THE EFFECTIVENESS OF GRADED MOTOR IMAGERY FOR REDUCING PHANTOM LIMB PAIN AND DISABILITY IN AMPUTEES

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Declaration

I, Katleho Limakatso, hereby declare that the work on which this thesis is based is my original work (except where acknowledgements indicate otherwise) and have used the Vancouver system of referencing. I declare that neither the whole work nor part of it has been, is being, or is it to be submitted for another degree at the University of Cape Town or any other university.

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Abstract

Introduction

Phantom limb pain (PLP) is described as painful sensations felt in the missing portion of an amputated limb. PLP occurs in up to 85% of amputees, making it the most common painful condition secondary to amputation. PLP interferes with sleep, mobility, and work, general activities of daily living and enjoyment of life. Current pharmacological and non-pharmacological interventions have shown limited efficacy for reducing PLP, perhaps because they do not effectively target the mechanisms that have been proposed to underlie PLP in people who have undergone amputations. Graded motor imagery (GMI) is a cortical mechanisms-based intervention which aims to reduce PLP using a graded sequence of strategies including left/right judgements, imagined movements and mirror therapy. The aim of this thesis was to investigate whether the GMI programme is effective for reducing PLP and disability in people who have undergone amputations.

Methods

A single blinded randomised controlled trial was conducted at Somerset, Khayelitsha and Victoria hospitals in Cape Town, South Africa. The experimental group underwent a 6-week GMI programme where each phase was carried out for two weeks, during which the patient received treatment for 30 minutes on two separate days of the first week (at least one day apart) and continued with a structured home-exercise programme during the first week until the end of the second week. The control group continued with routine care. Data on the outcomes- PLP severity, pain interference with function and health-related quality of life were collected at baseline, 6 weeks and 3 months by a blinded outcome assessor.

Results

The study recruited 21 participants from which 11 and 10 were randomly allocated to the experimental and control groups respectively. Within group analysis showed that participants in both the experimental and control groups had improved pain severity scores immediately after treatment and at 3-month follow-up. The between-group analysis showed that the experimental group had significantly greater improvements in pain immediately after treatment (p=0.02). However, there was no difference between groups at 3-months follow-up (p=0.14). To explore clinically meaningful improvements in pain, the Number Needed to Treat (NNT) were calculated using a cut-off of 3 points on a 0-10 scale. The NNT were 2 [95% CI: 1.1 – 6.5] and 3 [95% CI: 1.9 – 7.1] immediately after treatment and at 3-months follow-up respectively.

For pain interference with function, within group analysis showed that participants in the experimental group had significant improvements immediately after treatment and at 3-month follow-up. The between-group analysis showed that the experimental group had significantly greater improvements in pain interference with function immediately after treatment (p=0.007) and at 3-month follow-up (p=0.02). The NNT were 1.4 [95% CI: 1 – 1.8] and 1.9 [95% CI: 1.1 – 6.5] immediately after treatment and at 3-months follow-up respectively. For disability, the experimental group had significantly fewer problems with mobility than the control group at 3 months ($\chi 2 = 9.8$; p= 0.04).

Conclusion

The results of the current study provide support for the use of GMI to treat PLP based on the proposition that PLP is driven by cortical mechanisms and that GMI effectively targets these mechanisms. On the basis of the significant pain reduction within the GMI group, the lack of serious adverse effects, and the ease of application, GMI may be a viable treatment for treating PLP in people who have undergone amputations. While more studies using rigorous methodology, including sham treatment, larger sample sizes and a more generalisable sample, are required, the efficacy of GMI coupled with its affordability and low risk, suggest that it is applicable in a resource-constrained primary health setting in South Africa.

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List of Abbreviations

ARR	Absolute Risk Reduction
BPI	Brief Pain Inventory
CER	Control Event Rate
CI	Confidence Interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CRPS1	Complex Regional Pain Syndrome Type 1
DARE	Database of Abstracts of Reviews of effects in the Cochrane Library
EER	Experimental Event Rate
GMI	Graded Motor Imagery
HRQOL	Health-related Quality Of Life
IASP	International Association of the Study of Pain
ICF	International Classification of Functioning, Disability and Health
LILACS	Literatura Latino Americana em Ciências da Saúde
M1	Primary Motor
MD	Median Difference
NMDA	N-methyl-D-aspartate
NNT	Number Needed to Treat
NOI	Neuro Orthopaedic Institute
NRS	Numerical Rating Scale
OR	Odds Ratio

PACTR	Pan African Clinical Trials Registry
PEDro	Physiotherapy Evidence Database
PGIC	Patient Global Impression of Change
PIS	Pain Interference Score
PLP	Phantom Limb Pain
PRISMA	Preferred Reporting Items for Systematic review and Meta-analysis
PSFS	Patient-Specific Functional Scale
PSS	Pain Severity Score
RCT	Randomised Controlled Trial
RRR	Relative Risk Reduction
S1	Primary Somatosensory
TENS	Transcutaneous Electrical Nerve Stimulation
TOFHLA	Test of Functional Health Literacy in Adults
UCT	University of Cape Town
VAS	Visual Analogue Scale
WCHD	Western Cape Health Department

Chapter 1: Introduction and Scope of Thesis

Phantom limb pain (PLP) is described as painful sensations felt in the missing portion of an amputated limb [1]. PLP occurs in up to 85% of amputees, making it the most common painful condition secondary to amputation [2]. The onset of PLP is often immediate, although in some cases, may be after many years [3], with painful sensations varying between sharp, shooting, throbbing, stabbing, and aching. PLP negatively impacts the patient's psychological well-being and quality of life [4]. Furthermore, PLP interferes with sleep, mobility, and work, general activities of daily living and enjoyment of life [5].

PLP remains ineffectively treated, perhaps because of the poor understanding of the proposed underlying mechanisms. Current pharmacological and non-pharmacological interventions have shown limited efficacy for reducing PLP [6-9]. The limited efficacy of these interventions is not altogether surprising because they do not effectively target the mechanisms that have been proposed to underlie PLP in people who have undergone amputations [3, 10].

Previous studies have argued that PLP is primarily driven by peripheral mechanisms, including the presence of persistent pre-operative pain in the amputated limb, driving central upregulation of subsequent peripheral input [3, 11] and exaggerated nociceptive activity from neuromas located in the stump [12]. However, PLP has also been reported in traumatic amputees who do not experience persistent pre-operative pain, and in congenital amputees who clearly do not suffer nerve trauma preceding PLP [13]. This evidence suggests that peripheral processes alone are insufficient to account for the phenomenon of PLP.

Recent neurophysiological evidence suggests that PLP is a perceptual output primarily driven by cortical reorganization in the brain [14]. This evidence is supported by neuroimaging studies of patients with PLP which reveal the functional shifting of neighbouring somatosensory and motor areas into an input-deprived cortical area of the brain contralateral to the amputated limb (Figure 1) [15]. These neuroplastic cortical changes are positively correlated with the severity of PLP in amputees [14] and similar to those recorded in patients with Complex Regional Pain Syndrome Type 1 (CRPS1) [16, 17]. The changes can be reversed using components of the Graded Motor Imagery (GMI) programme, and there is a strong association between reversal of these changes and relief of PLP in people who have undergone amputations [18, 19].

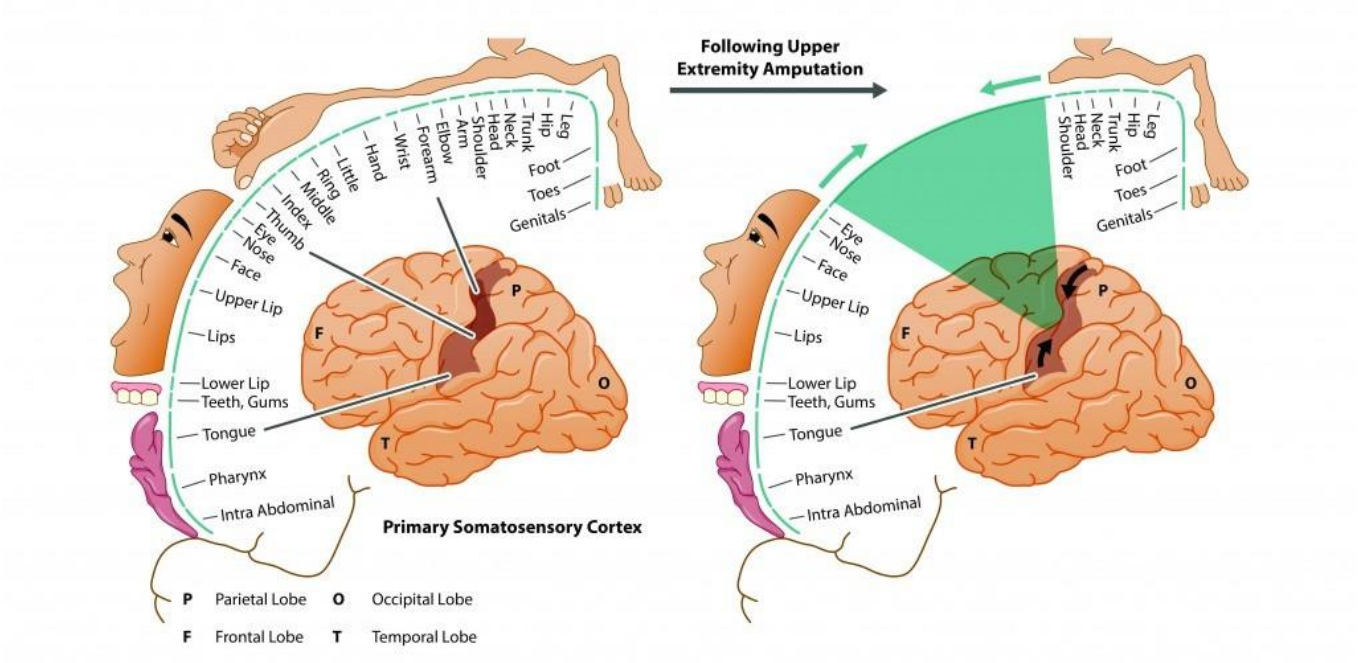

Figure 1: Cortical reorganisation after limb amputation

Graded motor imagery is a cortical mechanisms-based intervention which aims to reduce PLP using a graded sequence of strategies including left/right judgements, imagined movements and mirror therapy [20]. Left/right judgement, the ability to distinguish left from right, is dependent on an intact body schema in the somatosensory and motor cortices of the brain, and is important for the planning of movement and recovery from pain [21]. Imagined movements involves the imagined movement of the phantom limb to adopt a desirable posture. Mirror therapy involves concealing the amputated limb behind a mirror and simultaneously moving the phantom portion of the amputated limb (a movement intention) and the intact limb while observing the reflection of the intact limb in the mirror [22].

Thus far, only one randomised controlled trial (RCT) has investigated whether GMI is effective for reducing PLP in people who have undergone amputations [20]. The findings suggested that GMI may be effective for reducing PLP. However, the previous study had a sample of only nine participants from which only five were allocated to the GMI group, and all had lower limb amputations. Given the small sample size and the restricted representation of the sample in the study, the results may not apply to a broader population of people who have undergone amputations. There appears to be sufficient evidence to support the use of GMI in patients with CRPS1. However, there is limited evidence regarding its efficacy for reducing PLP in people who have undergone amputations, and research in this area remains a priority.

The aim of this thesis was to thoroughly investigate whether the GMI programme is effective for reducing PLP and disability in people who have undergone amputations. Therefore, this study was intended to contribute to the existing literature and inform clinical practice and further research on this subject.

1.2 Thesis outline

This thesis is divided into six chapters. Chapter one provides a background on PLP and provides a theoretical framework for the thesis. In addition, this chapter discusses cortical mechanisms that have been proposed to underlie PLP, and how individual components of the GMI programme target these mechanisms to reduce PLP in people who have undergone amputations. Chapter two is a systematic literature review that critically appraises the literature to determine the efficacy of GMI and its individual components for reducing PLP and PLP-related disability in people who have undergone amputations. The systematic review was based on a pre-published protocol (Appendix A), and will be submitted for publication.

Chapter three includes a survey describing the physiotherapy modalities for PLP, as well as the frequency of their use by physiotherapists in a clinical setting. Chapter four describes the methodological procedure which was followed in conducting the RCT while Chapter five presents the results of the RCT. Chapter six discusses the results of the RCT in relation to the findings of the systematic review, as well as the implication of these findings for research and clinical practice. Chapter seven summarises the key findings in this study, and provides evidence-informed recommendations for research and clinical practice.

1.3 Theoretical framework

1.3.1 Pain: A high-order somatosensory construct.

According to the International Association of the Study of Pain (IASP) pain is “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such” [23]. Chronic pain is a major health problem that has a serious impact on the patient’s quality of life, and social, work and family relationships [24]. For many years, the biomedical model of health guided the clinical assessment and treatment of painful conditions. The application of the biomedical model involves two steps: diagnosis is made by observation of physical signs or diagnostic tests of the injured tissue, and intervention focuses on fixing the presenting problem [25]. The biomedical model does not acknowledge the role of the brain in a painful experience but, rather, views pain as a direct consequence of tissue injury [26]. Therefore, this model has limitations concerning painful conditions such as PLP, when there is no physical limb to account for pain.

The social model of health views pain as a consequence of social and environmental factors. This model focuses on addressing social and environmental determinants of pain through education, policy changes and health promotion [27]. Although the social model of health addresses the influence of social factors on pain, its limitation is that it does not acknowledge the physiological causes of pain.

The International Classification of Functioning, Disability and Health (ICF) integrates the biomedical model and social model into a broader biopsychosocial framework of health. The ICF was introduced as a conceptual framework for health and disability in 2001 [28]. The biopsychosocial model of the ICF views pain as an output that results from a dynamic interaction between biological, psychological and social factors unique to each patient [29]. This view is in line with the IASP's definition of pain acknowledging that pain has unpleasant sensory and emotional components which are driven by the brain and influenced by various factors [23]. The sensory component of pain in particular, is an output from the interaction of several cortical areas of the brain including but not limited to the primary somatosensory, secondary somatosensory, pre-motor and primary motor cortices. PLP is theorised to be an output from the brain driven by reorganisation in the aforementioned cortical areas [11, 14, 18, 30-33].

1.3.2 Cortical reorganisation in phantom limb pain.

The primary somatosensory cortex, an area lying within the post-central gyrus, has a somatotopic representation of the contralateral side of the body. The primary somatosensory cortex receives nociception from the thalamus via thalamocortical afferents, and is responsible for the sensory discrimination processing of the peripheral source of nociception [34]. The secondary somatosensory cortex lies adjacent to the primary somatosensory cortex and is involved in quantifying the nociceptive input, thus its activity probably partially informs pain intensity [35]. The primary motor cortex is an area of the frontal lobe lying within the precentral gyrus, anterior to the primary somatosensory cortex and posterior to the pre-motor cortex of the brain. The primary motor cortex is one of the primary areas involved in motor function, and it is responsible for the control and execution of limb movements [36]. The pre-motor cortex lies within the frontal lobe of the brain, anterior to the primary motor cortex. The pre-motor cortex is responsible for the planning of movement, and for spatial and sensory guidance of movement [37].

A substantial body of evidence describes cortical reorganization in primary and secondary somatosensory cortices, as well as in the premotor and primary motor cortices following limb amputation, with a positive correlation between the extent of reorganization and PLP severity in

people who have undergone amputations [30, 33]. The findings from a study that studied the reorganization of the somatosensory and motor cortices in upper extremity amputees with PLP showed the functional invasion of the somatosensory and motor areas of the lips into a cortical representation of the amputated hand, with a strong correlation between the extent of the cortical shifting and the PLP severity [15, 34-36, 38]. The findings from the abovementioned study strongly suggest that PLP is associated with, and may be driven by, the functional changes recorded in the primary and secondary somatosensory, premotor and primary motor cortices in the brain.

1.3.3 Graded Motor Imagery - a potential treatment for PLP

Graded Motor Imagery (GMI) is a treatment programme which might be effective for alleviating PLP and disability [20]. Using a graded sequence of strategies including left/right judgements, imagined movements and mirror therapy, GMI aims to promote cortical re-organisation by progressively activating cortical areas without triggering pain [39]. The GMI programme is well-designed to address the mechanisms proposed to underlie PLP in a step-wise fashion. In fact, one study showed that the ordered application of the components of the GMI programme produce a superior effect compared to the unordered GMI programme [40].

The first strategy in the GMI programme is left/right judgements – a strategy based on three steps: initial judgement, mental manoeuvre and confirmation [41]. Together, the three steps activate the somatosensory, premotor and supplementary motor areas of the cortex contralateral to the phantom limb, without activating the primary motor cortex [42]. The activation of these cortical areas below a threshold that would activate a pain neurotag is required for the planning of movement and recovery from pain.

To identify the side of the limb presented on a computer screen, initially, the patient will subconsciously identify the limb presented in the photograph as either a left or right limb (initial judgement). Once this initial judgement is made, a subconscious manipulation of the virtual limb is made to match the orientation in the image (mental manoeuvre). The initial choice is confirmed if there is matching of the limbs during the mental manoeuvre. However, if the mental manoeuvre reveals that the limb selected is incorrect, the mental manoeuvre of manipulating the “virtual” limb is rerun on the virtual representation of the opposite limb [41]. Left/right judgements have two outcomes: accuracy and reaction time. The accuracy is recorded as a percentage, and it reflects the acuity of the working body schema (i.e how well one can mentally manoeuvre a body part) [43]. The reaction time is recorded in seconds, and it reflects the total time it takes to match the side of the limbs presented on the computer screen. In addition, it can inform us about the brain’s capacity to process incoming information, and this capacity is usually reduced in patients with chronic pain [41].

The second strategy in the GMI programme is imagined movements. Imagined movements activates the primary somatosensory, premotor and primary motor cortices contralateral to the phantom limb in a further step towards achieving movement, but does not generate actual movement [36, 44, 45]. This controlled, progressive activation is proposed to retrain areas of the brain that are involved in movement preparation, without generating pain.

The third strategy in the GMI programme is mirror therapy. Mirror therapy appears to address changes in the primary somatosensory and primary motor cortices by providing visual feedback that matches the motor command, thus resolving a visuomotor mismatch that may be capable of causing pain [18]. The therapeutic effect associated with mirror therapy may also be due to activation of mirror neurons in the brain hemisphere contralateral to the amputated limb [19]. It is thought that mirror neurons fire during observation and execution of movement [19].

The GMI programme is clearly well-designed to address the mechanisms proposed to underlie PLP in a step-wise fashion. In fact an ordered application of the components of the GMI programme seem to produce a superior effect compared to the unordered GMI programme [40]. However, there is limited clarity about the effectiveness of GMI for reducing PLP in people who have undergone amputations. Therefore, a systematic review of the literature was conducted to assess the evidence that GMI reduces PLP and PLP-related disability in people who have undergone amputation.

Chapter 2: Systematic Literature Review

The aim of this systematic literature review was to gather and critically appraise relevant literature regarding the effectiveness of GMI for PLP in amputees. This systematic literature review was based on a published protocol (Appendix A) and has been submitted for publication.

2.1 Background

Every year, one in every 400 people has an amputation [46]. Of those, up to 85% develop persistent pain in the absent limb - phantom limb pain (PLP) - with associated psychological distress [4], problems with prosthesis use [47] and poorer health-related quality of life [5] than those without PLP. PLP remains poorly understood and difficult to treat [48].

Pharmacological treatments recommended for PLP are marginally effective at best, and no more effective than placebo [49]. There is level 1 evidence that pharmacological treatments are ineffective: memantine (30mg/day for 4 days), gabapentin (2.4g/day for 6 weeks) and amitriptyline (10 - 125mg/day for 6 weeks) showed no benefit over placebo [50]. The lack of effectiveness of these interventions is not altogether surprising because they do not target cortical reorganisation - a brain mechanism shown to be an important contributor of PLP.

Recent neuroimaging evidence shows that PLP is linked to cortical reorganisation of the sensorimotor cortex, in which the cortical area that previously represented the missing limb comes to represent other body parts [30, 38]. Similar disruptions to cortical representation have been found in Complex Regional Pain Syndrome Type 1 (CRPS1) [16]. In fact, neuroimaging evidence in CRPS1 revealed disruptions to the primary and secondary somatosensory cortices [14, 51], as well as to the primary motor and supplementary motor cortices [16]. Interestingly, in both CRPS1 and PLP, the extent of these disruptions is positively associated with pain severity. Moreover, reversal of the disruptions is associated with pain reduction [16, 18, 52].

Mirror therapy was proposed as a treatment for PLP because it was thought to address a theorised mismatch between motor and sensory inputs [22]. Mirror therapy involves positioning a mirror in the sagittal plane of the body and moving the intact limb while viewing its reflection in the mirror, such that the reflection appears to be the missing limb. Mirror therapy has also been used as the third component of a three-phase “Graded Motor Imagery” (GMI) programme, which was developed to target cortical disruptions in CRPS1. GMI has systematic review evidence to support its use in CRPS1 [39]. The similarities between the cortical changes seen in CRPS1 and PLP suggest that the GMI programme in its entirety could also be a viable treatment for PLP.

Single studies have investigated mirror therapy, the other components of GMI (left/right judgements and imagined movements), and the full GMI programme for alleviating PLP, but to our knowledge there has been no attempt to systematically synthesise this literature. We therefore aimed to gather and critically appraise all relevant literature regarding the efficacy of the three components of GMI and the entire GMI programme for reducing PLP, to guide ongoing research and clinical practice.

2.2 Methods

This review was developed using the Cochrane methodology for systematic reviews [53]. The protocol of this review has been published elsewhere [54].

2.2.1 Identification of studies

We used a customised search strategy (Appendix B) to search the following electronic databases: PubMed, Cochrane Central register of Controlled Trials, Medline (via Ebscohost), PsychINFO (via Ebscohost), Physiotherapy Evidence Database (PEDro), Scopus, Cumulative Index to Nursing and Allied Health Literature (CINAHL) (via Ebscohost), Literatura Latino Americana em Ciências da Saúde (LILACS), Database of Abstracts of Reviews of effects in the Cochrane Library (DARE), Africa-Wide Information (via Ebscohost) and Web of Science. In addition, we searched clinicaltrials.gov, the Pan African Clinical Trials Registry (PACTR) and the EU clinical trials register for ongoing research. Electronic databases and clinical registries were searched from their inception until June 2016. The literature search will be updated, and the updated manuscript will be submitted for publication in a journal.

To identify grey literature, we searched OpenGrey and contacted experts to seek published, unpublished, and ongoing trials that may be eligible for inclusion.

2.2.2 Screening and study selection

Three reviewers (KL, VJM & RP)[1] independently screened titles and abstracts of potential studies. We compared results and retained studies that tested left/right judgements, imagined movements tasks, mirror therapy, or GMI. After the initial screening, we independently reviewed full articles for eligibility. Studies were eligible for inclusion if they were randomised or non-randomised controlled trials, studied adults (>18yrs) with chronic (>3months) PLP after amputation of an upper or lower limb, used a control treatment, assessed at least one of our outcomes of interest and were written in English. If studies included participants with other pathologies or measured other outcomes, only

[1] KL is the principal investigator in this systematic review. VJM is the primary supervisor of this systematic review. RP is the co-supervisor of this systematic review.

the data relevant to the question of this review were extracted and used. We used Cohen's Kappa to determine the measure of agreement between reviewers as either minimal (0 - 0.39), weak (0.40 - 0.59), substantial (0.60 - 0.79) or strong (0.80 - 0.90) [55].

