sub-study research-related activities are ongoing
☐	Study is closed → Please submit a Study Closure Form (FHS010)

4. Enrolment

Number of participants enrolled to date	86 (de- identified audit)
Number of participants enrolled, since last HREC Progress report (continuing review)	N/A
Additional number of participants still required	0

5. Refusals

Total number of refusals (participants invited to join the study, but refused to take part)	N/A

6. Cumulative summary of participants

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

Total number of participants who provided consent	N/A
Number of participants determined to be ineligible (i.e. after screening)	N/A
Number of participants currently active on the study	N/A
Number of participants completed study (without events leading to withdrawal)	N/A
Number of participants withdrawn at participants' request (i.e. changed their mind)	N/A
Number of participants withdrawn by PI due to toxicity or adverse events	N/A
Number of participants withdrawn by PI for other reasons (e.g. pregnancy, poor compliance)	N/A
Number of participants lost to follow-up. Please comment below on reasons for loss of follow-up.	N/A
Number of participants no longer taking part for reasons not listed above. Please provide reasons below:	N/A

7. Progress of study

Please provide a brief summary of the research to date including the overall progress and the progress since the last annual report as well as any relevant comments/issues you would like to report to the HREC:
Data has been collected and analysis in progress. Full report to be written and completed within the next two months.

8. Protocol violations and exceptions (tick ✓ all that apply)

☐√	No prior violations or exceptions have occurred since the original approval
☐	Prior violations or exceptions have been reported since the last review and have already been acknowledged or approved
☐	Unreported minor violations that have occurred since the last review, as well as significant deviations not yet reported, are attached for review

9. Amendments (tick ✓ all that apply)

☐√	No Prior amendments have been made since the original approval
☐	Prior amendments have been reported since the last review and have already been approved

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

☐	New protocol changes/ amendments are requested as part of this continuing review (See note below)

Note: If new protocol changes are being requested in this review, please complete an amendment form (FHS006).
Specific changes in the amended protocol and consent/assent forms must be **bolded**, *italicised* or tracked and all changes must include a rationale.

10. Adverse events

10.1 Please provide below or attach a narrative summary of serious adverse events and/ or unanticipated problems since the last progress report. Please indicate changes made to the protocol and informed consent document(s) as a result (if not already reported to the HREC). Please comment on whether causality to any study procedure or intervention could be established.
Nil

10.2 Have participants received appropriate treatment/ follow-up/ referral when indicated (e.g. in the case of abnormal or incidental clinical findings, distress or anxiety)?		
☐ Yes	☐ No	☐ √ Not applicable
If yes, please describe:		

11. Summary of Monitoring and Audit Activities (tick ✓)

11.1 Was this study monitored or audited by an external agency (e.g. SAHPRA, FDA)?		
☐ Yes	☐ No	☐ √ Not applicable

11.2 Did a Data and Safety Monitoring Board publish a report?		
☐ Yes	☐ No	☐ √ Not applicable

11.3 If yes, please identify the agency and attach a summary of the findings.					
Agency Name		Report attached	☐ Yes	☐ No	☐ Not applicable
		DSMB report attached	☐ Yes	☐ No	☐ Not applicable

11.4 Has there been any agency, institutional or other inquiry into non-compliance in this study, or any finding of non-compliance concerning a member of the research team?	
☐ Yes	☐ √ No
If yes, please explain:	

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

12. Level of risk (tick ✓)

12.1 In light of your experience of this research, please indicate whether the level of risk to participants has:	
☐	Increased
☐	Decreased
☐√	Shown no change
If there has been a change, please explain:	

12.2 Please provide a narrative summary of recent relevant literature that may have a bearing on the level of risk.

13. Insurance

Please confirm that valid no fault insurance is still in place? **(tick ✓)**			
☐ Yes	☐ No	☐ √Not Applicable – N/A	
If yes, please complete the following:			
Insurer's name:			
Policy no.		*Coverage Period:	
For UCT sponsored studies please liaise the Insurance office via fhs.sponsorship@uct.ac.za regarding the required documentation and information required obtain a renewed UCT No-fault Insurance Certificate.			

14. Statement of conflict of interest

Has there been any change in the conflict of interest status of this protocol since the original approval? (tick ✓)	
☐ Yes	☐ √ No
If yes, please explain and if necessary, attach a revised conflict of interest statement (Section #7 in the New Protocol Application Form FHS013):	

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

15. Signature

My signature certifies that the above is complete and correct.			
Signature of PI	Signed by candidate	Date	28/02/2024

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)