2.2.3 Outcomes

The primary outcome of interest was PLP defined as pain felt in the missing portion of an amputated limb [13]. The secondary outcomes were function, adverse effects, psychosocial function, patient global impression of change (PGIC) (>3 months after intervention) and health-related quality of life (HRQOL).

2.2.4 Data extraction

Two reviewers (KL & VJM) independently extracted data from included studies using a piloted, customised sheet. Extracted data included: the study design, setting, discipline of clinician delivering experimental/control intervention, exclusion/inclusion criteria, number of participants per group, participants' age and gender and type of amputation; treatment description, duration of treatment, frequency of treatment per week, follow-up period (weeks) and number of participants lost to follow-up; co-morbidities, adverse effects and outcome measures; at baseline, after the intervention and at subsequent follow up. We compared results and resolved disagreements through discussion.

2.2.5 Assessment of risk of bias in included studies

We followed a conservative approach to assessing risk of bias by using a customised risk of bias assessment guide (Appendix C) informed by the Cochrane risk of bias tool [56]. Each study's summary risk of bias score was set as "high risk" if the study scored "high risk" for any individual category, "low risk" if it scored "low risk" for every category, and "unclear" if it scored "unclear" for any category and did not score "high risk" for any category. For the "other sources of bias" category, we considered statistical methods, sample size, and authors' conflicts of interest. Statistical tools with poor reliability and validity, a sample size of fewer than 50 participants per group [57] and conflicts of interest were considered to introduce a high risk of bias due to the potential for overestimation of the treatment effect. The individual items that met this criterion were therefore classified as "high risk". In addition, we considered any allocation procedure that was not truly random (e.g. pseudo-randomisation, counterbalancing, randomisation based on arrival time) to carry a high risk of bias. We used Cohen's Kappa to determine the measure of agreement between reviewers as either minimal (0 - 0.39), weak (0.40 - 0.59), substantial (0.60 - 0.79) or strong (0.80 - 0.90) [55]. All disagreements were resolved through discussion.

2.2.6 Data analysis

For continuous outcomes, we determined the mean change in self-reported pain score at a within-subject level by subtracting the pre-intervention mean from the post-intervention mean. An improvement in pain was therefore indicated by negative score on a 0-100 mm visual analogue scale (VAS). A decrease in pain of ≥ 30 mm on a 0-100mm VAS was considered clinically meaningful [58].

Results were analysed at study level first. Change in pain score was compared between the groups in each study using an independent, uncorrected, two-tailed t-test with significance level set at 0.05. Furthermore, we calculated a 95% confidence interval (CI) for the mean difference (0-100 mm VAS) between groups. Next, results were pooled when possible. Study-level data were entered using the inverse variance function of the Review Manager 5 [59] and pooled with the random effects model option. We assessed statistical heterogeneity using I^2 statistic. Heterogeneity was considered high if it exceeded 50% [60].

2.3 Results

The initial literature search yielded 158 studies after removal of duplicates. Initial screening by title and abstract yielded 18 studies that were eligible for full-text screening. Full-text screening identified six studies that were eligible to be included in this review. One study [20] investigated GMI, two clinically heterogeneous studies [61, 62] investigated imagined movements, and three trials [63-65] investigated mirror therapy. No study examined left/right judgements as a stand-alone treatment. Because one study [64] compared the experimental intervention to two control interventions, we re-used data from the experimental group in two analysis. Therefore, 7 between-group comparisons were included in our analysis. The screening process reflected a substantial agreement (Kappa = 0.70) between reviewers. The screening process is illustrated in the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) flow diagram (Figure 2).

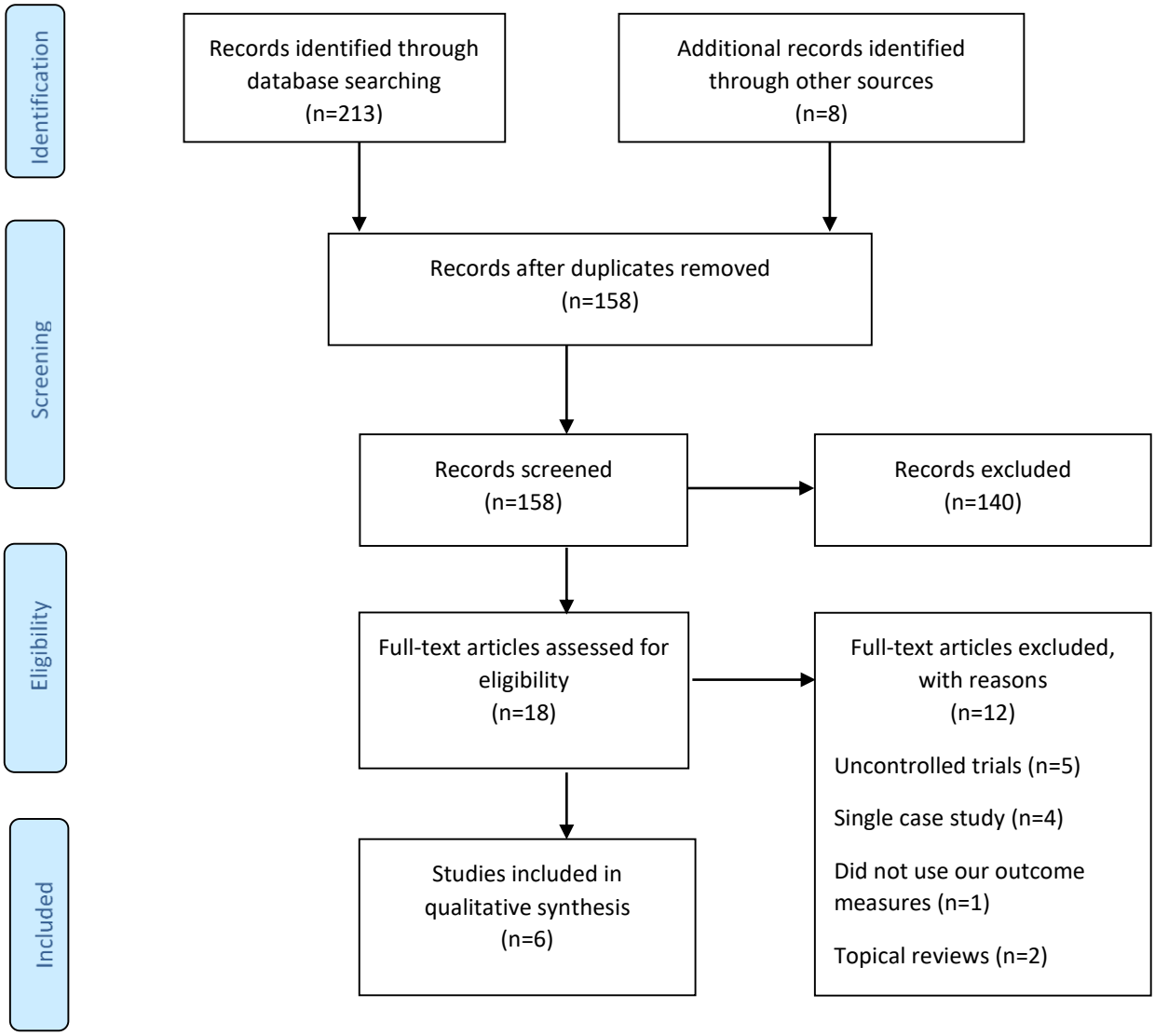

Figure 2: The PRISMA flow chart

2.3.1 Participants

The six eligible studies provided data from a total of 173 participants (126 male; 47 female), of whom 20 reported PLP in an upper limb and 153 reported PLP in a lower limb. Further details of participants' characteristics are provided in Table 1.

2.3.2 Interventions

The treatment parameters used in the different studies varied: each treatment session lasted between 10 and 50 minutes; treatment frequency ranged between 1 and 7 sessions per week, and the total duration of interventions ranged between 1 [63] and 42 days [20]. Only one study [20] reported follow-up measures six months after the intervention. Details of the interventions are summarised in Appendix D.

2.3.3 Outcomes

All included studies used a 100mm Visual Analogue Scale to assess pain by self-report. One study [20] also assessed PLP-related disability as a secondary outcome, using the Patient-Specific Functional Scale (PSFS) [66], which requires the patient to rate their ability to perform five self-selected activities on a Likert-type scale (0-10 VAS: 0=completely unable to perform; 10=able to perform normally). None of our other secondary outcomes of interest was measured in the included studies.

2.3.4 Risk of bias assessment

The results of the risk of bias assessment are reported in Table 2. All included studies had high risk of bias in the blinding category: no participants or treating clinicians were blinded to group allocation. Four of the six included studies did not report on blinding of outcome assessors. All studies scored a high risk of "additional bias" for using fewer than 50 participants per group. One study [64] did not score 'low risk' for any category of bias. The risk of bias assessment revealed substantial agreement (Kappa= 0.69) between reviewers prior to discussion.

Table 1: Characteristics of patients in included studies.

Author	Total number of Participants	Experimental Group: Age Mean ± SD	Control Group: Age Mean ± SD	Experimental Group: Amputated limb LL/UL	Control Group: Amputated limb LL/UL	Experimental Group: Sex M/F	Control Group: Sex M/F
Brodie et al., 2007	80	54 ± (--)	57 ± (--)	41/0	39/0	35/6	28/11
Chan et al., 2007	18	_____	-	6/0	12/0	0/6	0/12
Moseley, 2006	9	41 ± 14	41 ± 14	3/2	2/2	2/3	2/2
Tilak et al., 2016	26	42.62 ± 10.69	36.38 ± 9.55	9/4	10/3	12/1	11/2
Tung et al., 2014	20	_____	_____	9/0	11/0	9/0	11/0
Ulger et al., 2009	20	41.60 ± 4.17	42.10 ± 4.48	5/5	6/4	____	____

Table 2: Risk of bias assessment

Author	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other bias	Overall Classification
Brodie et al., 2007	High	Unclear	High	Unclear	Low	Low	High	High
Chan et al., 2007	Unclear	Unclear	High	Unclear	High	High	High	High
Moseley, 2006	Low	Unclear	High	Low	Low	Low	High	High
Tilak et al., 2015	High	Low	High	Low	High	Low	High	High
Tung et al., 2014	Low	Unclear	High	Unclear	Low	Low	High	High
Ulger et al., 2009	High	High	High	Unclear	Low	Low	High	High

2.3.5 Effects of the interventions on pain (primary outcome)

(a) Mirror therapy

Brodie et al [63] compared one session of mirror therapy to one session of obscured mirror therapy for reducing pain. Participants were assessed immediately after one therapy session, and our analysis showed no significant difference between the experimental and control groups, t(13) = -0.58, p = 0.56. Participants who performed mirror therapy showed a clinically insignificant mean change in pain of -17mm, which was no better than the control group's mean change of -4 mm (between-group comparison favoured the intervention group by -11mm, 95% CI: -48.03 - 26.03mm).

Chan et al [64] compared 28 sessions (1 session/day) of mirror therapy to 28 sessions (1 session/day) of obscured mirror therapy for reducing pain. Participants were assessed immediately after the final (28^{th}) therapy session, and our analysis showed no significant difference between the experimental and control groups (t(11)=1.41, p=0.16). Participants who performed mirror therapy showed a clinically insignificant mean change in pain of -24mm, which was no better than the control group's mean change of -3mm (between-group comparison favoured the intervention group by –16.83mm, 95% CI: -41.31, 7.65).

Tilak et al [65] compared 4 sessions (1 session/day) of mirror therapy to 4 sessions (1 session/day) of Transcutaneous Electrical Nerve Stimulation (TENS) for reducing pain. Participants were assessed immediately after the final (4^{th}) therapy session, and our analysis showed no significant difference between the experimental and control groups, t(24)=-0.61, p=0.55. Participants who performed mirror therapy showed a clinically meaningful mean change in pain of -33.8 mm, which was no better than the control group's mean change of -25.4 mm (between-group comparison favoured the intervention group by –3.8mm, 95% CI: -16.03, 8.43mm).

The clinical heterogeneity between these studies meant that pooling them for meta-analysis was not feasible. In summary, one [65] of three studies found that mirror therapy produced a clinically meaningful improvement in pain at a group level, but all three studies showed mirror therapy to be no better than the comparator treatments for yielding clinical improvements in pain.

(b) Imagined movements

Ulger et al [61] compared 28 sessions (1 session/day) of imagined movements (imagined movements) to 28 sessions (1 session/day) of a general exercise programme comprising prosthetic training and strengthening exercises, for reducing pain. Participants were assessed immediately after the final (28^{th}) therapy session, and our analysis showed no significant difference between the

experimental and control groups, t(18)= -5.3, p= 0.34. Participants who performed imagined movements showed a clinically meaningful mean change in pain of -31.0 mm, which was no better than the control group's mean change of -17 mm (between-group comparison favoured the intervention group by –15mm, 95% CI: -20.61, -9.39).

Tung et al [62] compared 28 sessions (1 session/day) of imagined movements to 28 sessions (1 session/day) of direct limb-movement observation tasks for reducing pain. Our analysis showed no significant difference between the experimental and control groups when assessed immediately after the final (28^{th}) therapy session, t(10)=-0.14, p= 0.90. Participants who performed imagined movements showed a clinically insignificant mean change in pain of -10mm, which was no better than the experimental group's mean change of -26 mm (between-group comparison favoured the intervention group by –1mm, 95% CI: -15.56, 13.56).

Chan et al [64] compared 28 sessions (1 session/day) of imagined movements (imagined movements) to 28 sessions (1 session/day) of obscured mirror therapy for reducing pain. Our analysis showed no significant difference between the experimental and control groups when assessed immediately after the final (28^{th}) therapy session, t(10)=1.93, p= 0.08. Participants who performed imagined movements showed a clinically insignificant mean change in pain of +14mm, which was no better or worse than the experimental group's mean change of -3 mm (between-group comparison +23.5mm, 95% CI: -0.36, 47.36).

The clinical heterogeneity of these studies meant that pooling them for meta-analysis was not feasible. In summary, one [61] of the three studies found that imagined movements produced a clinically meaningful improvement in pain at group level, whereas one [64] found that it produced worsening of pain symptoms that may not be clinically meaningful (+14mm). These three studies showed imagined movements to be no better than the comparator treatments (general exercise, direct limb-movement observation and obscured mirror therapy).

(c) Graded Motor Imagery Programme

Moseley [20] compared a 6-week course of GMI to a 6-week course of routine physiotherapy for reducing pain. Our analysis showed a significant difference between the experimental and control groups when assessed immediately after the final therapy session (6 weeks), t(7)=-3.57, p= 0.04. At that stage, participants who performed GMI showed a clinically meaningful mean change in pain of -32.4 mm, which was significantly better than the control group's change of -17mm (between-group comparison favoured the intervention group by –25mm, 95% CI: -38.74, -11.26). Six-month follow-

up data confirmed this difference between groups: our analysis showed a clinically meaningful difference between the experimental and control groups at six months after therapy, t(7)=-2.4, p= 0.04. At this six-month follow up, participants who had received GMI showed a clinically meaningful mean change in pain of -38.4 mm, which was significantly better than the control group (between-group comparison favoured the intervention group by –30mm, 95% CI: -54.9, -5.10).

In summary, one study found clinically meaningful improvements in pain immediately after therapy and at six-months follow up. In addition, this study showed that GMI was significantly better than routine physiotherapy immediately after therapy and at six-month follow up.

2.3.6 Effects of interventions on disability (secondary outcome)

Graded Motor Imagery Programme

Moseley's [20] comparison of a 6-week course of GMI to a 6-week course of routine physiotherapy also assessed pain-related disability, using the patient-specific functional scale [66]. Our analysis showed a significant difference between the experimental and control groups when assessed immediately after the final therapy session (6 weeks), t(7)=2.97, p= 0.03. Participants who performed GMI showed a mean change in task performance of 2.20, which was 1.5 points better than the control group (between-group comparison favoured the intervention group by 1.5, 95% CI: 0.82 - 4). However, our analysis of the six-month follow-up data showed no difference between the experimental and control groups, t(7)=1.3, p= 0.31. Participants who performed GMI showed a mean change in performance of patient-specific tasks of 3.8, which was 2.3 points better than the control group (between-group comparison favoured the intervention group by –2.3, 95% CI: -0.71, 3.31). The results of the effects of intervention are summarised in Table 3.

Table 3: The effects of GMI and its individual components on PLP.

Authors	Intervention	Control group	Experimental group (n)	Control group (n)	Experimental group Mean ± SD	Control group Mean ± SD	Experimental group Mean Difference	Control Mean Difference	Mean Difference (0-100mm VAS)
Brodie et al.[63]	Mirror feedback	Obscured mirror	8	7	29±31.9	40±40.1	-17 mm	-4 mm	-11 [-48.03, 26.03]
Chan et al., (a) (2007)	Mirror feedback	Obscured mirror	7	6	17.17±21.2	34.0±22.05	-24 mm	-3mm	-16.83 [-41.31, 7.65]
Chan et al., (b) (2007)	Imagined movements	Obscured mirror	6	6	57.5±20.08	34.0±22.05	+14 mm	-3 mm	+23.5 [-0.36, 47.36]
Moseley (2006)	GMI	Routine care	5	4	21±0.8	46±14	-32.4 mm	-5.8 mm	-25 [-38.74, -11.26]
Tilak et al., (2016)	Mirror feedback	TENS	13	13	20.8±16.2	24.6±15.6	-33.8 mm	-25.4 mm	-3.8 [-16.03, 8.43]
Tung et al., (2014)	Imagined movements	Movement observation	9	11	27.5±21	28.5±8.25	-10 mm	-26.5 mm	-1 [-15.56, 13.56]
Ulger et al., (2009)	Imagined movements	General exercise	10	10	61.0±7.4	76.0±5.2	-31 mm	-17 mm	-15 [-20.61, -9.39]

2.4 Discussion

The aim of this systematic review was to evaluate the effectiveness of GMI and its components on PLP in amputees. We found six eligible studies, all of which had a high risk of bias. Only the full GMI programme was found to be more effective than a control intervention for reducing PLP in people who have undergone amputations.

2.4.1 Effects of GMI and its components on PLP

(a) Mirror therapy

Mirror therapy is the most studied of all the interventions included in this review [67]. However, we found that most studies of mirror therapy were small, non-controlled trials which were not eligible for inclusion in this review [68-72]. Importantly, three studies of mirror therapy that were eligible for this review had high risk of bias, and none followed their participants beyond the immediate post-treatment assessment. Only one study showed marginally positive outcomes of mirror therapy, but it did not show any benefit of mirror therapy over the comparator intervention of Transcutaneous Electrical Nerve Stimulation [65]. The quality of studies in this field is of concern, and we found no data on the long-term effects of mirror therapy. This weak evidence provides no basis for recommending mirror therapy as a stand-alone treatment for PLP. Anecdotally, clinicians seem to favour mirror therapy for PLP, but the weak evidence for mirror therapy suggests that this favouring might be based on its logical hypothesis, rather than the quality of evidence supporting for its efficacy.

(b) Imagined movements

We found conflicting results regarding the efficacy of imagined movements for reducing PLP. Ulger et al [61] reported clinically meaningful pain reductions, Tung et al [62] reported no effect on PLP, and Chan et al [64] reported worsening of pain. It is worth noting that the last two studies [62, 64] used imagined movements as a *control* intervention, while the first (the only study with positive findings) [61] used imagined movements as an *experimental* intervention. Further, all three studies scored poorly for risk of bias. It is therefore possible that the varied results across this pool of three studies are an artefact of various kinds of bias. The most notable concerns regarding study design were lack of random sequence generation, allocation concealment and blinding [73].

An alternative explanation for the conflicting findings of these three studies emerges from a consideration unique to the use of imagined movements in amputees. Raffin et al [74, 75] have pointed out that clinicians using imagined movements with people with intact limbs are able to verify the absence of movement-generating neural activity by monitoring movement of the intact

limb. However, such visual monitoring is not feasible in amputees, because the relevant body part is not present to be watched. It is therefore impossible to visually verify the absence of movement-generating neural activity in amputees participating in imagined movements – yet this verification is necessary, because any such activity would place a higher demand on the neural system than is desirable during imagined movements exercises [75]. In line with this idea, Raffin et al [74] asked amputees with PLP to perform imagined movements, or movements of the phantom limb, and they monitored cortical activity, stump muscle activity, and felt sensations during the task. They found that performance of imagined movements was associated with neural activity in the pre-motor cortex and posterior lobe of the cerebellum, absent stump muscle activity and no pain. In contrast, the task to move the phantom limb was associated with neural activity in the primary somatosensory and primary motor cortices, and the anterior lobe of the cerebellum, increased stump muscle activity and pain. These results support the suggestion that conflicting findings across the three included studies that test the efficacy of imagined movements for reducing PLP in amputees could be due to discrepancies in accurate performance of the imagined movements tasks. In other words, participants asked to *imagine* performing movements may, in fact, have been performing movements, resulting in more neural activation than is desired.

(c) Left/right judgements

We found no studies that evaluated left/right judgements as a stand-alone treatment for PLP. This is surprising in light of data linking left/right judgements to inhibitory 'priming' of brain areas that are involved in preparation for movement [76]. Those data provide a logical rationale for the use of left/right judgements as the first step in the GMI programme [39], yet other studies that applied GMI to a group with mixed chronic pain conditions found left/right judgements alone to have no effect on pain [20, 40].

(d) Graded Motor Imagery Programme

Only one study that was eligible for inclusion in this review [20] evaluated GMI as a treatment for PLP and pain-related disability. It showed that GMI had a beneficial and lasting effect, corroborating the results of a retrospective case series [77] in which GMI produced significant pain reductions in three of four traumatic amputees with PLP. Nonetheless, the generalisability of its findings is limited, due to a small sample size (n=9) and a homogenous sample of lower limb amputees. Replicating these positive findings in robust randomised, controlled trials will be important to shed light on the efficacy of GMI in both upper and lower amputees with PLP.

2.5 Limitations

The current review excluded studies written in languages other than English, due to a lack of translation resources. Of the studies included, two were randomised controlled trials, all had high risk of bias and only one study followed up participants beyond the time of treatment cessation. Therefore, the strength of our findings is limited by the quality of the literature base itself and the effects of the interventions over the long term is apparent for the full GMI programme only. The included studies represented a small number (n=20) of upper limb amputees, so the results may have limited generalisability to PLP of the upper limb.

In conclusion, this systematic review found weak evidence that the full Graded Motor Imagery programme is effective for reducing PLP in amputees, and that neither imagined movements nor mirror therapy yields benefits that are superior to comparator interventions. This conclusion was derived from the results of few studies with relatively small sample sizes. More evidence and higher-quality studies are needed to generate a definitive conclusion regarding the efficacy of the Graded Motor Imagery programme for reducing phantom limb pain in amputees.

Chapter 3: What modalities are physiotherapists using to manage PLP? A cross-sectional descriptive study

Several interventions for reducing PLP have been proposed in the literature. However, there is no intervention that has been established as a first line of treatment for PLP [78]. There is systematic review evidence suggesting that GMI is more effective than routine physiotherapy interventions for managing PLP [39, 79]. However, little is known about what interventions are used by physiotherapists working in the government health-care system in South Africa. To fill the gap in the literature, the pilot survey was designed and conducted to describe the modalities used by physiotherapists for managing PLP, and to determine how frequently these modalities are used for treating PLP, particularly GMI which seems superior to other modalities for reducing PLP. The pilot survey will be used to inform a future nationwide e-survey of physiotherapy practice for PLP. The results from the nationwide e-survey will be used to motivate for the design and implementation of education programmes on the effective management of PLP in people who have undergone amputations.

3.1 Aim

To describe the modalities used by physiotherapists for managing PLP.

3.2 Research design

A cross-sectional descriptive survey was designed. This design was chosen because it analyses data at a specific time-point thus providing information on the outcomes of interest at a given point in time. In addition, because data is collected at a specific time-point, cross-sectional designs are not susceptible to loss to follow-up. Further, cross-sectional surveys are generally quick and cost-effective [80].

3.3 Participants

The whole population of physiotherapists practicing at New-Somerset, Khayelitsha and Victoria hospitals during the period of the study was considered. The participants were excluded if they were physiotherapy students or unregistered with the Health Professional Council of South Africa.

3.4 Instrumentation

3.4.1 Physiotherapy Modalities Questionnaire

To identify which modalities are used by physiotherapists to treat PLP, we used a purpose-designed questionnaire (Appendix E) that was based on information found on Physiopedia (www.physio-

pedia.com) that described evidence-based physiotherapy modalities commonly used to manage PLP in amputees. On our questionnaire, each treatment modality was referenced with literature indicating its efficacy for PLP. On the list of treatment modalities, physiotherapists were asked to indicate how often they have used these treatment techniques to manage PLP, with options of "never" to "seldom", "sometimes" or "often".

3.5 Recruitment and Procedure

All the physiotherapists working in the respective hospitals were provided with study information sheets and if they were interested in participating in the study, asked to sign consent forms (Appendix F). Physiotherapists who agreed to take part in the study were given the questionnaires to complete in a private space. The completed questionnaires were then collected for analysis.

3.6 Statistical Analysis

Data were entered into an excel spread sheet and summarised as median (range) where appropriate. Results are presented as frequency tables with treatment techniques ranked from those most often used to those least often used.

3.7 Ethical considerations

This study adhered to the biomedical ethical values of autonomy, non-maleficence, beneficence, confidentiality, justice and informed consent originally described by Beauchamp and Childress [81].

3.7.1 Autonomy

Autonomy was upheld by providing participants with a comprehensive information pack (Appendix F) written in lay terms. The information pack outlined the study's main aims and objectives, as well as the participant's rights and responsibilities, and a consent form which participants signed as an agreement to participate in the study.

3.7.2 Non-Maleficence

The questionnaires were completed in a secure environment with limited risks. The process of completing the questionnaires was brief and had no potential side effects on the participants.

3.7.3 Beneficence

Currently there is no treatment that is recommended as a stand-alone treatment for PLP. The purpose of this study was to identify modalities used for PLP and the quality of evidence supporting their use in clinical practice, to inform research and clinical practice on this subject.

3.7.4 Justice

Participants were treated in an unbiased and just manner, regardless of their race, gender, ethnicity, income or socio-economic status.

3.7.5 Confidentiality

The names of the participants were not recorded but instead, each participant was assigned a numerical code. Data were stored on a password-protected external drive, accessible to the principal investigator and the responsible supervisors only.

3.8 Results

3.8.1 Participant demographics

The results presented below are for a sample of eight female physiotherapists working in the government health care sector at three hospitals in the city of Cape Town. The median age of the participants was 31 (25-36) years. The median years of experience between the participants was 8.5 (1-12).

3.8.2 Physiotherapy modalities for PLP

The detailed results of the modalities used by physiotherapists for managing PLP are presented in Table 4. Exercise (n=7) and massage (n=5) were the most often used modalities for managing PLP. TENS (n=4), mirror therapy (n=2) and therapeutic ultrasound (n=3) were the least used modalities. None of the participants used GMI, biofeedback, or sensory discrimination training for managing PLP.

Table 4: Routine physiotherapy modalities used by physiotherapists for managing PLP.

Physiotherapy modalities	**Frequency of use (n=8)**			
	Never	Seldom	Sometimes	Often
Exercise	0	0	1	7
Massage/Desensitization	0	0	3	5
TENS	3	4	1	0
Mirror therapy	6	2	0	0
Therapeutic Ultrasound	5	3	0	0
Graded motor imagery	8	0	0	0
Biofeedback	8	0	0	0
Sensory discrimination training	8	0	0	0

3.9 Discussion

The results of this pilot survey show that exercise and massage are the most commonly used modalities by physiotherapists for reducing PLP. Although the results of the systematic review suggest that GMI is more effective than routine physiotherapy, none of the physiotherapists included in this survey has ever used GMI as a treatment for reducing PLP, but often used exercise and massage instead. Judging from the number of years of experience [8.5 (1-12)], it is concerning that the participants have never utilised GMI, which has been shown to be more effective than routine physiotherapy modalities for reducing PLP [20]. These results suggest that the participants might not be informed about the treatment and its potential efficacy for reducing PLP. This raises an awareness about the importance of translating and disseminating research findings with health professionals to improve the quality of primary health-care in South Africa. Regardless of these findings, a definitive conclusion cannot be drawn from this pilot-survey because of a small and less representative sample of physiotherapists involved in the study. However, the results from this study will be used to inform a future nationwide e-survey of physiotherapy practice for PLP.

Conclusion

The results of this pilot survey suggest that physiotherapists may not be informed about GMI and its potential efficacy for reducing PLP in people who have undergone amputations. Considering a small sample size and a less representative sample of physiotherapists in this pilot study, this pilot study will be upgraded to a large nationwide e-survey from which a conclusion concerning modalities used by physiotherapists for treating PLP will be drawn.

Chapter 4: The effectiveness of GMI for PLP and Disability in upper and lower limb amputees. A randomised controlled trial - Methods

In this chapter, the aims and objectives of the study will be presented followed by a brief description of a research design with reasons justifying its implementation in this research study. Furthermore, this chapter will elaborate on the instruments used to collect data, and provide the details of the research methodology.

4.1 Aims and Objectives

4.1.1 Aims of the study

The aim of this study is to investigate the effectiveness of GMI in upper and lower limb amputees with PLP.

4.1.2 Objectives of the study

1. To determine whether GMI reduces PLP as assessed using the Brief Pain Inventory (BPI).
2. To determine whether GMI improves health-related quality of life as assessed on the Euro-Qol (EQ-5D-5L).
3. To determine whether GMI is more effective than routine physiotherapy for reducing PLP in people with upper and lower limb amputations.

4.1.3 Hypothesis

GMI is more effective than routine physiotherapy in alleviating PLP and disability in people who have undergone upper and lower limb amputations.

4.1.4 Null Hypothesis

GMI is not more effective than routine physiotherapy in alleviating PLP and disability in people who have undergone upper and lower limb amputations.

4.2 Research Design

A single-blind randomised, controlled trial (RCT) was designed. The independent outcome assessor was blinded to group allocation, whereas the treating clinician was blinded to outcome assessment. This design was chosen because the randomisation minimises selection and allocation bias, thus ensuring a balance of participants' characteristics in the experimental and control groups [73]. In addition, having a control group allows for comparison of the efficacy of the experimental intervention against the control intervention [73]. Furthermore, the blinding of the outcome

assessment minimises bias, which in turn reduces the risk of overestimating the overall treatment effect [82].

4.3 Research setting

The study was conducted in the physiotherapy out-patient departments of New-Somerset, Victoria and Khayelitsha hospitals. These secondary-level hospitals are based within the Cape Town Metropolitan area and serve patients from within and outside the Western Cape Province of South Africa. These three hospitals share a similar frequency of amputation surgeries throughout the year.

4.4 Participants

The population of interest were adults (≥18 years) who had undergone unilateral upper or lower limb amputations and had self-reported PLP persisting beyond three months after amputation. The names and contact details of patients who had undergone amputations between January 2013 and December 2016 were retrieved from hospital records. The patients were then contacted telephonically to inform them about the study and invite them to participate. The patients interested in the study were screened against the inclusion/exclusion criteria using a telephone-administered questionnaire. The patients were excluded if they had double amputations, psychopathological disorders, motor problems, or severe systemic illness, previous GMI treatment, or visual impairment such that they cannot read unaided or with their reading glasses. The eligible participants were invited to the hospital for further screening, informed consent and baseline outcome assessment. The rest of the inclusion and exclusion criteria are listed in Table 5.

4.5 Sample Size Determination and Power Analysis

The study sample size was determined by using data from a previous, similar study [20]. The required sample size was calculated to have sufficient power to determine a risk ratio using a minimal clinically meaningful change of 3 (SD=2.1) on a scale of 0-10 for pain severity on the Brief Pain Inventory (BPI). Statistical significance and power were set at 0.05 and 0.9 respectively. The sample size was calculated using the online sample size calculator available at http://hedwig.mgh.harvard.edu/sample_size/size.html and showed that 22 participants were required, with 11 participants in each treatment arm.

Table 5: The Inclusion and exclusion criteria for participation in the study.

Inclusion Criteria	Exclusion Criteria
Amputees with self-reported phantom limb pain as assessed on the brief pain inventory.	Double amputees
Amputations due to diabetic peripheral neuropathy, cardiovascular diseases, infection and trauma.	Psychopathological disorders as recorded in their medical folder.
Trans-humeral and Trans-radial amputations; Elbow and wrist disarticulations, Trans-femoral and Trans-tibial amputations; Knee and Ankle disarticulations.	Motor Problems screened through cerebellar dysfunction tests (Walker, Hall & Hurst, 1990).
3 or more months since amputation.	Visual impairment such that they are unable to read the information sheet and informed consent forms unaided or with their normal reading glasses.
Medically stable for a period of 3 months post amputation	Associated severe medical problems preventing participation.
18 years and older.	Previous graded motor imagery treatment

4.6 Outcome Measures

The Brief Pain Inventory was used to measure the primary outcome – PLP (Appendix H). The EuroQol (EQ-5D-5L) was used to measure secondary outcomes: disability and health-related quality of life (Appendix I). These instruments were made available in the participants' language of choice (English, isiXhosa or Afrikaans) to allow the participants to answer the questionnaires easily and accurately. The participant demographics questionnaire (Appendix J) was used to gather participants' characteristics. The assessment tools are described below.

4.6.1 Pain

Most studies only assess pain by quantifying its severity on a 0-10 scale, without assessing its emotional and functional effects. Taking into consideration the complex bio-psychosocial nature of pain, using a numerical scale (0-10) for assessment of pain would not be sufficient. The Brief Pain Inventory is aligned with a broad bio-psychosocial framework, due to its ability to assess the sensory,

emotional and functional aspects of the pain experience [83]. There is substantial evidence showing that pain affects these three spheres of life [84]. Therefore, the BPI was used to comprehensively assess the participants' pain experience.

The Brief Pain Inventory was primarily designed to assess cancer-related pain [85]. However, its use has been extended to several other chronic pain conditions including but not limited to PLP, CRPS1 and low-back pain [86, 87]. The first section of the BPI consists of four questions which require the patient to rate the severity of their worst, average, least and current pain from 0 to 10. A mean score is then calculated from these four ratings to determine the pain severity score (PSS) out of 10. The second section consists of seven questions exploring the interference of pain (from 0-10) with general activity, mood, walking ability, and work, relations with other people, sleep and enjoyment of life. A mean score is then calculated from seven ratings to determine the pain interference score (PIS) out of 10.

The BPI has been validated [88, 89] and used in several studies [90, 91] to assess the severity (ICC=0.81) and interference (ICC=0.89) of PLP in amputees. It has also been validated for the assessment of pain severity (ICC=0.77) and pain interference (ICC=0.83) in a sample of amaXhosa women living with Human Immunodeficiency Virus (HIV) living in Cape Town, and translated and validated in several South African languages, including isiXhosa and Afrikaans [89]. The instrument thus appears to be a valid and reliable measure of pain in people from Cape Town suffering from PLP whose home language is English, Afrikaans or isiXhosa.

4.6.2 Disability

The EQ-5D-5L is a comprehensive instrument that assesses disability which has been used in several studies to assess the quality of life in upper and lower limb amputees with PLP [92-94]. The EQ-5D-5L assess five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Responses to these dimensions are presented in five levels: "no problems", "slight problems", "moderate problems", "severe problems", or "extreme problems". The second section of this instrument requires the patient to rate the quality of their health on a visual analogue scale ranging between 0 (worst imaginable health state) and 100 (best imaginable health state). Three of the dimensions of the EQ-5D-5L (mobility, usual activity and pain) overlap with components of the pain interference scale of the BPI. The overlapping dimensions between the two instruments enabled us to monitor consistency in the participants' self-reports.

The English version of the EQ-5D-5L instrument has been translated and validated in urban groups who speak isiXhosa (ICC=0.63) [95] and Afrikaans (ICC=0.79) [95]. The instrument thus appears to be

a valid and reliable tool to measure health related quality of life in people from Cape Town suffering from PLP whose home language is English, Afrikaans or isiXhosa.

4.6.3 Demographics

A customised self-report demographic questionnaire was developed to obtain information on the participants' characteristics, including home language, age, gender, highest level of education, employment status, cause of amputation, number of months since amputation and co-morbidities.

4.7 Procedure

The research process was initiated by submission of the research proposal to the University of Cape Town (UCT) Faculty of Health Sciences Human Research Ethics Committee (HREC) for approval. Once the ethical approval was obtained (Appendix K; HREC Ref: 244/2016), the trial was registered with the Pan African Clinical Trials Registry (PACTR), PACTR ref: PACTR201701001979279 (http://www.pactr.org). Visits to each hospital were then conducted to discuss the project with the rehabilitation team at each site to ensure that the study would not have a negative impact on service delivery. Subsequently, the application for research approval was sent to the Western Cape Health Department (WCHD) using the online submission system. Following the approval of the study by WCHD (WC_2016RP11_259), formal letters requesting support to conduct research in hospitals were forwarded to the head of the physiotherapy department at each hospital (Appendix L).

4.7.1 Data Collection

An independent outcome assessor who was blinded to group allocation collected pre-intervention data using the demographic questionnaire, BPI and EQ-5D-5L. The blinded outcome assessor is a qualified occupational therapist who is fluent in English and isiXhosa languages, and trained in the administration of the instruments. Participants allocated to the experimental group were then treated by the researcher, using GMI, while those in the control group were advised to continue rehabilitation at their respective physiotherapy outpatient departments. The same blinded outcome assessor collected data immediately after the intervention and three months later.

4.7.2 Experimental Intervention

The GMI programme sequentially activates the cortical motor networks to achieve a therapeutic effect [40]. During the planning and execution of movement, cortical networks are activated in the order of pre-motor, primary Somatosensory (S1) and Primary Motor cortices (M1) [96]. The three GMI phases therefore activate cortical networks in this order, to achieve a progressive therapeutic effect. During the initial session, the rehabilitation protocol was explained in detail by the treating

clinician to the participants. The clinician explained that PLP is a painful condition driven by functional changes in brain and that GMI is a treatment strategy which aims to manage PLP by retraining the brain.

As illustrated in Table 6, each GMI phase was carried out for two weeks, during which the patient received treatment for 30 minutes on two separate days of the first week (at least one day apart) and continued with a structured home-exercise programme (Appendix M) during the first week until the end of the second week. To maximise adherence to the programme, participants received weekly telephonic calls to remind them to continue with the home-programme and to record their participation in a journal (Appendix N). Patients were provided transport to and from the hospital for the physiotherapy appointments and a home exercise pack, two magazines, a journal, a pen and a mirror (300mm x 300mm).

Table 6: Details of the GMI programme.

Treatment Phase	**Frequency**	**Home Program**
Left/right judgements	Week 1 (Therapy twice/week) Week 2 (Home program)	- Magazines - 10 min/every waking hour
Imagined movements	Week 3 (Therapy twice/week) Week 4 (Home program)	- Folder with 20 photos in postures involving simple movements. - Document with home instructions - 10 min/every waking hour.
Mirror therapy	Week 5 (Therapy twice/week) Week 6 (Home program)	- 300mm x 300mm mirrors with stands. - 10 min/every waking hour.

(a) Left/right judgements

The Neuro Orthopaedic Institute (NOI) recognise™ software application was set to “vanilla”, in which images are presented on a plain background to minimise distractions [97]. Fifty photographs of the limb representing the amputated limb were presented in various positions and alignments on a computer screen in front of a comfortably seated participant. Each photograph was presented for five seconds, during which the participant matched the side of the presented photograph by pressing a left or right key on the tablet. The recognise software recorded the duration of the trial, response time and the accuracy of each response. These left/right judgements tasks were looped for 30 minutes per treatment session.

For the home-exercise programme, participants were instructed to identify and circle limbs which matched the side of their amputated limb in magazines they were provided. Participants were asked to perform these tasks for 10 minutes during every waking hour from 9:00am - 9:00pm every day (12 sessions daily).

(b) Imagined movements

During imagined movements, participants were shown an image of the amputated limb in an easy to attain position, following which they were instructed to imagine moving their amputated limb slowly and smoothly from rest to the presented posture and back to the starting position. Participants were advised to imagine themselves performing the movement instead of imagining someone else performing the movement. Imagined movements tasks were performed repeatedly, using three photographs for each 30-minute treatment session.

For the home exercise programme, participants replicated the instructions of the treatment session and performed exercises for 10 minutes of every waking hour from 9:00am - 9:00pm every day (12 sessions).

(c) Mirror therapy:

During mirror therapy, the amputated limb was concealed behind a mirror (300mm x 300mm) with the intact limb positioned comfortably in front of the mirror. The patient was then shown a picture of the unaffected limb in an easy to attain position and instructed to simultaneously move the intact limb and the phantom limb into the presented posture while observing the reflection of the intact limb in the mirror. Mirror therapy was performed for 30 minutes per treatment session.

During the home exercise programme, participants replicated the instructions of the treatment session and performed exercises for 10 minutes of every waking hour from 9:00am - 9:00pm every day (12 sessions).

4.7.3 Control Intervention

Patients in the control intervention arm were advised to continue rehabilitation at their respective out-patient departments and to continue with home programmes of their own preference as frequently as possible or as prescribed by their clinicians. Participants were provided a pen and a diary in which to record their participation throughout the study.

4.8 Ethical Considerations

This study adhered to the biomedical ethical values of autonomy, non-maleficence, beneficence, confidentiality, justice and informed consent originally described by Beauchamp and Childress [81].

4.8.1 Autonomy

Autonomy was upheld by providing participants with a comprehensive information pack (Appendix O) written in lay terms. The information pack outlined the study's main aims and objectives, potential risks and benefits involved in partaking in the study, as well as the participant's rights and responsibilities, and a consent form which participants signed as an agreement to participate in the study. This information was provided to allow the participants to partake in the study willingly, without being manipulated. If participants wished to withdraw from the study for any reason, they were allowed to do so without any consequences.

4.8.2 Non-Maleficence

GMI was conducted by a qualified and registered physiotherapist to ensure that treatment was performed appropriately and effectively. GMI is a non-invasive and low risk intervention [40]. However it can increase pain and swelling in some patients [40].

4.8.3 Beneficence

Recent literature has revealed the potential beneficial effects of GMI and its components on PLP [79]. The purpose of this study was to determine whether these beneficial findings could be replicated to allow amputees with PLP to receive accessible and cost-effective treatment in their communities.

4.8.4 Justice

Participants were treated in an unbiased and just manner, regardless of their race, gender, ethnicity, income or socio-economic status. Participants were equitably provided with transport and clinical resources at no cost. GMI is a low-resource intervention and the skills required to deliver it can easily be acquired by physiotherapists, making it a viable treatment option in the South African healthcare system. The positive results of this study will be used to motivate for training in GMI for physiotherapists to allow people who have undergone amputations (including those in control arm of this study who will be contacted and advised to make an appointment with their physiotherapist) to receive GMI from their clinicians as part of their ongoing management.

4.8.5 Confidentiality

The names of the participants were not recorded but instead, each participant was assigned a numerical code. Data were stored on a password-protected external drive, accessible to the principal investigator and the responsible supervisors only. Physiotherapist in participating out-patient departments were reminded to uphold the ethical principle of confidentiality throughout this study.

4.9 Data Analysis

Data from the printed BPI and EQ-5D-5L assessment forms were entered electronically and organised on a Microsoft Excel spreadsheet (2016). These data were then stored in password-protected electronic folders accessible to the researcher and designated supervisors. In addition, back-up data was saved on various online storage platforms. The hard copies were destroyed. Data was analysed using STATISTICA software [98]. A clinically meaningful reduction in pain (pain reduction of 3 or more) was used to classify treatment as successful. The results from the BPI showed that the pain severity scores at baseline were non-normally distributed. Therefore, non-parametric statistics were used to analyse numerical data and Pearson Chi-squared (χ^2) tests for categorical data. In addition, the median difference (MD) was calculated by subtracting the median pain scores at 6 weeks and 3 months from the median pain scores at baseline. The Absolute Risk Reduction (ARR) [control event rate (CER) – $\mathrm{experimental\ event\ rate\ (EER)}$], Relative Risk Reduction (RRR) [$\frac{ARR}{CER}$], Number Needed to Treat (NNT) [$\frac{1}{ARR}$] and Odds Ratio (OR) were calculated to determine the efficacy of treatment at multiple data collection points. As illustrated in Table 7, the odds ratio were calculated by dividing the product of exposed cases (*a*) and non-exposed controls (*d*) by the product of non-exposed cases (*c*) and exposed controls (*b*). Statistical significance was accepted at $p<0.05$.

Table 7: The odds ratio calculation.

	Cases (+)	Controls (-)
Exposed (+)	*a*	*b*
Non-Exposed (-)	*c*	*d*

$$OR = \frac{a\ x\ d}{c\ x\ b}$$

Summary of the methods

To realise the aim and objectives of the study, a single-blind randomised, controlled trial was conducted in three secondary level hospitals in Cape Town, South Africa. The population of interest were adults (≥18 years) who had undergone unilateral upper or lower limb amputations and had self-reported PLP persisting beyond three months after amputation. The pain severity scale of the brief pain inventory (BPI) was used to assess the primary outcome – PLP. The pain interference scale of the BPI and the EuroQol EQ-5D-5L were used to assess the secondary outcomes- Pain interference with function and HRQoL respectively. Participants in the experimental and control group performed treatment for six weeks. Outcome assessment was conducted at baseline, immediately after treatment (week 6), and 3-months and 6-month follow-up. Data were analysed using non-parametric statistics. Statistical significance was accepted at $p<0.05$.

Chapter 5: The effectiveness of GMI for PLP and Disability in upper and lower limb amputees. A randomised controlled trial – Results

5.1 Socio-demographic information

The results presented below are for the sample of 21 participants (experimental n=11; control n=10). As illustrated in Figure 3, from the population of 224, 147 people were unreachable. Of the remaining 77 potential participants, nine were deceased, and 68 were available for the initial telephonic screening. Forty-three participants were excluded on telephonic screening because they did not have PLP. Twenty-five people attended hospital for full screening, to provide written informed consent, and to undergo baseline testing. At that session, four participants were excluded due to pathology in the intact limb (n=1), severe motor impairment of the intact limb (n=1) or double amputation (n=2). The remaining participants (n=21) were allocated to the experimental and control groups using a randomised computer-generated list, during which 11 and 10 participants were allocated to the experimental and control groups respectively.

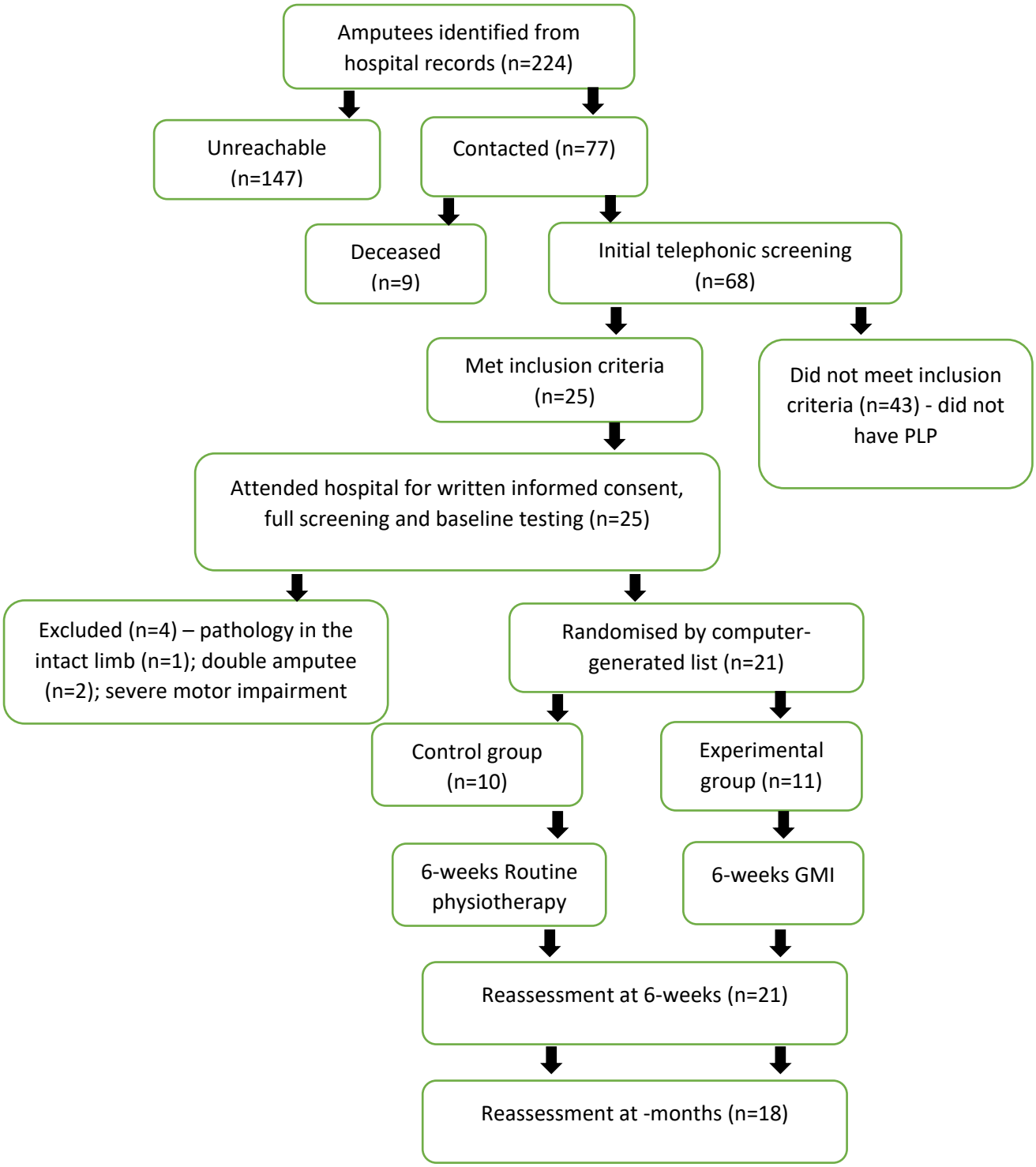

Figure 3: Consort diagram illustrating the process from recruitment to data collection (3-month follow-up).

5.1.1 Participants

The median age of the participants was 62 (35-79) years. There was no difference in age between the participants in the experimental and control groups [61.5 (35-77) vs 63 (39-79); U=51.5; p=0.83]. The majority of participants were male (n=16) with no difference in distribution of males/females in the experimental and control groups (χ^2=0.15; p=0.69). The most common reason for amputation was diabetic complications (n=16), with trauma (n=3) and infection (n=2) the other causes. Only one participant had undergone an upper limb amputation (above elbow); and an equal number (n=10) of participants had undergone above knee and below knee amputations respectively. The participants had undergone their amputation surgery a median of 17 (7-46) months prior to recruitment. There was little difference in the number of months since surgery between the experimental and control groups [17 (10-46) vs 20 (7-37); U=53.5; p=0.94] (Table 8).

Table 8: Gender, causes of amputation, types of amputation, and level of amputation of the participants (N=21).

Variable	Participants n=21 Number (%)	Experimental n=11 Number (%)	Control n=10 Number (%)	Statistical Test
Gender				χ^2=0.15; p=0.69
Male	16 (76)	8 (73)	8 (80)	
Female	5 (24)	3 (27)	2 (20)	
Reason for Amputation				χ^2=0.54; p=0.76
Diabetes	16 (76)	9 (82)	7 (70)	
Infection	2 (10)	1 (9)	2 (20)	
Trauma	3 (14)	1 (9)	1 (10)	
Type of Amputation				χ^2=1.15; p=0.28
Lower limb	20 (95)	11 (100)	9 (90)	
Upper limb	1 (5)	0 (0)	1 (10)	
Level of Amputation				χ^2=1.35; p=0.51
Below Knee	10 (48)	6 (55)	4 (40)	
Above Knee	10 (48)	5 (45)	5 (50)	
Above elbow	1 (4)	0 (0)	1 (10)	

5.2 Phantom Limb Pain

5.2.1 Characteristics of PLP

There were no differences between groups for any of the clinical characteristics assessed (Table 9). The words used to describe PLP were burning (n=14), stabbing (n=10), tingling (n=8), itching pain (n=6), cramping (n=5), and shocking (n=3). Twelve (57%) participants had had pain prior to amputation. Most of the participants (n=16) had intermittent PLP while only five had constant PLP.

Table 9: The clinical characteristics of PLP of the participants (N=21)

	Participants N=21 Number (%)	Experimental n=11 Number (%)	Control n=10 Number (%)	Statistical Test
Pattern of Phantom Limb Pain				χ^2=2; p=0.16
Intermittent	16 (76)	7 (64)	9 (90)	
Constant	5 (24)	4 (36)	1 (10)	
Pre-amputation Pain				χ^2=0.06; p=0.80
Yes	12 (57)	6 (55)	6 (60)	
No	9 (43)	5 (45)	4 (40)	
Words to describe Phantom Limb Pain				
burning				χ^2=0.09; p=0.75
yes	14 (67)	7 (64)	7 (70)	
no	7 (33)	4 (36)	3 (30)	
stabbing				χ^2=0.44; p=0.51
yes	10 (48)	6 (55)	4 (40)	
no	11 (52)	5 (45)	6 (60)	
shocking				χ^2=0.51; p=0.48
yes	3 (14)	1 (9)	2 (20)	
no	18 (86)	10 (91)	8 (80)	
cramping				χ^2=0.15; p=0.69
yes	5 (24)	3 (27)	2 (20)	
no	16 (76)	8 (73)	8 (80)	
tingling				χ^2=0.03; p=0.86
yes	8 (38)	4 (36)	4 (40)	
no	13 (62)	7 (64)	6 (60)	
itching				χ^2=0.69; p=0.40
yes	6 (29)	4 (36)	2 (20)	
no	15 (71)	7 (64)	8 (80)	

5.3 Pain Severity Score (PSS) and Pain Interference Score (PIS)

Error! Reference source not found. illustrates the Pain Severity Scores (PSS) and Pain Interference Scores (PIS) obtained from the BPI at baseline, 6 weeks and 3-months follow up. There were no between-group differences in PSS (U=40; p=0.31) or PIS (U=27; p=0.05) scores at baseline.

5.3.1 Pain Severity Score

There was a statistically significant improvement in PSS within both groups at 6 weeks [experimental group MD 4.25, p=0.007; control group MD 1.75, p=0.002] and 3 months after the interventions [experimental group MD 5, p=0.0004; control group MD 1.37, p=0.001] (Figure 4).

Figure 5 illustrates individual changes over time and suggests that, at an individual level, improvements in pain may have been greater in the experimental group than the control group. This suggestion is supported by an odds ratio of 10.5 [95% CI: 1.36 – 81.1, p=0.02] and 4.5 [95% CI: 0.63 – 32.3, p=0.14] at 6 weeks and 3 months respectively. This means that the experimental group had a 10.5 greater chance of having a clinically meaningful improvement in their pain immediately after treatment.

For pain severity, the absolute risk reduction was 0.52 at 6 weeks and 0.32 at 3 months. The relative risk reduction was 0.74 at 6 weeks and 0.64 at 3 months. The number needed to treat was 1.9 [95% CI: 1.1 – 6.5] at 6 weeks and 3 [95% CI: 1.9 – 7.1] at 3 months.

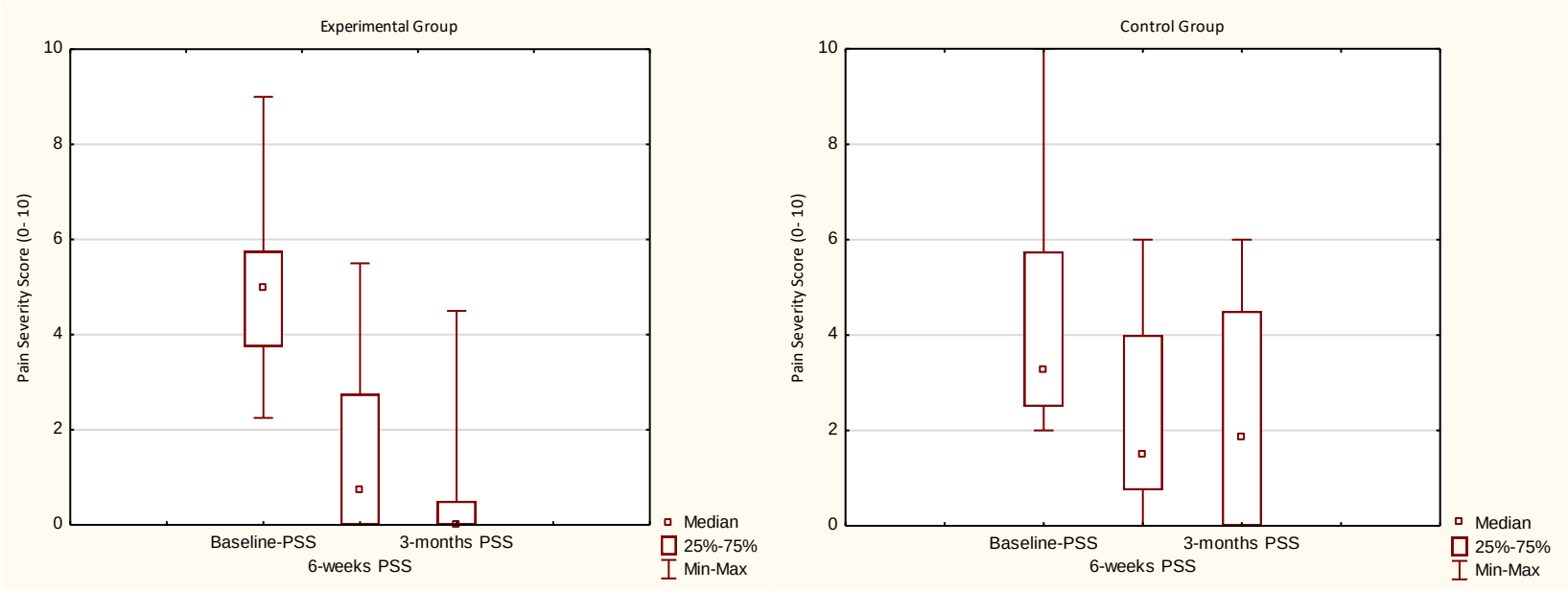

Figure 4: Friedman's ANOVA of change in Pain Severity Scores for the Experimental (n=11) and Control (n=10) Groups over time.

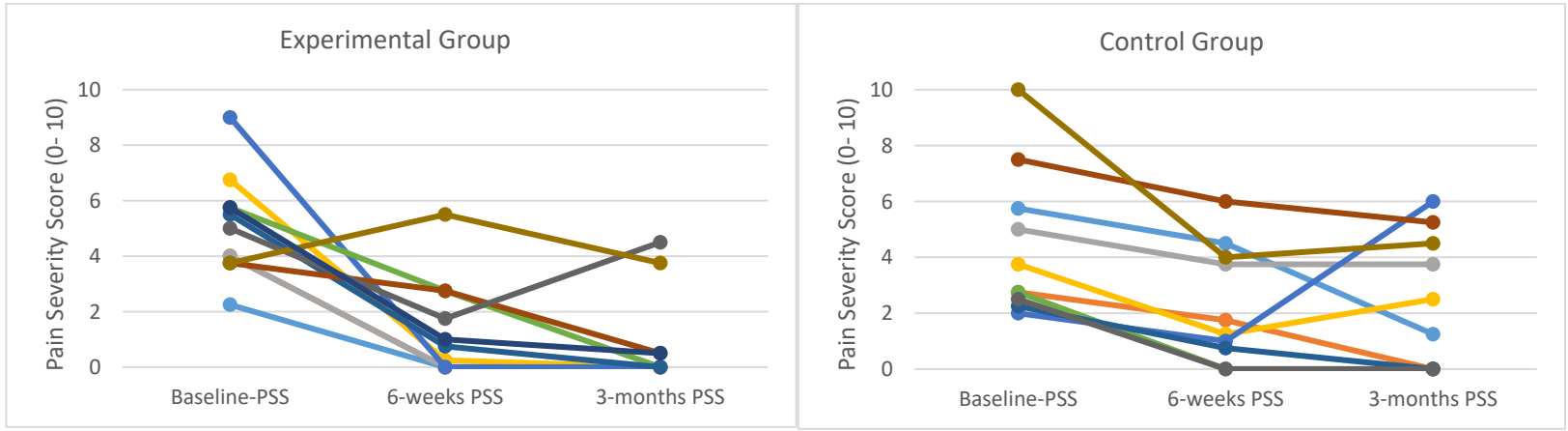

Figure 5: Spaghetti Plots of change in Pain Severity Scores for the Experimental (n=11) and Control (n=10) Groups.

5.3.2 Worst, least, average and current pain scores.

The experimental group had significant improvements in all the components of the PSS from baseline to 3 months follow-up (**Error! Reference source not found.**). The control group showed significant improvements in "worst pain" (MD 2; p=0.007) and "average pain" (MD 1, p=0.005), but no difference in "least pain" (MD 1; p=0.10) and "current pain" (MD 2.5; p=0.16), from baseline to 3-months follow-up. Between-group analysis showed no statistical difference between groups for changes in any of the components of the PSS.

Table 10: Detailed brief pain inventory (BPI) scores showing the worst, least, average and current pain.

	Baseline	6-weeks	3-months	Statistical test
Worst Pain				
Experimental	8 (4-10)	2 (0- 6)*	0 (0- 8)**	*Wk6: (MD: 6; p=0.002) **3 months: (MD: 8; p=0.002)
Control	6 (2- 10)	2.5 (0- 7)*	4 (0- 8)**	*Wk6: (MD: 3.5; p=0.003) 3** months: (MD: 2; p=0.007)
Least Pain				
Experimental	3 (0- 8)	0 (0- 4)*	0 (0 -3)**	*Wk6: (MD: 3; p=0.01) **3 months: (MD: 3; p=0.01)
Control	2 (0- 10)	0 (0- 5)	1 (0 -5)	Wk6: (MD: 2; p=0.16) 3 months: (MD: 1; p=0.10)
Average Pain				
Experimental	5 (3- 8)	1 (0- 5)*	0 (0- 4)**	*Wk6: (MD: 4; p=0.007) **3 months: (MD: 5; p=0.001)
Control	3.5 (0- 10)	2 (0- 5)*	2.5 (0- 5)**	*Wk6: (MD: 1.5; p=0.008) 3** months: (MD: 1; p=0.005)
Current Pain				
Experimental	5 (0- 10)	0 (0 -7)*	0 (0- 4.5)**	*Wk6: (MD: 5; p=0.03) **3 months: (MD: 5; p=0.002)
Control	2.5 (0- 10)	2 (0- 8)	0 (0- 9)**	Wk6: (MD: 0.5; p=0.53) **3 months: (MD: 2.5; p=0.16)

* and ** indicate significant improvement within groups

5.4 Pain Interference Score

There was a significant improvement in PIS within the experimental group at 6 weeks [MD 5.43, p= 0.0009] and 3 months after interventions [MD 5.43, p= 0.00009]. There was no improvement in PIS within the control group at 6 weeks [MD 0.1; p= 0.74] or 3 months after interventions [MD -0.92; p=0.43] (Figure 6).

Figure 7 shows individual changes over time and suggests that, at an individual level, improvements in pain may have been greater in the experimental group than the control group. This suggestion is supported by an odds ratio of 78 [95% CI: 3.3 – 1849, p=0.0069] and 10 [95% CI: 1.4 – 81.1, p=0.02] at 6 weeks and 3 months respectively. This means that the experimental group had 78 times and 10 times greater chance of having a clinically meaningful improvement in their pain interference at 6 weeks and 3 months respectively.

For pain interference, the absolute risk reduction was 0.73 at 6 weeks and 0.52 at 3 months. The relative risk reduction was 0.95 at 6 weeks and 0.74 at 3 months. The number needed to treat was 1.4 [95% CI: 1 – 1.8] at 6-weeks and 1.9 [95% CI: 1.1 – 6.5] at 3 months.

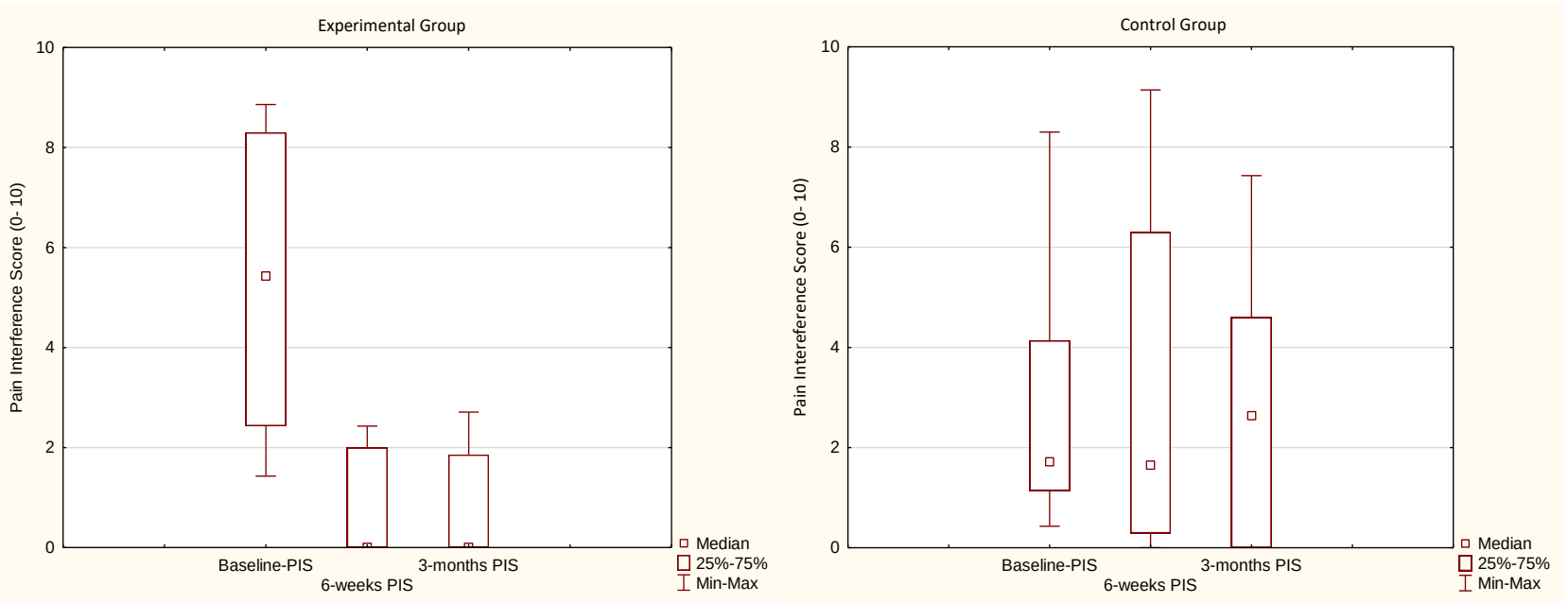

Figure 6: Friedman's ANOVA of change in Pain Interference Scores for the Experimental (n=11) and Control (n=10) Groups over time.

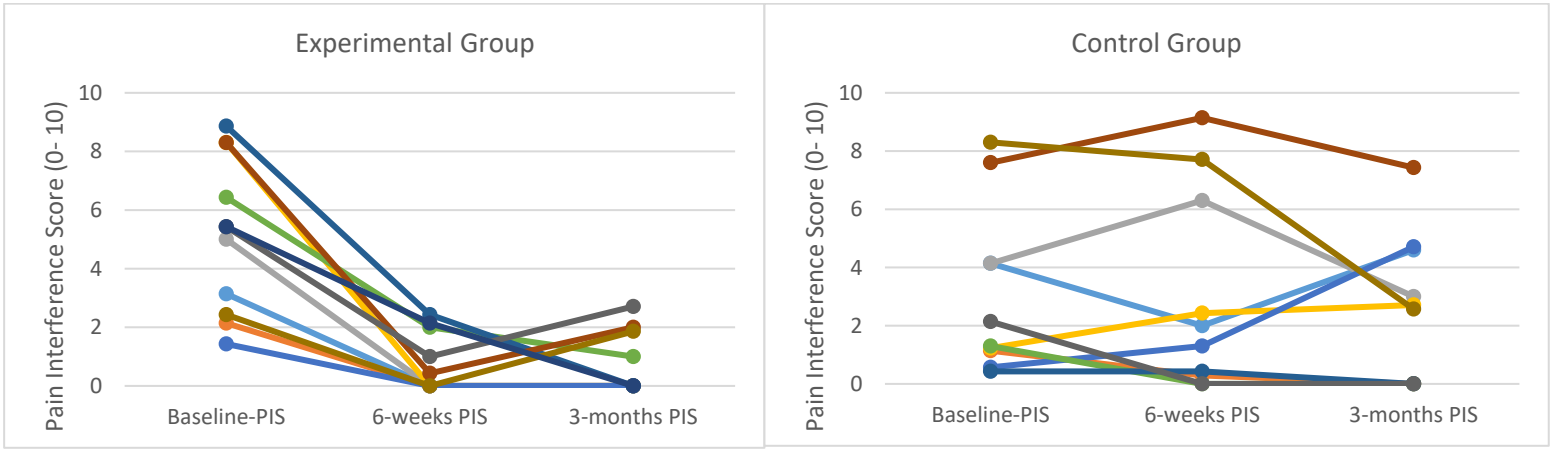

Figure 7: Spaghetti Plots of change in Pain Interference Scores for the Experimental (n=11) and Control (n=10) Groups.

5.4.1 Components of the pain interference scale

The experimental group showed significant improvements in all the component of the PIS from baseline to 3-months follow-up. The control group had no improvement in any of the components of the PIS from baseline to 3-months follow-up (*Table 11*a and *Table 11*b).

Table 11a: Pain interference scores on activity, mood, walking, and work, relations with people, sleep, and enjoyment of life.

	Baseline	6 weeks	3 months	Statistical test
Activity				
Experimental	5 (0- 10)	0 (0- 5)*	0 (0- 5)**	*Wk6: (MD: 5; p=0.008)* **3 months: (MD: 5; p=0.03)*
Control	2.5 (0- 9)	2.5 (0- 9)	2 (0- 8)	Wk6: (MD: 0; p=0.74) 3 months: (MD: 0.5; p=0.33)
Mood				
Experimental	6 (0- 10)	0 (0- 3)*	0 (0- 3)**	*Wk6: (MD: 6; p=0.008)* **3 months: (MD: 6; p=0.01)*
Control	3 (0- 8)	2.5 (0- 10)	3 (0- 8)	Wk6: (MD: 0.5; p=0.5) 3 months: (MD: 0; p=0.68)
Walking				
Experimental	5 (0- 10)	0 (0- 4)*	0 (0- 3)**	*Wk6: (MD: 5; p=0.002)* **3 months: (MD: 5; p=0.0002)*
Control	0.5 (0- 10)	1.5 (0- 10)	2.5 (0- 10)	Wk6: (MD: -1; p=0.71) 3 months: (MD: -2; p=0.90)
Normal Work				
Experimental	4 (0- 10)	0 (0- 3)*	0 (0- 3)**	*Wk6: (MD: 4; p=0.02)* **3 months: (MD: 4; p=0.007)*
Control	2 (0- 10)	1.5 (0- 9)	2 (0- 8)	Wk6: (MD: 0.5; p=0.71) 3 months: (MD: 0; p=0.9)

Table 11b: Pain interference scores on activity, mood, walking, and work, relations with people, sleep, and enjoyment of life.

	Baseline	6 weeks	3 months	Statistical test
Relations with other people				
Experimental	4 (0- 10)	0 (0- 3)*	0 (0- 2)**	*Wk6: (MD: 4; p=0.002)* **3 months: (MD: 4; p=0.0002)*
Control	0 (0- 10)	0 (0- 9)	0 (0- 9)	Wk6: (MD: 0; p=0.6) 3 months: (MD: 0; p=0.61)
Sleep				
Experimental	7 (0- 10)	0 (0- 1)*	0 (0- 3)**	*Wk6: (MD: 7; p=0.002)* **3 months: (MD: 7; p=0.0004)*
Control	3.5 (0- 10)	1 (0- 10)	0 (0- 8)	Wk6: (MD: 2.5; p=0.71) 3 months: (MD: 3.5; p=0.10)
Enjoyment of life				
Experimental	7 (0- 10)	0 (0- 6)*	0 (0- 7)**	*Wk6: (MD: 7; p=0.003)* **3 months: (MD: 7; p=0.002)*
Control	1.5 (0- 8)	0 (0- 10)	0 (0-7)	Wk6: (MD: 1.5; p=0.70) 3 months: (MD: 0; p=0.50)

Analysis of change over time showed that the experimental group had significant improvements over time for pain interference with general activity, mood, walking ability, interference with work and sleep while there were no improvements in the control group (8-12).

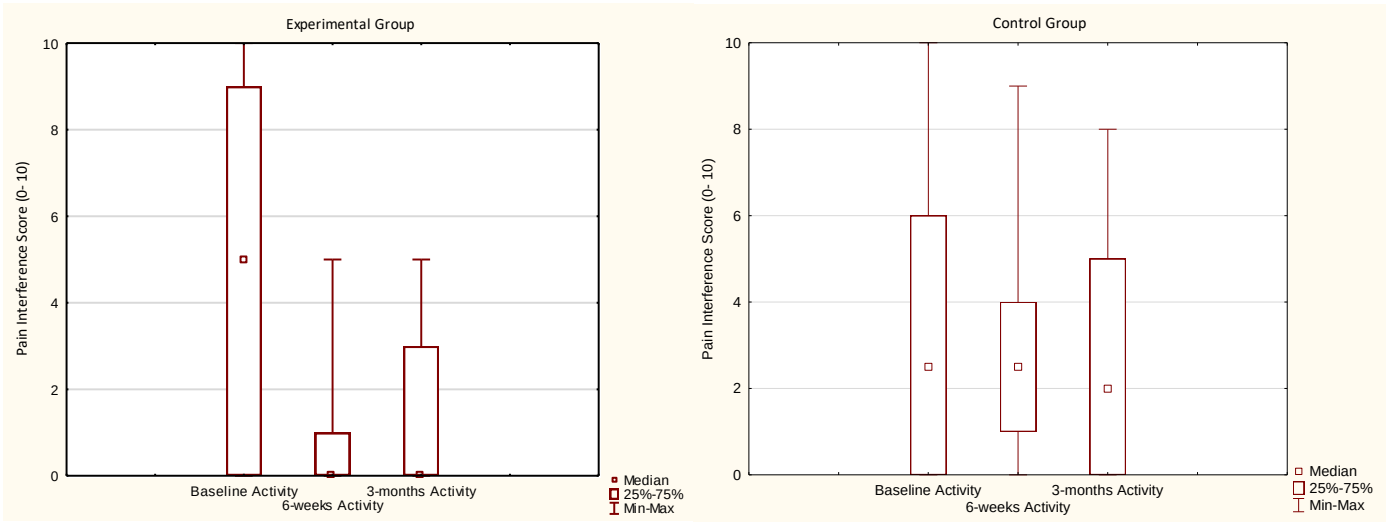

Figure 8: Friedman's ANOVA of change in Pain interference with General Activity for the Experimental (n=11) and Control (n=10) Groups (MD: 5; p=0.03).

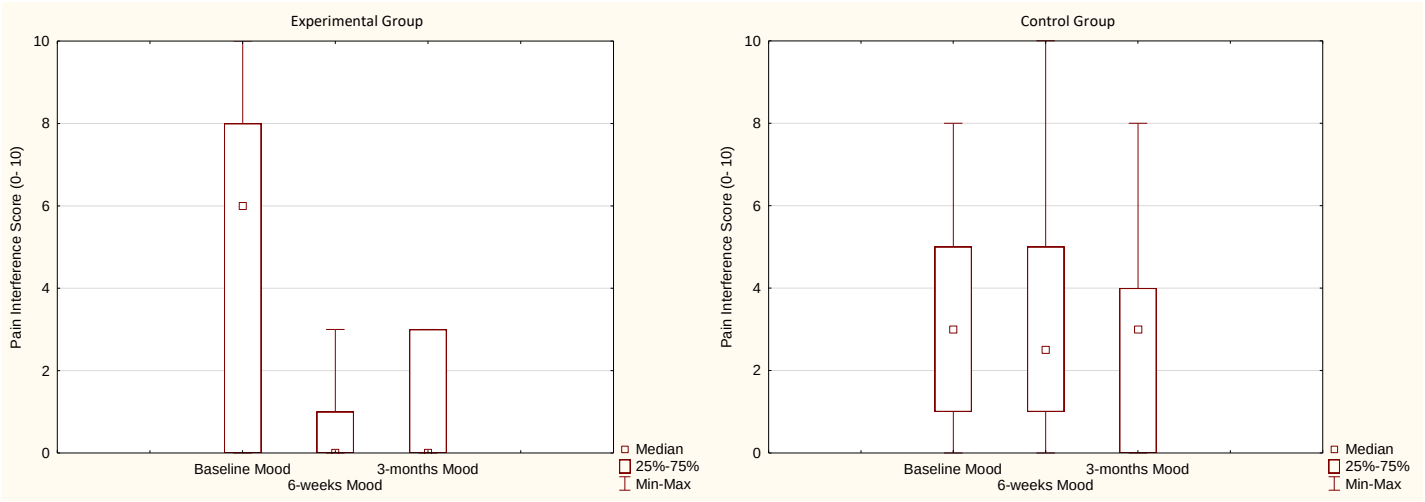

Figure 9: Friedman's ANOVA of change in Pain interference with Mood for the Experimental (n=11) and Control (n=10) Groups (MD: 6; p=0.01).

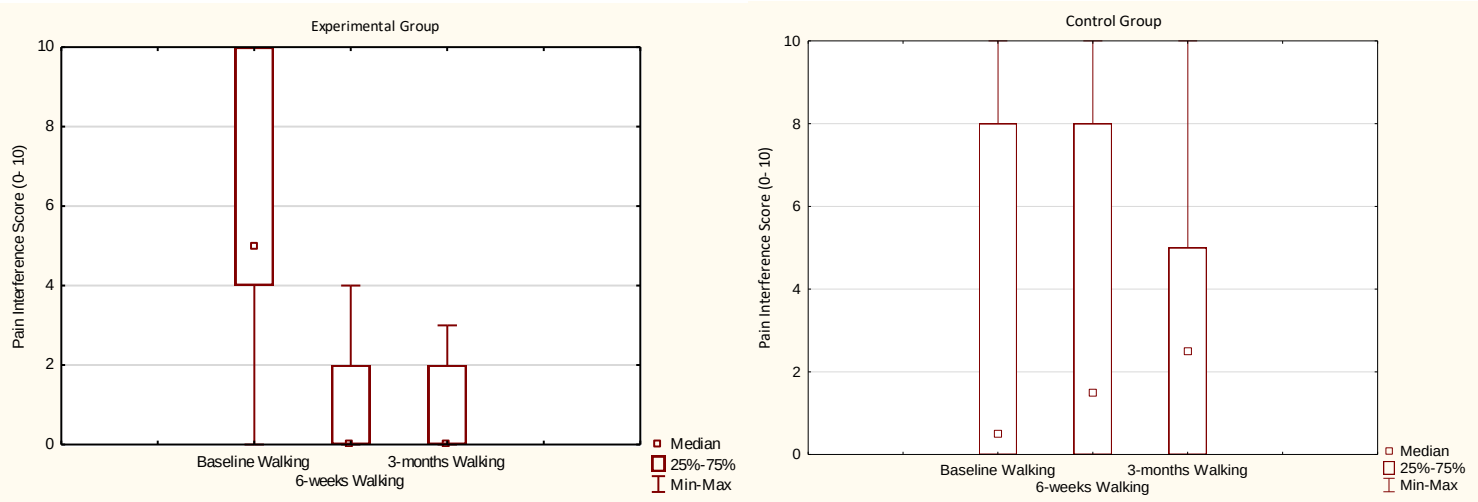

Figure 10: Friedman's ANOVA of change in Pain interference with walking for the Experimental (n=11) and Control (n=10) Groups (MD: 5; p=0.0002).

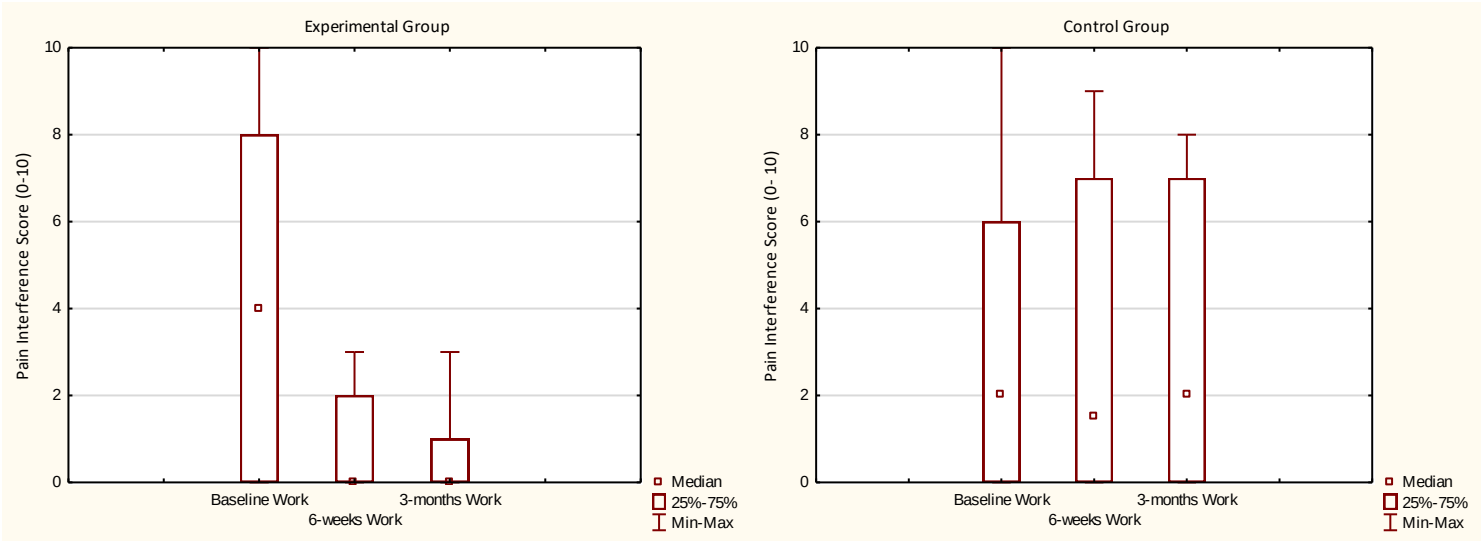

Figure 11: Friedman's ANOVA of change in Pain interference with work for the Experimental (n=11) and Control (n=10) Groups (MD: 4; p=0.007).

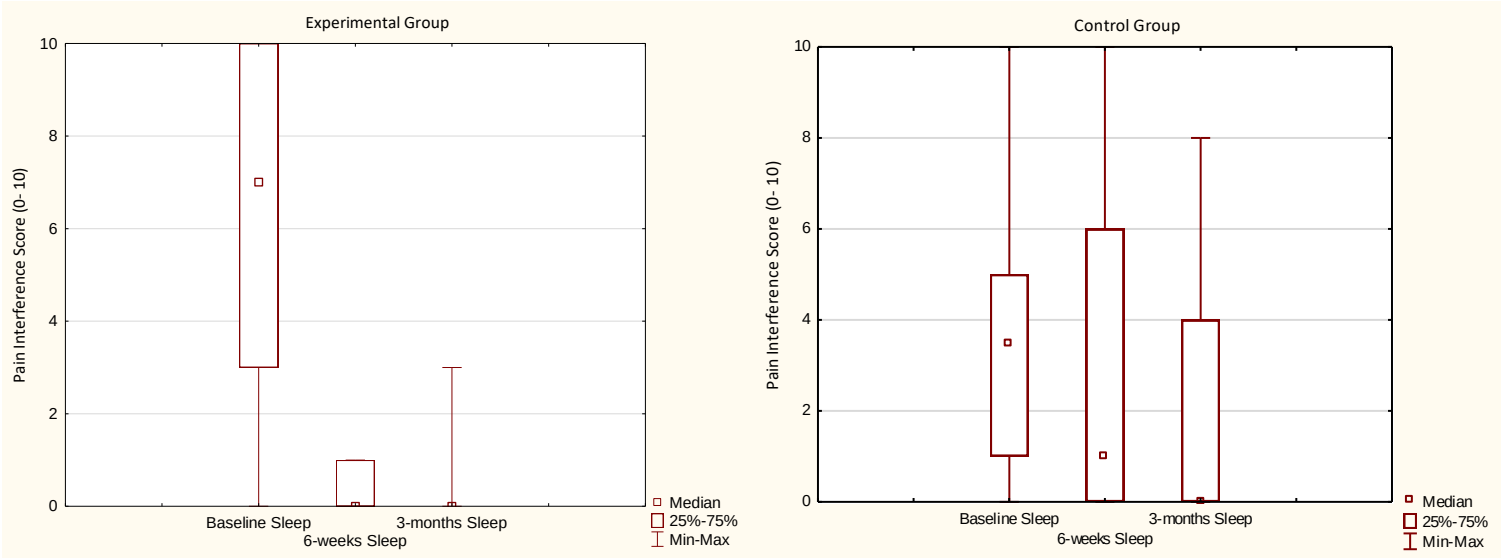

Figure 12: Friedman's ANOVA of change in Pain interference with sleep for the Experimental (n=11) and Control (n=10) Groups (MD: 7; p=0.0004).

5.5 Health-related Quality of Life

5.5.1 EQ-5D-5L health index

There was no between-group difference in any of the dimensions of HRQoL at baseline. The detailed HRQoL results are presented in Appendix P. The experimental group had significantly fewer problems with mobility than the control group at 3-months follow up ($\chi 2=9.8$; $p=0.04$) (Figure 13) but there were no between-group differences for the other dimensions (self-care, activity, pain, and anxiety) ($p>0.70$).

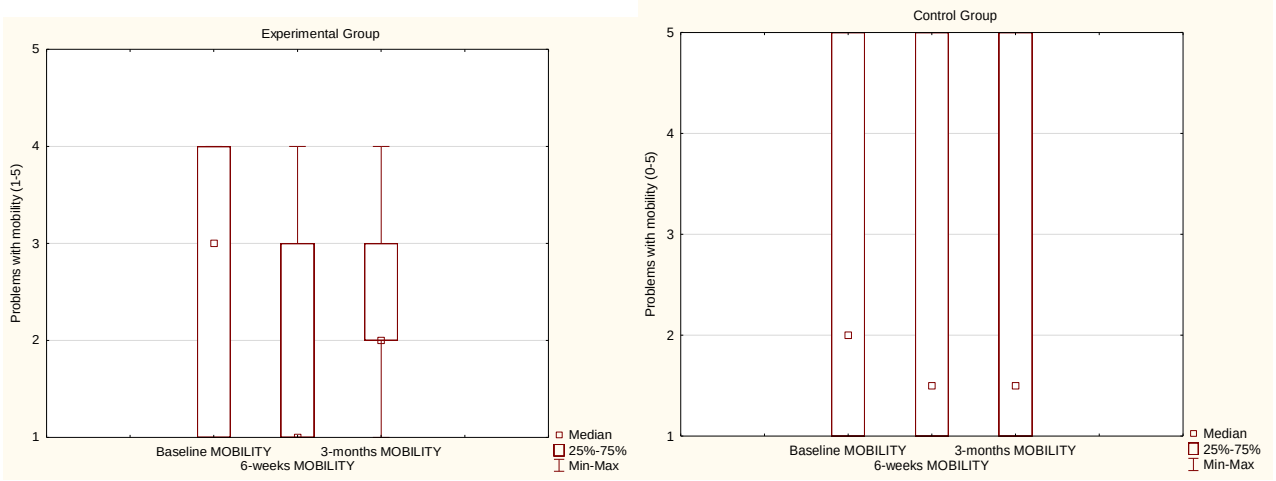

Figure 13: Friedman's ANOVA of change in Mobility for the Experimental (n=11) and Control (n=10) Groups.

5.5.2 EQ-5D VAS

There was a significant improvement in the EQ-5D VAS in the experimental group [6 weeks, $p=0.003$] but no improvement in the control group [6 weeks, $p=0.06$] (Figure 14 & 15). There was a significant improvement of the EQ-5D VAS in both groups at 3-months follow up [experimental group, $p=0.002$; control group, $p=0.03$]. Between-group analysis showed no between-group difference at 6 weeks ($U=35$; $p=0.16$) and 3-months follow up ($U=46$; $p=0.16$).

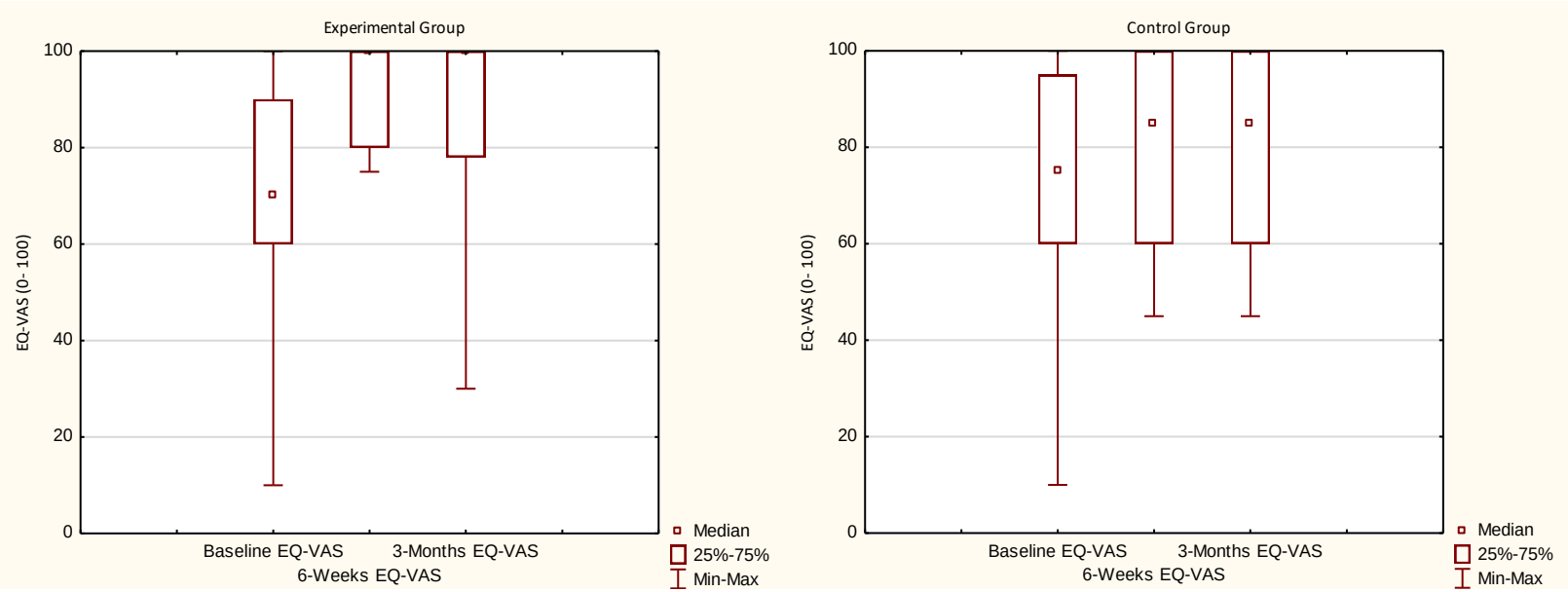

Figure 14:Figure 14: Friedman's ANOVA of change in EQ-VAS scores for the Experimental (n=11) and Control (n=10) Groups over time

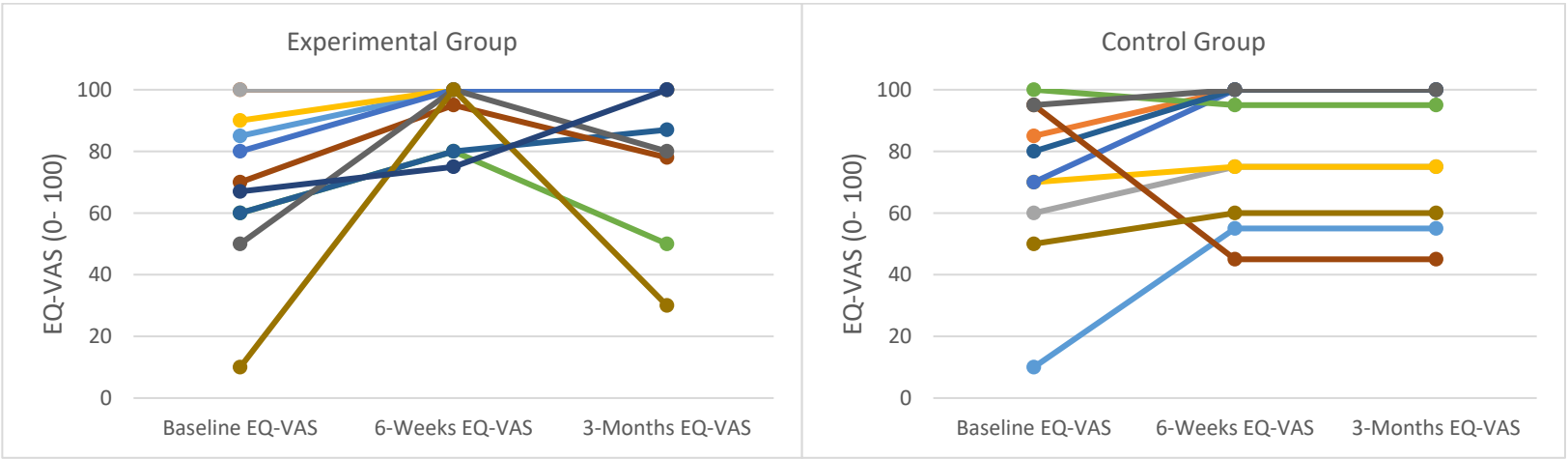

Figure 15: Spaghetti Plots of change in EQ-VAS scores for the Experimental (n=11) and Control (n=10) Groups.

5.6 Summary of results

The experimental group showed greater improvements than the control group for pain severity, pain interference, mobility and health-related quality of life immediately after, and 3 months after the intervention. The NNT for pain severity was 1.9 [95% CI: 1.1 – 6.5] at 6-weeks and 3 [95% CI: 1.9 – 7.1] at 3-months follow up. Similarly, the NNT for PIS was 1.4 [95% CI: 1 – 1.8] at 6 weeks and 1.9 [95% CI: 1.1 – 6.5] at 3 months.

The experimental group improved significantly more than the control group in the "mobility" dimension of the EQ-5D-5L at 3-months follow up ($\chi 2=9.8$; $p=0.04$) despite having been no different to the control group immediately after treatment.

Chapter 6: The effectiveness of GMI for PLP and Disability in upper and lower limb amputees. A randomised controlled trial - Discussion

The aim of this study was to determine the effectiveness of GMI for reducing PLP and disability in people who have undergone upper and lower limb amputations. The participants who received treatment with GMI had clinically meaningful improvements in PLP severity and interference, and disability immediately after treatment. These improvements were maintained at 3-months follow-up.

6.1 The effects of GMI on pain

Clinically meaningful pain reductions were seen at 6 weeks (4.25; 0-10 VAS) and at 3 months follow-up (5.0; 0-10 VAS) in the participants who were treated with GMI. It is evident that the pain reductions at both data collection points exceed the cut-off of three points on a 10-point VAS, which is widely accepted in the literature as an accurate indication of successful pain reduction following intervention [99]. In addition, it has been revealed that patients who have a pain reduction of at least three points following treatment, have a higher likelihood of reporting their treatment as "successful"[100].

Another statistical concept usually used to determine the success or failure of treatment is the NNT. The NNT of 1.9 [95% CI: 1.1 – 6.5] indicates approximately two people need to be treated with GMI (rather than the control intervention) for one to have a clinically meaningful reduction in pain. The ideal value for NNT is one, where every participant in the experimental group but none in the control group has improved [101]. However, having a treatment of such effect is often not feasible. As such it was established that absolute numbers in proximity to one, can be an indication of an effective intervention [102].

The positive findings from this study corroborate those of two similar studies on the effects of GMI on PLP in people who have undergone amputations [20, 77]. A randomised controlled trial [20] showed that people given GMI reported a clinically meaningful reduction in pain (3.2; 0-10 VAS) immediately after treatment. In that study, the NNT for a 3/10 decrease in pain immediately after treatment was 3 [95% CI: 2-6]). Further improvements were seen at 6-months follow up: those given GMI reported a clinically meaningful reduction in pain (3.8; 0-10 VAS), with an NNT of 2 [95% CI: 1-5]. Similarly, a recent retrospective case series [77] of GMI in four amputees revealed clinically meaningful pain reductions (3.3; 0-10 VAS) at the end of the GMI programme. The consistent positive findings from these studies reinforce that GMI may be a viable treatment for PLP.

The development of peripheral neuropathies in people with diabetes have been proposed to aggravate the perception of PLP [103]. In the current sample, diabetes type II was the leading cause of amputations. A retrospective study which examined the proportion of amputations due to diabetes in four public hospitals in Cape Town, also found that a high proportion (72.3% of 1134 patients) of amputations were attributed to complications of diabetes type II. The burden of diabetes-related amputations in South Africa is high 72.3% [95% CI: 69.8 - 74.7] [104], particularly in low-income households [105] and these households often cannot afford expensive medical interventions for PLP, which have also been shown to be ineffective and have many adverse effects. In light of this, GMI may have a significant role towards decreasing the burden of PLP and pain-related disability in South Africa as the results suggest that it is effective for producing clinically meaningful PLP reductions with minimal adverse effects [40]. In addition, GMI is economical, thus making it accessible to low-income households.

6.2 The effectiveness of GMI compared to routine treatments

Numerous interventions for PLP have been recommended for clinical practice. Despite the variety of available interventions for PLP, there is currently no treatment which is recommended as a first line approach [78]. Indeed, this seemed to be the case with the physiotherapists who completed the survey reported on in Chapter 3. While most of the survey respondents used exercise (87.5%), massage (62.5%) or TENS (50%), some of them also used therapeutic ultrasound (37.5%) and mirror therapy (25%). None of the survey respondents used GMI to manage PLP, therefore, the aim of the RCT was to evaluate the effectiveness of GMI compared to routine treatments for reducing PLP.

Evaluating the pain reductions within the GMI and routine physiotherapy groups at 6 weeks (4.2 vs 1.75; 0-10 VAS) and 3 months (5.0 vs 1.37; 0-10 VAS), it is evident that a clinically meaningful pain reduction was present in the GMI group. The positive findings from this study are in agreement with the results from a similar randomised controlled trial where pain reductions were significantly greater in the GMI group at 6 weeks (3.2 vs 0.6; 0-10 VAS) and at 6 months (3.8 vs 0.7; 0-10 VAS) [20]. Judging from the positive findings in both these studies, GMI appears to be more effective than routine physiotherapy for reducing PLP immediately after the intervention and at short term (3 months) and long term (6 months) follow up. In addition, the high relative risk reduction suggests that GMI may be the best treatment for PLP in patients who have failed to respond to routine physiotherapy treatments.

The reason why the GMI programme is so effective for reducing PLP might well be because it effectively targets the cortical mechanisms underlying PLP. As discussed in Chapter One, PLP appears to be driven by neuroplastic changes in the primary somatosensory and Motor cortices of the brain contralateral to the amputated limb; where the cortical representation of the amputated limb is invaded by adjacent cortical areas [3]. The rationale for the three components of the GMI programme is that they progressively correct these neuroplastic changes by activating the cortical representation of the amputated limb in a graded manner. This graded progression is credited for the success of the GMI programme. In fact, one study compared the ordered application of the components of GMI to an unordered application of the same components in people with CRPS type 1 and demonstrated that the ordered application has a superior effect for reducing chronic pain [40]. One explanation for this is that imagined movements or mirror therapy alone seem to be capable of aggravating pain [40, 106]. To avoid the triggering of the protective pain response in the brain, a less demanding exercise (left/right judgements) may be needed first. Perhaps, in a sense, left/right judgements is to imagined movements what standing is to walking, and imagined movements is to mirror therapy what walking is to running.

As mentioned previously, the positive results from this study are consistent with those from a similar study [20] showing that one out of every two patients treated with GMI will have a clinically meaningful improvement in pain. The high NNT values and wide confidence intervals for the trials of each class of pharmacological interventions presented in Table 12, stand in contrast to the results of the GMI trials, suggesting that drug-based therapy may have a limited role in the treatment of PLP. These pharmacological interventions which include opioids, anti-epileptics, N-methyl-D-aspartate (NMDA) receptor-antagonists and anti-depressants, are marginally effective at best, and no better than placebo [50]. The lack of effectiveness of these treatments suggests that the peripheral and spinal cord mechanisms which they target are not major contributors to PLP.

Table 12: Pharmacological intervention used for the management of PLP.

Treatments for PLP	Number Needed to Treat (NNT)
Graded Motor Imagery ***(current study)***	
Immediate	1.9 [95% CI: 1.1-6.5]
3-months follow-up	3 [95% CI: 1.9-7.1]
Graded Motor Imagery ***(Moseley, 2006)***	
Immediate	3 [95% CI: 2-6]
6-months follow-up	2 [95% CI: 1-5]
Morphine infusion ***(Wu et al., 2002)***	
30 minutes	1.9 [95% CI: 1.3-3.7]
Lidocaine infusion ***(Wu et al., 2002)***	
30 minutes	3.8 [95% CI: 1.9-16.6]
Memantine ***(Maier et al., 2003)***	
3-weeks	4.5 [95% CI: 2.1-10.6]
Amitriptyline ***(Robinson et al., 2004)***	
6-weeks	5.2 [95% CI: 3.6-9.1]
Pregabalin ***(Finnerup et al., 2007)***	
4-weeks	8 [95% CI: 5.9-32]

Of the treatments listed in Table 12, Amitriptyline is the most accessible drug recommended as a first line of treatment for neuropathic pain syndromes [107]. Amitriptyline is a tricyclic antidepressant used primarily for management of depressive disorders through a balanced inhibition of serotonin and noradrenaline reuptake in the presynaptic neuron located in the dorsal horn of the spinal cord, and in the brain [108]. It has been shown that amitriptyline achieves analgesic effects by binding to opioid receptors and blocking voltage-gated sodium (Na+) channels in the spinal cord, thus maintaining the availability of serotonin and norepinephrine available to the brain [109]. Although analgesic effects produced by this drug have been reported in peripheral neuropathic pain syndromes (NNT=2 [95% CI: 2.1-2.7] [110], the majority of evidence suggests that it is ineffective for treating PLP in amputees [48, 111]. The lack of effectiveness of amitriptyline suggests that the mechanisms which it targets are not major contributors to PLP. While its efficacy for reducing PLP is better than that of pregabalin (5.2 [95% CI: 3.6-9.1]), a recent randomised controlled trial of amitriptyline for PLP (n=36) found that amitriptyline was not superior to placebo [111]. Of some concern is that 15 adverse treatment effects were reported

in the amitriptyline group and, interestingly, the placebo group reported higher satisfaction with life. It was therefore concluded that amitriptyline is unlikely to be clinically useful in treating PLP [111].

Pregabalin is an anticonvulsant which is thought to bind to alpha-2-delta receptors and block voltage-gated calcium channels (Ca^{2+}) in the spinal cord [112]. It has been shown to alleviate epileptic seizures, as well as hyperalgesia and allodynia in various neuropathic pain syndromes other than PLP [113]. It is theorised that pregabalin may be effective in these conditions because it is primarily active in the spinal cord. The NNT for pregabalin (NNT=8 [95% CI: 5.9-32]) indicates that eight patients with PLP need to use the treatment before one has beneficial pain outcomes [114]. Such a high NNT suggests the drug has a limited clinical role for treating PLP.

Memantine is an NMDA receptor antagonist primarily used to reduce the rate of memory loss in patients with dementia or Alzheimer's disease. This drug reduces nerve activity by blocking NMDA receptors in synapses within the central nervous system [115]. The results from a double-blind randomised controlled trial showed that memantine is no more effective than placebo for reducing PLP (NNT=3.8 (±2.3) vs 3.2 (±1.5), p=0.67). That memantine was not superior to placebo suggests that it may not target the mechanisms underlying PLP in amputees.

Similarly, lidocaine does not appear to reduce PLP in amputees. Lidocaine is an anti-arrhythmic drug primarily used for the management of cardiovascular conditions [116]. Its use has been extended to the management of neuropathic pain syndromes based on its ability to block voltage-gated sodium (Na^{+}) channels at the periphery and in the spinal cord [117]. A double-blind randomised controlled trial of lidocaine for PLP found that lidocaine was not superior to placebo for reducing PLP but was significantly better for reducing stump pain [118]. This suggests that the mechanisms underlying PLP and stump pain may be different [119]. Although these drugs have been shown to be effective to manage conditions that they are primarily intended for, the mean pain reductions for respective treatments, and the NNT presented in Table 12 show that these treatments have limited efficacy for reducing PLP in people who have undergone amputations.

Infused morphine is the only pharmacological intervention with a relatively low NNT (1.9 [95% CI: 1.3-3.7]) for PLP. However, this NNT is based on measurements taken 30 minutes after administration [118]. Therefore, the long-term effects of this intervention (if there are any) are unknown. Morphine is classified as an opioid - a class of treatments used to induce an analgesic effect [120] by binding to

opioid receptors, thus inhibiting the release of excitatory neurotransmitters (glutamate & substance P) in the dorsal horn of the spinal cord, as well as by activating descending inhibitory control in the midbrain [121].The analgesic effect produced by an opioid infusion is typically short-lived - a matter of hours - and ongoing nociceptive activity in the spinal cord can result in a decreased sensitivity to opioids, which in turn results in decreased drug potency and worsened pain. In fact, one study showed that although the oral administration of morphine produced pain relief, any attempts to wean the patients off the drug resulted in rebound pain of greater severity compared to baseline [122]. These findings suggest that morphine may not suitable for achieving sustained relief of PLP.

The pharmacological classification of these interventions, except for opioids, suggest that they were not designed primarily for treating pain, but rather for reducing nociception. For example, treatments such as lidocaine which target peripheral nociception by blocking of voltage-gated sodium (Na^+) channels might be effective if the PLP were nociceptive - for example, due to damaged peripheral nerves in the stump developing neuromas that typically emit spontaneous nociceptive impulses [123]. However, the failure of this intervention to reduce PLP is an indication that the primary driver of PLP is not nociceptive. This idea is also supported by reported cases of PLP in congenital amputees [124] who clearly had not had amputations and did not present with nerve damage. The failure of nociception-targeted pharmacological treatments and the existence of PLP in congenital amputees speak in support of a cortical mechanism for PLP.

Although there is a body of evidence to support that PLP is primarily driven by cortical changes in the somatosensory and motor cortices of the brain [30, 31], it is apparent from the evidence above that most of the pharmacological interventions recommended for PLP attempt to reduce pain by inhibiting the transmission of nociception at the periphery and in the spinal cord. This may be the reason why these interventions are not effective in amputees where the mechanism underlying their pain is not a peripheral source of nociception. Furthermore, the poor pain outcomes from these interventions may be attributed to their inability to address the cortical changes associated with PLP and reinforce the theory that PLP is a consequence of brain mechanisms i.e. cortical reorganisation. The effectiveness of GMI appears to lie in the efficacy of the individual components of GMI to reverse the cortical reorganisation associated with PLP [39]. Therefore, the successful reduction of PLP in the short- and long-term indicates that GMI is a viable treatment because it targets the cortical changes underlying PLP.

It is evident from the presented evidence that GMI is more effective than pharmacological interventions for achieving clinically meaningful reductions in PLP in both the short and long term. These findings indicate that GMI should be a preferred choice of treatment for PLP or at least be used in combination with other interventions for PLP in clinical practice.

Stump massage is a non-pharmacological intervention which is thought to reduce PLP through the gate control mechanism (Helms & Barone, 2008). According to the gate control theory, the stimulation of the stump by massage activates the fast-conducting myelinated A-beta fibres which interfere and impede nociception transmitted by slow-conducting unmyelinated C-fibres at spinal-cord level, thus resulting in pain-relief [125]. Theoretically, the pain-relief is strictly limited to the stimulated area (stump). Therefore, the gate control theory does not justify the idea that the stimulation of the stump may result in reduced PLP severity. Overall, the mechanisms by which massage attempts to reduce PLP are poorly understood, and there is little evidence to determine the effectiveness of massage for reducing PLP. Therefore, further research is required in this area. Another non-pharmacological intervention commonly used to manage PLP is exercise [126]. Exercise is proposed to reduce pain through the endogenous opioid mechanism, where the endogenous opioids released from the central nervous system bind to the opioid receptors in the peripheral and central nervous system, particularly in the rostroventromedulla and periaqueductal grey matter - areas important in pain modulation [127]. There is substantial evidence that exercise moderately reduces chronic pain including pain syndromes thought to have a neuropathic component [128]. However, there is little evidence to determine the effects of exercise on PLP, and research in this area remains a priority.

6.3 The effects of GMI on pain interference

The holistic assessment and management of pain requires not only the assessment of pain severity but also the interference of pain on activities of daily living [129]. It is has been shown that the chief complaint of people suffering with chronic pain is the interference of pain with quality of life [130]. Therefore, one of the objectives of the study was to determine whether GMI is effective in reducing the interference of pain. The findings of this study indicate that GMI is effective for reducing the interference of pain in all the components of the pain interference scale immediately after treatment and these effects are sustained three months later. Further, GMI was clearly more effective than the control intervention for reducing pain interference at 6 weeks and at 3 months after intervention.

The absolute risk reduction scores [6 weeks, 0.73; 3-months, 0.52] and NNTs [6 weeks, 1.4; 3-months, 1.9] in this study are remarkable. The absolute risk reductions show that 73% (at 6 weeks) and 52% (at 3 months) of the participants who received GMI had significantly greater reductions in pain interference than they would have had, had they received the control intervention. In addition, the NNTs show that nearly every patient treated with GMI would have significant reductions in pain interference at 3 months. As previously discussed, the ideal absolute value of the NNT is 1, which would indicate that each and every patient will benefit from the treatment [131]. The odds ratio calculation at 6-weeks and 3 months showed that participants who received GMI had 78 times and 10 times greater chance of having clinically meaningful reductions in pain interference. The relative risk reduction (RRR=0.95) also showed that almost all the participants who did not benefit from routine physiotherapy, would significantly improve from receiving GMI. The overall improvements recorded in the experimental group for pain interference were contributed to by significant improvements in the seven individual categories of the pain interference scale: General activity, mood, walking ability, interference with work and sleep.

Currently, no similar studies which have used the BPI pain interference scale to assess the interference of PLP in people who have undergone amputations could be identified. However, one study used a patient-specific functional scale where patients selected five activities that they regularly performed before amputation but now found difficult because of PLP, and recorded the degree of difficulty on a numerical rating scale (NRS: 0-10) [20]. At the end of that trial, the GMI group had significantly greater improvements in function than the control group. Together, these findings support the idea that GMI may be a suitable intervention to reduce the interference of PLP with amputees' daily functioning.

Phantom limb pain has been reported as a main contributor of anxiety and depression [132]. The significant PLP reductions in the current study may account for the improvement in the interference of pain with mood from baseline to 3-months follow up. There is a bidirectional relationship between depression and social isolation, suggesting that patients with low mood are prone to isolation and vice versa [133]. The positive improvements in this category (mood) suggests that patients may be able to socially interact with other people and have a higher likelihood of enjoying life. In addition, less interference with an ability to walk would facilitate general activities and mood or enjoyment of life.

Difficulties with walking are common in people who have undergone lower limb amputations [134]. There was a significant improvement in the interference of pain with walking ability from baseline to 3-months. In addition to walking difficulties caused by the lower limb amputation itself, PLP can cause

challenges with mobility and prosthetic use [135]. The reduced interference of pain with walking ability in the present study implies that patients may be able to ambulate with either crutches or a prosthetic leg with less difficulty than before the intervention.

There was a significant improvement in the interference of pain with work from baseline to 3-months follow up. The literature shows that pain interferes with work in relation to reduced productivity and increased number of sick leave days taken from work [136]. This category also assesses the interference of PLP with house work, and therefore accommodates participants who may be unemployed or have retired from work. The improvements in this category suggest that participants who received GMI may have reduced pain interference with work and improved productivity, both of which would contribute to an improvement in quality of life.

It is known that PLP is among the causes of sleep disturbance in amputees. It has been shown that 62% of amputees with PLP have impaired sleep quality [137]. Disturbances in sleep can result in low mood, decreased energy levels and productivity. It is encouraging that there was a significant improvement in the interference of pain with sleep from baseline to 3-months follow up in the present study as improvements in this category suggest that GMI may be effective for improving the outcomes in amputees with PLP.

It is encouraging to see that the reduction in pain interference with function is also reflected by the improvement in the health-related quality of life. These results provide concurrent validity for the results.

6.4 The effect of GMI on Health-Related Quality of Life

The experimental group had greater improvements than the control group in mobility at the 3-month follow-up point as reported on the EQ-5D-5L. These findings are consistent with those from the pain interference scale of the BPI where participants reported significant reductions in the interference of pain with their walking ability. As previously discussed, PLP negatively affects function with regards to mobility and prosthetic use [138]. It is on this basis that it was expected that significant PLP reductions may result in improved mobility. Nonetheless, in lower limb amputees, separating the interference of pain from the interference of the structural impairment on walking ability is usually a challenge. Amputations, particularly lower limb amputations, alter the biomechanics of human movement. The change in body biomechanics can result in impaired dynamic balance and poor coordination which in

turn will result in impaired gait [139]. On the other hand, PLP or phantom sensations can provide a genuine perception that the missing portion of the amputated limb is present. For example, one may unconsciously attempt to step with the phantom leg if they feel as if their leg is still present. This real perception of the phantom leg may account for a high number of falls reported in lower limb amputees, as well as difficulty with mobility [135]. Since it is impossible to restore the missing portion of the amputated leg, reducing PLP and restoring movement biomechanics through rehabilitation seem to be the most suitable way to improve mobility in lower limb amputees [140].

The EQ VAS showed a significant improvement in participants' HRQoL within the experimental group and no improvement in the control group at 6 weeks. However, significant improvements were observed in both groups at 3-months follow up, at which point there was no between-group difference in HRQoL. This equivalence suggests that participants might have improved because of the Hawthorne effect - where participants improve due to the meaning of the attention they are receiving rather than the efficacy of treatment [141]. Alternatively, the lack of difference between groups may be attributed to the high baseline scores in both groups, leading to a ceiling effect.

6.5 The prevalence of PLP

Of the 68 participants who were screened telephonically for potential inclusion in the current study, 25 (37%) reported PLP. To our knowledge there are no studies which have determined the prevalence of PLP in South Africa. A review of European and American studies has reported the prevalence of PLP as high as 80% [4]. This startling difference could be due to a genuine difference, or it could be a detection bias. There are anecdotal reports that in some South African communities, PLP is associated with mental illness or punishment from "evil spirits" because of its ambiguous presentation. In the fear of being stigmatized as being mentally ill, some patients may choose not to report their pain for fear of being judged or diagnosed with a mental disorder [142]. Sherman & Sherman [2] reported that, although 61% of amputees reported their PLP, only 17% received treatment while the remaining majority were told by their doctors that they were mentally ill. While we found no quantitative data on the prevalence of stigma in people suffering with chronic pain, there is substantial qualitative evidence suggesting that pain stigma is a common experience in different settings [143]. The stigma associated with chronic pain is experienced not only in hospitals but also in communities and households. For example, some patients suffering from chronic pain report that their families do not believe them and often make comments like "the pain is in your head" [144]. It has been reported that patients who feel

misunderstood are less likely to seek subsequent medical assistance, at least from the same medical practitioner [145]. One of the features that perpetuates stigma in chronic pain is that pain is a private experience. Unlike other medical conditions in which a subjective report can be confirmed by objective tests, pain can only be assessed through subjective report [146]. In a case of PLP, where there is no peripheral source of pain, clinicians may doubt the patient's subjective report primarily due lack of understanding of the mechanisms underlying PLP or perhaps because they are practising from a biomedical model, which clearly has limitations regarding the comprehensive assessment and treatment of PLP and various chronic pain conditions.

Another example of how stigma influences behaviour is in relation to people living with HIV/AIDS. Many patients do not test for HIV in their communities for fear of being discriminated should they be HIV positive. For those who are already HIV positive, they do not access ARV clinics in their own communities for fear of being recognised and stigmatised, but rather opt to access medication in private [147]. These examples indicate that stigma and discrimination associated with chronic illnesses and chronic pain may be the primary cause of why patients may not report their pain or seek medical attention and may be why the prevalence of chronic pain in this study was low. It may therefore be useful to implement pain education programmes relevant to an African context with the aim of educating both patients and clinicians about the physiological mechanisms underlying PLP and chronic pain with the objective of reducing this stigma.

6.6 The reasons for amputations

The most common reason for amputations in this study was diabetes (76%) with trauma (14%) and infection (10%) being the least. In 2009, the prevalence of diabetes in South Africa was estimated at 4.5% [148]. By 2015, it had increased to 7% [149]. At that time, 7% represented 3.85 million South Africans living with diagnosed diabetes. It is estimated that 0.63 to 2.39 million South Africans live with undiagnosed diabetes [148]. On the basis of the drastic rise in cases reported from 2009 to 2015, the prevalence of diabetes is predicted to rise significantly in the future [150]. This lifestyle disease largely affects people in low-income households, who are less educated about the condition and have difficulty maintaining healthy eating habits due to the perceived high cost of healthy food [151]. In addition, it has been shown that low health-literacy levels are common among diabetic patients. In their study Williams et al [152] reported that 47% of 402 people had an average health literacy score of 13.2 on 0-100 Test of Functional Health Literacy in Adults (TOFHLA). The low health-literacy scores were associated with poor self-management strategies, deterioration in health status and increased chances of hospitalization, and

complications which may result in amputations [152]. Further, another study suggest that diabetic patients with low-literacy levels may benefit from comprehensive diabetes management programmes which aim to equip patients with strategies to successfully manage their condition [87].

The cost of food influences our perception of how expensive it is. This means cheap foods are thought to be unhealthy. However, it has been shown that readily accessible food (take-aways) are far more expensive than healthy fruits and vegetables [153]. Based on this evidence, public health promotion strategies which promote healthy eating have been implemented. For example, an education-based intervention aimed to improve the perception of healthy food affordability has been shown to be an effective strategy to promote healthy nutrition in low-income communities [154]. Therefore, the high prevalence of diabetes type II in this study cohort and the positive findings from the above studies indicate a need to implement educational programmes which will improve health literacy and perception of food affordability in South African communities.

6.7 Limitations of the study

The current study was a single-blind randomised controlled trial: the outcome assessor was blinded. It would have been preferable to have ensured blinding of participants. In studies of this nature, blinding of participants requires a convincing sham intervention, which was lacking in the current study. Participants who received GMI might have been aware that they were receiving an experimental intervention which was proposed to be superior to conventional treatment. Conversely, the participants in the control groups may not have had as much contact with a treating clinician as those in the experimental group. Due to these factors, the interventions were not equal in patient-clinician contact, and may have been unequal in believability. Future studies would do well to include a sham intervention with the same frequency of clinical contact.

Although this study was adequately powered to determine a difference between the groups, the small sample size (n=21) is a limitation. A sample size smaller than 50 participants per group can result in either underestimation or overestimation of the treatment effect [57]. Therefore, the results of this study should be interpreted with care. Further only one of the 21 participants included in this study had had an upper limb amputation, limiting the generalisability of the results to people with PLP of an upper limb.

Considering these limitations, further studies with larger samples that include upper and lower limb amputees would help to expand the literature on the effectiveness of GMI in amputees with PLP. In addition, future studies should ensure that patients in the control group receive a plausible sham treatment to control for the potential effect of the therapeutic relationship, and sham and experimental interventions should be equivalent in terms of participant-clinician contact and allocation of research resources.

The recruitment rate in this study was low. This was largely because 147 (66%) of the 224 patients identified by hospital record could not be contacted. This is a known problem in trials that involve recruitment by hospital record, and can sometimes be attributed to patients providing false information on their hospital records, not providing secondary contact details or moving to a different home [155]. A particular feature of the local context of the current study is that a considerable number (1.6 million) of people living in South Africa are immigrants from neighbouring countries who also access health care [156]. Due to internal socio-political issues in South Africa, there is also a high rate of migration as people search for employment in neighbouring provinces and countries or, in some cases, are deported. This creates a challenge to research in terms of recruitment, as well as to follow-up. Some authors have suggested that hospitals store secondary contact details to reduce the risk of loss to follow up [89]. This approach could improve the recruitment and follow up process during research, and improve continuity of care of patients with chronic pain in clinical practice.

Chapter 7: Conclusion

This thesis aimed to:

1. Systematically review the literature to determine whether there is evidence to support the use of GMI to treat PLP.
2. Determine what treatments physiotherapists working in Cape Town hospitals were using to manage PLP.
3. Determine whether GMI was superior to routine physiotherapy for the management of PLP.

7.1 Systematic Review

The systematic review found weak evidence that GMI and mirror therapy are effective for reducing PLP in amputees. The studies that investigated imagined movements and mirror therapy did not follow up their participants beyond the time of treatment cessation. Therefore, we are unable to draw conclusions about the long-term effects of these interventions. All the included studies had a high risk of bias, and a small homogenous sample of lower limb amputees. Therefore, these limitations may have limited the generalisability of the results to upper limb amputees.

7.2 The physiotherapy treatments for PLP

The results of the survey showed that physiotherapists primarily perform exercise and massage to reduce PLP despite the lack of evidence supporting their use for PLP in clinical practice. The results of the systematic review and the randomised controlled trial show that GMI is more effective than routine treatments for PLP. Considering the number of years of experience of the physiotherapists involved in this study, the lack of GMI practice for people with PLP suggest that the physiotherapists might not be informed about the GMI and its potential efficacy for reducing PLP. Therefore, it is essential to translate research findings with health professionals to improve the quality of primary health-care in South Africa.

7.3 The effects of graded motor imagery on PLP

The results of the RCT showed that the participants who received GMI had clinically meaningful improvements in pain severity, pain interference and disability immediately after treatment and were maintained at 3 months. Although there was no difference between groups for HRQoL, the experimental group had greater improvements than the control group for the “Mobility’ dimension of the EQ-5D-5L.

The results of the current study provide support for the proposition that PLP is driven by cortical mechanisms, and that GMI may be effectively targeting these mechanisms to reduce PLP. On the basis of the significant reduction in pain within the participants who received GMI, the lack of adverse effects, and the ease of application, GMI may be a viable treatment for treating PLP in people who have undergone amputations.

While more studies using rigorous methodology, including sham treatment, larger sample sizes and a more generalisable sample, are required, the efficacy of GMI coupled with its affordability and low risk, suggest that it is applicable in a resource-constrained primary health setting in South Africa. Health care professionals treating people post amputation should be trained in the administration of the technique.

The main limitations of the current study were the small sample in a restricted setting (Western Cape of South Africa), single treating clinician and the lack of a sham treatment. A larger multicentre trial using a valid sham treatment, conducted in multiple provinces of South Africa by different clinicians may provide a definitive conclusion regarding the efficacy of GMI within a broader South African context.

Chapter 8: Summary of recommendation

The systematic literature review found weak evidence that the full Graded Motor Imagery programme is effective for reducing PLP in amputees, and that neither imagined movements nor mirror therapy yields benefits that are superior to comparator interventions. The strength of our findings is limited by the quality of the literature base itself. Therefore, more evidence and higher-quality studies are needed to generate a definitive conclusion regarding the efficacy of the Graded Motor Imagery programme for reducing phantom limb pain in people who have undergone amputations.

The results of the survey are limited by a very small sample size of physiotherapists. An online survey targeting all physiotherapists in the Western Cape may enhance the study hugely and allow for a conclusion to be drawn from the results.

The results of the randomised controlled trial indicate that GMI may be effective for reducing PLP and pain interference with function. However, a multi-centre trial conducted in various areas by different clinicians using a plausible sham intervention may provide a definitive conclusion regarding the efficacy of GMI for reducing PLP.

References:

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Appendices

Appendix A: Systematic literature review protocol

Background:

Phantom limb pain (PLP) is characterized by the anatomical shifting of neighbouring somatosensory and motor areas into a deafferented cortical area of the brain contralateral to the amputated limb. It has been shown that maladaptive neuroplasticity is positively correlated to the perception of PLP in amputees. Recent studies support the use of graded motor imagery (GMI) and its component to alleviate the severity of PLP and disability. However, there is insufficient collective empirical evidence exploring the effectiveness of these treatment modalities in amputees with PLP. This systematic review will therefore explore the effects of GMI and its individual components on PLP and disability in upper and lower limb amputees.

Methods:

We will utilize a customized search strategy to search PubMed, Cochrane Central register of Controlled Trials, MEDLINE, Embase, PsycINFO, PEDro, Scopus, CINAHL, LILACS, DARE, Africa-Wide Information and Web of Science. We will also look at clinicaltrials.gov (http://www.clinicaltrials.gov/), Pactr.gov (http://www.pactr.org/) and EU Clinical trials register (https://www.clinicaltrialsregister.eu/) for ongoing research. Two independent reviewers will screen articles for methodological validity. Thereafter, data from included studies will be extracted by two independent reviewers through a customized pre-set data extraction sheet. Studies with a comparable intervention and outcome measure will be pooled for meta-analysis. Studies with high heterogeneity will be analysed through random effects model. A narrative data analysis will be considered where there is insufficient data to perform a meta-analysis.

Discussion

Several studies investigating the effectiveness of GMI and its different components on PLP have drawn contrasting conclusions regarding the efficacy and applicability of GMI in clinical practice. This systematic review will therefore gather and critically appraise all relevant data, to generate a substantial conclusion and recommendations for clinical practice and research on this subject.

Background

Description of condition:

Amputation is the removal of a body extremity which is generally caused by severe trauma, circulatory disorders, neoplasm, deformities and infection of the limb. In case of gangrene, infection or neoplasm, amputation is carried out as a control strategy for pre-operative pain or a disease process in the affected limb; in some cases, however, amputation surgery is performed as a preventative procedure for the abovementioned complications [31]. Despite this attempt to alleviate patients' pain and disability, up to 80 % of amputees report phantom limb pain (PLP) postamputation surgery [8]. PLP is defined as persistent painful sensations perceived in the missing portion of the amputated limb [7]. Previous research associates PLP with peripheral changes such as increased nociceptive input from the residual limb [39] and reduced near-surface blood-flow [34]. However, recent evidence suggests that PLP is a sensory output primarily driven by cortical changes in the brain [10]. Neuroimaging studies of patients with PLP revealed neuroplastic alterations of the somatotopic organization of the cortical and sub-cortical areas of the brain [9, 13]. These changes are characterized by the anatomical shifting of neighbouring somatosensory [18] and motor [4] areas into a deafferented cortical area of the brain contralateral to the amputated limb. Furthermore, these neuroplastic changes are positively correlated to the severity of PLP [15, 17]. These neuroplastic alterations can be reverted, with a correlation between the reversal of neuroplastic changes and pain relief in amputees with PLP [1, 11, 20].

Description of intervention:

Graded motor imagery (GMI) is a treatment strategy which has been shown to mitigate the severity of PLP and disability using a sequence of strategies including left/right judgements, imagined movements and mirror therapy [22]. Left/right judgements, the ability to distinguish left from right, is dependent on the intact body schema in the brain and is important in the planning of movement [32]. This left/right judgement is inaccurate and delayed in amputees with PLP [25]. In this first phase of GMI, images representing the amputated limb are presented randomly on a computer screen. The patient is then instructed to match the side of the presented limbs by pressing either the left or right key. During this task, emphasis is put on accuracy and speed. Left/right judgements is alternately known as implicit motor imagery, primarily because the patient is unconscious of mental movement processes involved to match the limb presented on the computer screen [5]. During the imagined movements phase of GMI, the patient mentally moves the amputated limb to adopt a desirable posture presented on the computer screen [14]. The last strategy of GMI is mirror therapy, during which the amputated limb is

concealed behind a mirror with the intact limb positioned comfortably in front of the mirror. This superimposes the ocular image of the intact limb on the phantom limb [28]. The patient is shown a picture of the unaffected limb in an easy to attain position. The patient then simultaneously moves the intact limb and the phantom limb (through imagination) to the presented position while observing the reflection of the intact limb in the mirror. This phase can commence with gross movements, progress to fine motor tasks and ultimately functional tasks.

How the intervention might work:

GMI is consistent with sequential activation of cortical premotor and motor networks [23]. The GMI intervention is founded on the principle of graded increase in activity, similar to that implemented in physiotherapy treatment modalities [2]. This graded exposure to activity aims to promote cortical re-organization without triggering the protective pain response. Left/right judgements activate premotor and supplementary motor areas, with an exception of the primary motor (M1) cortex [24]. Left/right judgements is therefore fundamental in preparation for subsequent phases of the GMI programme. Imagined movements activates the somatosensory (S1), premotor and M1 cortices contralateral to the phantom limb [17]. Activation of these areas is proposed to alleviate the perception of pain associated with imagination and observation of movement. This phase builds upon left/right judgements and serves as a foundation for the successive GMI phase. Mirror therapy addresses changes in the S1 and M1 cortices [26]. In addition, it provides visual input to the brain, that movement is executed normally without inhibition [21]. The therapeutic effect associated with mirror therapy may be due to activation of mirror neurons Limakatso et al. Systematic Reviews (2016) 5:145 Page 2 of 6 in the brain hemisphere contralateral to the amputated limb [3]. These mirror neurons have been shown to fire during observation and execution of movement [16, 30].

Importance of doing this review:

Several studies [3, 19, 20, 22, 36, 38], investigating the effectiveness of GMI and its different components on PLP, have drawn contrasting conclusions regarding the efficacy and applicability of GMI in clinical practice. This systematic review will therefore gather and critically appraise all relevant data, to generate a substantial conclusion and recommendations for clinical practice and research on this subject. It is important to note that Plumbe and associates have published a protocol with a similar topic. Despite this similarity, there is a significant distinction between the two protocols. In their review, Plumbe et al. [27] indicate that they will investigate the efficacy of GMI on chronic pain. However, this review will explore the effects of GMI and its components, specifically on PLP and disability. Bowering et al. [2] conducted a systematic review on a topic of interest. However, there is a need to update their review as there have been new studies since their publication.

Objectives

The purpose of this review is to explore the effects of GMI and its individual components on PLP and disability in upper and lower limb amputees.

Methods

The protocol was developed according to the Preferred Reporting Items of Systematic Reviews and Meta-Analyses Protocol (PRISMA-P) guidelines [33] and has been registered on PROSPERO database (Ref: CRD42016036471). The PRISMA-P checklist is included as an additional file (Additional file 1).

Criteria for selecting studies for this review

Types of studies:

This systematic review will consider published and non-published randomised controlled trials, quasi-experimental studies, randomised controlled cross-over trials and quasi-experimental cross-over studies published in English.

Types of participants:

Participants older than 18 years of age with unilateral amputation of the upper or lower limb who received intervention for their PLP three or more months post-amputation surgery will be included in this review. Studies with participants with pathology of the intact opposite limb will be excluded.

Types of interventions:

GMI and its individual components (left/right judgements, imagined movements and mirror therapy) will be compared to no treatment, conventional physiotherapy or other interventions. Studies investigating the efficacy of GMI plus additional treatment will also be included.

Conventional physiotherapy includes:

- Transcutaneous electrical nerve stimulation

-Muscle relaxation/Massage

-Heat/Cryotherapy

-Acupuncture

-Exercise

-Biofeedback

Other interventions include:

-Pharmacological interventions

-Psychotherapy

-Deep brain stimulation

-Motor cortex stimulation

-Spinal cord stimulation

Types of outcome measures:

Primary outcome measures:

- Self-reported PLP as assessed through a standardized pain scale post-intervention.
- Pain-related disability as assessed through a standardized function scale post-treatment.

Secondary outcome measures:

- Health related quality of life (HRQOL) as assessed by a standardized scale.
- Adverse effects.
- Psychosocial function as assessed by a standardized scale.
- Patient global impressions of change (PGIC).

Search strategy for identification of studies

Electronic searches

We will utilize a customized search strategy to search the following electronic databases: PubMed, Cochrane Central register of Controlled Trials, Medline (via Ebscohost), Embase, PsychINFO (via Ebscohost), Physiotherapy Evidence Database (PEDro), Scopus, Cumulative Index to Nursing and Allied Health Literature (CINAHL) (via Ebscohost), LILACS, Database of Abstracts of Reviews of effects in the Cochrane Library (DARE) Africa-Wide Information (via Ebscohost) and Web of Science. We will also look at clinicaltrials.gov (http://www.clinicaltrials.gov/), Pactr.gov (http://www.pactr.org/) and EU Clinical trials register (https://www.clinicaltrialsregister.eu/) for ongoing research.

Search of other sources:

The reference lists of identified studies will be searched for relevant additional trials. Experts in this field will be contacted for further identification of published, unpublished and ongoing studies with potential for inclusion in this review.

Data collection and analysis:

Selection of studies:

Databases will be searched by one reviewer to identify potential titles and abstracts. Two reviewers will independently screen these titles and abstracts for methodological validity. Full articles of relevant studies will be obtained and scrutinized by two independent reviewers to determine eligibility for inclusion in this review. Should there be a disagreement between reviewers, a consensus will be reached through discussion. However, should this fail, a third reviewer will be requested to take a decision.

Data extraction and management:

Data from included studies will be extracted by two independent reviewers through a customised pre-set data extraction sheet. Extracted data will include: country of origin, study design (parallel/cross-over/cluster, randomisation, allocation concealment & blinding) and professional discipline of clinician delivering the intervention; setting, number of participants per group and points estimates; comorbidities, exclusion/inclusion criteria, participants' age and gender; type and side of amputation, adverse effects, pain condition and period (months) post-amputation; assessment tools, type of treatment and control intervention received; duration of treatment (minutes), frequency of treatment per week, follow-up period (weeks) and number of patients lost to follow-up; baseline, post-intervention and follow-up results on outcome measures and author conflict of interest statement. Data

will be recorded into Review Manager 5 (RevMan, 2011). Disagreements concerning data extraction will be resolved through discussion. A third reviewer will be consulted where a consensus cannot be reached.

Assessment of risk of bias:

Two independent reviewers will utilize the Cochrane method for risk of bias assessment. Included studies will be classified as low, high or unclear risk of bias. Any disagreements between reviewers will be resolved through discussion. A third reviewer will be consulted where a consensus cannot be reached. We will acknowledge and report on concerns of bias that can influence the outcome of this review, in particular selection bias, performance bias and publication bias.

Measures of treatment effect:

For studies with a comparable outcome measure, we will pool data for meta-analysis. Continuous data will be presented as 95% confidence interval (CI) and mean difference (MD). The risk ratio (RR) and 95% CI will be calculated for dichotomous data. Furthermore, the number needed to treat (NNT) will be calculated. According to Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT), ≥15% pain reduction is minimally significant, ≥30% pain reduction is moderately significant and ≥50% is considerably significant (Dworkin, 2008).

Unit of analysis issues:

For cross-over experimental design studies, only the first set of data will be considered for analysis. When trials have more than one intervention group, the control group will be divided in half. Each group will separately be included in the meta-analysis (Ramsay, 2003).

We will classify follow-up outcome measures by duration; short term (up to three months post-treatment), medium-term (three months – nine months post treatment) and long-term (longer than two years post-treatment).

Dealing with missing data:

In case of missing data, we will contact authors to provide further information. When the authors fail to provide information within two months, we will use intention-to-treat analysis for extrapolated data. The impact of this will be reported in the discussion section of the systematic review.

Assessment of heterogeneity:

Clinical heterogeneity will be addressed by pooling studies which investigate the same intervention and outcomes in amputees with PLP. Methodological heterogeneity will be examined visually, whereas statistical heterogeneity will be assessed through I^2 statistics. We will consider a cut-off score of 50%.

Assessment of reporting biases:

We will compare the methods section of the articles with the results section. If sufficient data is included, we will assess reporting bias by using a funnel plot (Sterne 2008).

Data synthesis:

Studies with a comparable intervention and outcome measure will be pooled for meta-analysis using Review Manager 5 (RevMan, 2011). We will use the random effects model to analyse studies with high heterogeneity. We will consider a narrative synthesis approach where there is insufficient data to perform a meta-analysis.

Sensitivity analysis:

If numerous trials satisfy the inclusion criteria for this systematic review, sensitivity analysis will be conducted to examine the possibility of excluding studies with a high risk of bias.

Subgroup analysis:

A subgroup analysis depending on age, gender or type of amputee will be performed when applicable.

Competing interests:

The authors declare that they have no competing interests.

Contribution of authors:

KL drafted the protocol. RP and LC conceptualized and edited the protocol. All authors read and approved the final manuscript.

Sources of funding:

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The University of Cape Town, Health Sciences library for providing technical support.

Appendix B: Customised search strategy

1. (graded motor imagery OR motor imagery programme OR movement representation techniques)

2. (left/right judgements OR left right judge* OR implicit motor imagery)

3. (imagined movement OR imagined movements OR mental imagery)

4. (mirror therapy OR mirror therap* OR mirror technique* OR mirror box therap*)

5. (phantom limb pain OR phantom pain)

6. (amput*)

7. 1 OR 2 OR 3 OR 4

8. 5 AND 6

9. 7 AND 8

Appendix C: Risk of bias assessment guide

Sequence generation:

Low: If sequence generated by referring to a random number table OR using a computer random number generator OR shuffling of envelopes provided they are re-used (as in drawing of lots that are always present in equal numbers) OR coin tossing OR shuffling cards OR throwing dice OR likely true randomisation was used.

High: If sequence generated by odd or even date of birth OR by some rule based on date (or day) of admission or hospital or clinic record number. Allocation by judgment of the clinician OR by preference of the participant OR by availability of the intervention OR based on the results of a laboratory test OR by use of envelopes OR drawing lots when envelopes or lots are not re-used OR "pseudo randomisation"

Unclear: Insufficient information to permit judgment. E.g. Stating that "Randomisation was done" without providing the details of what was done, and information to suggest that randomisation was not true (equal group sizes)

Allocation Concealment:

Low: Participants and investigators enrolling participants could not foresee assignments before assigning subjects to groups because of the use of any of the following: central allocation (including telephone, web-based, and randomisation) OR use of sequentially numbered, opaque and sealed envelopes.

High: If participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: using an open random allocation schedule (e.g. a list of random numbers) OR assignment envelopes used without appropriate safeguards (e.g. use of unsealed, non-opaque or not sequentially numbered envelopes); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.

Unclear: Insufficient information to permit judgment. e.g. use of assignment envelopes is described, but it remains unclear if they were sequentially numbered, opaque and sealed.

Blinding of participants and personnel:

Low: Blinding of participants and key study personnel ensured AND use of post-trial questionnaire to assess the level of blinding in a trial OR blinding of participants and key study personnel ensured AND unlikely that the blinding could have been broken.

High: Lack of blinding of key study participants and personnel OR incomplete blinding of study participants and personnel OR blinding of key study participants and personnel attempted but blinding assessment not conducted post-trial AND likely that blinding could have been broken.

Unclear: Insufficient information to permit judgment.

Blinding of outcome assessors:

Low: Blinding of outcome assessment ensured AND blinding assessment conducted and confirmed that was blinding was adequate OR blinding of outcome assessment AND unlikely that blinding could have been broken.

High: Lack of blinding of outcome assessment OR blinding of outcome assessment attempted, but blinding assessment not conducted post-trial AND likely that blinding could have been broken OR blinding of outcome assessment AND post-trial blinding assessment demonstrates that blinding was inadequate.

Unclear: Insufficient information to permit judgement.

Incomplete outcome data:

Low: No missing outcome data OR reason for missing outcome data not likely to be related to true outcome, with balance in numbers or reasons for missing data across intervention groups; missing data but use of 'Intention-to-treat' analysis OR if missing data have been imputed using appropriate methods.

High: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups OR inappropriate handling of missing data (e.g intention-to-treat analysis); potentially inappropriate application of simple imputation.

Unclear: Insufficient information to permit judgment.

Selective outcome reporting:

Low: The study protocol is available AND all of the study's pre-specified outcomes of interest have been reported in the pre-specified way OR protocol is not available but it is clear that the published reports include all expected outcomes specified in the Methods section.

High: Not all of the study's specified outcomes have been reported OR One or more primary outcomes are reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified OR One or more reported outcomes were not pre-specified (unless clear justification

for their reporting is provided, such as an unexpected adverse effect) OR the study report fails to include results for a key outcome that would be expected to have been reported based on the aims of the study.

Unclear: Insufficient information to permit judgment.

Other sources of bias:

[Were the groups' outcome measures similar at baseline?]

Low: If primary and secondary outcomes are similar AND similarities in patients' demographics and characteristics; insignificant difference in outcomes and patients' demographics and characteristics

High: significant difference in reported primary and secondary outcomes OR significant difference in demographics and patients' characteristics.

Unclear: Insufficient information to permit judgement.

[Were eligibility criteria specified?]

Low: source of subjects AND the study's eligibility criteria reported.

High: source of subjects not reported OR study's eligibility criteria not reported.

Unclear: Insufficient information to permit judgement.

[Were assessment tools reliable and valid?]

Low: tool used is valid, reliable and appropriately used for specific assessed outcome.

High: tool used is not valid OR tool used is not reliable OR tool used is inappropriately used for specific assessed outcome.

Unclear: insufficient information to permit judgement.

[Were statistical methods used reliable and valid?]

Low: Statistical method used is valid, reliable and appropriately used for specific outcomes.

High: statistical method used is not valid OR statistical method used is not reliable OR statistical method used is inappropriately used OR statistical method is not specified.

Unclear: insufficient information to permit judgement.

[Did trials have a population sample of 50 or more participants per group?]

Low: recruited and reported sample size of 50 or more participants.

High: recruited and reported sample size of less than 50 participants.

Unclear: insufficient information to permit judgement

Declaration of conflicts of interest by authors.

Low: authors report no conflict of interest OR conflict of interest reported but unlikely to influence the outcomes of the study.

High: Authors report conflict of interest likely to influence the outcomes of the study.

Unclear: insufficient information to permit judgement.

Overall bias rating for this criterion

Low: If the study does not meet the criteria for either the High risk or Unclear judgement, then it should be classified as low risk of bias.

High: If a study meets any of the criteria for 'high risk', then it should be judged as having high risk of bias

Unclear: If it is not classified as high risk and has any unclear elements, then it should be classified as unclear.

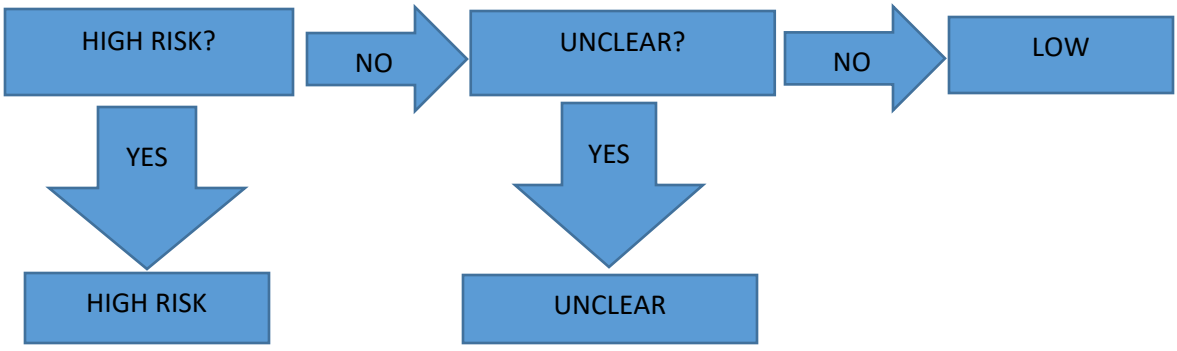

Figure 12. The bias rating chart

Appendix D: Characteristics of interventions in included studies.

Author	Experimental intervention	Control intervention	Minutes per session	Frequency of Intervention (per day)	Duration of Intervention (days)	Duration of intervention (h:min)	Follow-up period (weeks)	Outcome measures
Brodie et al	Mirror therapy: Prosthesis removed. 10 repetitions of 10 different movements with both phantom and intact legs whilst viewing the reflection of the intact limb.	Obscured Mirror therapy: Prosthesis removed. 10 repetitions of 10 different movements with both phantom and intact legs using a concealed mirror.	___	1	1	___	___	VAS(0-100mm)
Chan et al	Mirror therapy: movements with both phantom and intact legs whilst viewing the reflection of the intact limb.	Obscured mirror therapy: different movements with both phantom and intact legs using a concealed mirror.	15	1	28	7h 0min	___	VAS(0-100mm)

		<u>Imagined movements:</u> Imagined movements of the phantom limb.						
Moseley	<u>GMI:</u> 2/52 limb left/right judgements; matching the sides of limbs presented on the screen. 2/52 imagined movements; imagined movements of the phantom limb (2 reps per image/position; 2/52 mirror therapy: movements with both phantom and intact limbs whilst viewing reflection of intact limb.	<u>Routine physiotherapy:</u> 1 treatment/week plus home exercise programme including at least hourly training.	10	1	42	7h 0min	24	VAS(0-100mm)

	Plus monitoring, supervision, questioning opportunity.							
Tilak et al	Mirror therapy: movements with both phantom and intact legs whilst viewing the reflection of the intact limb.	TENS: Burst TENS applied to intact limb at site corresponding to site of PLP; strong current but comfortable with visible muscle contraction.	20	1	4	1h 20min	___	VAS(0-100mm) No pain-severe pain
Tung et al	Direct movement observation: Direct observation of someone else's lower limbs and feet moving coupled with voluntary movement of phantom limbs and feet to mimic	Imagined movements; Imagined movements of the phantom limb.	20	1	28	9h 20min	___	VAS(0-100mm) No pain-worst pain

	movement observed.							
Ulger et al	Imagined movements; Imagined movements of the phantom limb.	General exercise programme: Prosthetic training & individualised general strengthening, stretching, dynamic & isometric exercises.	___	1	28	___	___	VAS(0-100mm)

Appendix E: Questionnaire to establish what physiotherapy treatment modalities are currently used for phantom limb pain.

Below is a list of treatment modalities used to treat people who have had amputation and are suffering with phantom limb pain. Each treatment modality is referenced with literature indicating its efficacy for phantom limb pain. If you have previously used any of these modalities to treat amputees with phantom limb pain, please indicate with a tick how often you have used such modalities: never, seldom, sometimes or often.

Treatment Modalities for Phantom Limb Pain

Transcutaneous nerve stimulation (TENS) (Giuffrida, Simpson & Halligan, 2010)

☐ Never ☐ seldom ☐ sometimes ☐ often

(Subedi & Grossberg, 2011)

☐ Never ☐ seldom ☐ sometimes ☐ often

Graded motor imagery (Moseley, 2006)

☐ Never ☐ seldom ☐ sometimes ☐ often

Exercise (Weeks, Anderson-Barnes & Tsao, 2010)

☐ ☐ ☐ ☐

Never seldom sometimes often

Mirror therapy (Ramachandran & Ramachandran, 1996)

☐ Never ☐ seldom ☐ sometimes ☐ often

Biofeedback (Sherman, 1989)

☐ Never ☐ seldom ☐ sometimes ☐ often

Sensory discrimination training (Flor, 2002)

☐ Never ☐ seldom ☐ sometimes ☐ often

Therapeutic Ultrasound (Subedi & Grossberg, 2011)

☐ Never ☐ seldom ☐ sometimes ☐ often

Thank you for assisting us with our survey.

Appendix F: Letter to therapists and informed consent.

To whom it may concern:

I am a qualified physiotherapist registered for a masters (MSc) in physiotherapy degree at the University of Cape Town. I will be working with the Physiotherapy outpatient departments at your hospital to conduct a survey that will form part of the main research study titled: The effectiveness of graded motor imagery on phantom limb pain and function in upper and lower limb amputees

I am writing to invite you to participate in a survey as part of the study. The main reason for this survey is to find out which Physiotherapy and Occupational therapy modalities are commonly used in treating people who have had an amputation and are suffering with phantom limb pain.

In this survey, you will be given a short and simple questionnaire with a list of several treatment modalities for phantom limb pain. From this list, you will mark the treatment modalities you have previously used in the treatment of patients who are suffering with phantom limb pain following an amputation. On the list of treatment modalities you will be asked to indicate how often you have used these treatment techniques ranging from “never” to “seldom”, “sometimes” or “often”.

No risks are involved in participating in this study. Furthermore, your participation will not have any negative effects on your professional practise. No payments or benefits will be given to individuals for their participation in this study.

This survey should take at most five minutes. Taking part in the survey will therefore not interrupt your normal daily schedule. Taking part is completely voluntary and nothing bad will happen to you should you choose not to participate. If you do choose to take part, you may withdraw at any time and you may choose not to answer certain questions if you do not want to answer them.

Confidentiality will always be maintained throughout this study. The results of this study will be stored safely in a password-protected electronic folder. Your name will not be used in publications.

Your participation is highly appreciated.

CONSENT FORM:

TITLE OF STUDY: THE EFFECTIVENESS OF GRADED MOTOR IMAGERY ON PHANTOM LIMB PAIN AND FUNCTION IN AMPUTEES

I, _____ have read the information sheet. I understand the outline of this study. I do not feel forced to partake in this study and am doing so willingly. I know that I can withdraw from the study anytime and there will not be any penalty for my action.

Signed: (write name and surname)

Participant: _____ Date and Place:

Researcher: _____ Date and Place:

Witness (if necessary): _____ Date and Place:

For further information:

Researcher:

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Supervisor:

Associated Prof Romy Parker: Tel: (Work) 021-406 6571

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Chairperson FHS human research ethics committee:

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Co-supervisor:

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E-mail: shamila.manie@uct.ac.za

Appendix G: Questions for telephonic screening:

This call should take at most five minutes of your time. During this call, I will ask you simple questions that will help me to gather whether or not you qualify to take part in this study. I need you to answer as honestly as you can. Should you need clarity on some question, do not hesitate to ask, I am more than happy to explain further in such a case.

1. Do you have phantom limb pains in your amputated limb? Phantom limb pains are painful sensations felt in the missing part of the amputated limb.

2. Are you 18 years old or above?

3. Do you live within the Cape Town metropolitan area?

4. Can you understand, read or write either English, isiXhosa or Afrikaans?

5. I understand you have had an amputation of the upper/lower limb. Have you had any other amputation surgeries?

6. Has it been more than 3 months since your amputation?

7. Do you have pain or any medical conditions in the limb opposite to your amputated limb?

8. Do you have any eye problems that have affected your ability to see nearby objects clearly?

   - If "yes" , Do you have glasses to help you see close objects clearly?

9. Has your health been stable for more than three months?

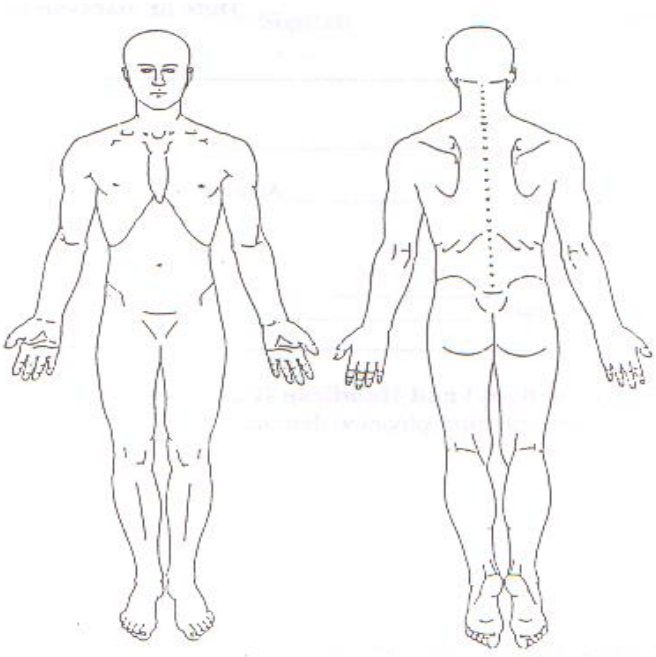
10. Were any of these conditions a reason for your amputation; Diabetes, cardiovascular diseases, infection and trauma?

During this interview, if any of the patient's answer contradicts the inclusion criteria of this study, stop the interview, thank them for their time and politely inform them that they do not qualify to take part in this study but that they will continue with their usual physiotherapy treatment.

Appendix H: Brief Pain Inventory

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain during the last week?

   Yes No



2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.
3. Please rate your pain by circling the one number that best describes your pain at its ***worst*** in the last week.

0 1 2 3 4 5 6 7 8 9 10

No Pain Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its ***least*** in the last week.

0 1 2 3 4 5 6 7 8 9 10

No Pain as bad as

Pain you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the ***average.***

0 1 2 3 4 5 6 7 8 9 10

No Pain as bad as

Pain you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have ***right now.***

0 1 2 3 4 5 6 7 8 9 10

No Pain as bad as

Pain you can imagine

What treatments or medications are you receiving for your pain?

---

7. In the last week, how much ***relief*** have pain treatments or medications provided? Please circle the one percentage that most shows how much *relief* you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No										Complete
Relief										Relief

8. Circle the one number that describes how much, during the past week, pain has ***interfered with*** your:

A. ***General Activity***

0	1	2	3	4	5	6	7	8	9	10
Does not										Completely
interfere										interferes

B. ***Mood***

0	1	2	3	4	5	6	7	8	9	10
Does not										Completely
interfere										interferes

C. ***Walking Ability***

0	1	2	3	4	5	6	7	8	9	10
Does not										Completely

interfere interferes

D. ***Normal Work*** (includes both work outside the home and housework)

0 1 2 3 4 5 6 7 8 9 10

Does not Completely

interfere interferes

E. ***Relations with other people***

0 1 2 3 4 5 6 7 8 9 10

Does not Completely

interfere interferes

F. ***Sleep***

0 1 2 3 4 5 6 7 8 9 10

Does not Completely

interfere interferes

G. ***Enjoyment of life***

0 1 2 3 4 5 6 7 8 9 10

Does not Completely

interfere interferes

Scoring:

Pain Severity Score = Mean of items 3–6 (pain at its worst, pain at its least, average pain)

Pain Interference Score = Mean of items 9A–9G (interference of pain with: general activity, mood, walking, normal work, relations, sleep, enjoyment of life).

Appendix I: EuroQoL EQ-5D-5L

EQ-5D-5L Health Questionnaire

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ☐

I have slight Problems in walking about ☐

I have moderate problems in walking about ☐

I have severe problems in walking about ☐

I am unable to walk about ☐

SELF-CARE

I have no problems washing or dressing myself ☐

I have slight problems washing or dressing myself ☐

I have moderate problems washing or dressing myself ☐

I have severe problems washing or dressing myself ☐

I am unable to wash or dress myself ☐

USUAL ACTIVITIES *(e.g. Work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ☐

I have slight problems doing my usual activities ☐

I have moderate problems doing my usual activities ☐

I have severe problems doing my usual activities ☐

I am unable to do my usual activities ☐

PAIN / DISCOMFORT

I have no pain or discomfort ☐

I have slight pain or discomfort ☐

I have moderate pain or discomfort ☐

I have severe pain or discomfort ☐

I have extreme pain or discomfort ☐

ANXIETY /DEPRESSION

I am not anxious or depressed ☐

I am slightly anxious or depressed ☐

I am moderately anxious or depressed ☐

I am severely anxious or depressed ☐

I am extremely anxious or depressed ☐

We would like to know how good or bad your health is TODAY.

This scale is numbered from 0 to 100.

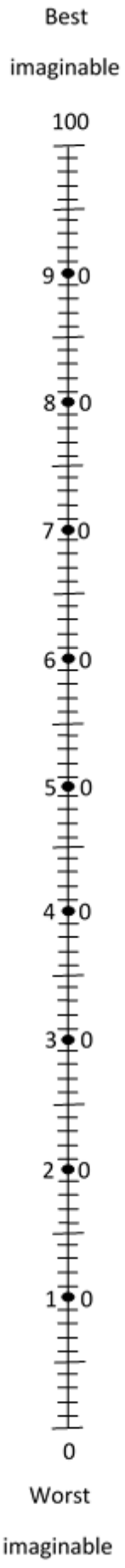
100 means the best health you can imagine.

0 means the worst health you can imagine.

Mark an X on the scale to indicate how your health is TODAY.

Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐


Best
imaginable
100
90
80
70
60
50
40
30
20
10
0
Worst
imaginable

Appendix J: Demographics questionnaire

Research Code: _____ Date: _____

Group allocation: _____

Home language: _____

Date of birth: _____

Gender: _____

Contact details:

Telephone number: _____

Cell phone number: _____

Which area do you live in? _____

What is your highest level of education? _____

Are you currently employed? If so, what do you do? _____

When did you get your amputation surgery? _____

Do you use an assistive device? _____

If so, what assistive device you use? _____

Do you have any other medical conditions? If so, please name them:

_____

_____

_____

Are you on medication? If so, please name them?

_____

_____

_____

_____

_____ _____

Additional useful information gathered from the patient's folder:

_____
_____
_____

Appendix K: Ethical Approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room ES2-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
Email: nusi.tsoma@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

16 May 2016

HREC REF: 244/2016

A/Prof R Parker
Physiotherapy Division
Health & Rehab Sciences
Old Main Building

Dear A/Prof Parker

PROJECT TITLE: THE EFFECTIVENESS OF GRADED MOTOR IMAGERY ON PHANTOM LIMB PAIN AND FUNCTION IN UPPER AND LOWER LIMB AMPUTEES: A QUASI-EXPERIMENTAL STUDY :(MSc-candidate-K Limakatso)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

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 May 2017.

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)

We acknowledge that the student Katleho Limakatso will also be involved in this study.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval before the research may occur.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

T Burgess

pp **PROFESSOR M BLOCKMAN**
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

HREC 244/2016

Appendix L: Letter to the Head of Physiotherapy Department

Division of Physiotherapy

Department of Health and Rehabilitation Sciences

Faculty of Health Sciences

University of Cape Town

Anzio Road

Observatory 7925

Cape Town

The Western Cape Department of Health

PO Box 2060

Cape Town

8000

REQUEST FOR PERMISSION TO CONDUCT RESEARCH IN FOUR HOSPITALS IN THE WESTERN CAPE

To whom it may concern,

I am a registered Masters (MSc) student at the University of Cape Town, Faculty of Health Science, Department of Health and Rehabilitation Sciences in the Division of Physiotherapy. I aspire to conduct a research study entitled: "The effectiveness of graded motor imagery on phantom limb pain and function in amputees."

I am writing to you to inform and to request your authorization to conduct my research study within your department. The aim of this study is to investigate the effectiveness of graded motor imagery in upper and lower limb amputees with phantom limb pain.

Physiotherapist and occupational therapists treating amputees will be asked to inform patients about the study and ask for permission to forward their names to the researcher if they are interested in participating. These patients will be contacted telephonically to explain the study and to invite them to participate and for initial screening of inclusion criteria using a questionnaire. Patients who meet these criteria will then be asked to attend physiotherapy and occupational therapy departments at their hospital to meet with the researcher for completion of full consent, screening of exclusion criteria, education and where appropriate measurement of baseline data. Patients will be reimbursed transport costs for this appointment.

Patients will be randomly allocated to a treatment or control group.
Re-assessment will take place again at the end of the six-week treatment period, at three months and six months post recruitment. All research treatments will be conducted by the researcher and no additional work will be required of hospital staff.

This study will contribute to the existing literature, filling in the gap whether graded motor imagery reduces phantom limb pain and disability in upper and lower limb amputees. The results of this study should also stoke interest and prompt further research in this particular field.

The study will be supervised by Associate Professor Romy Parker *(PhD)*, Department of Anaesthesia and Perioperative Medicine, Faculty of Health Sciences, University of Cape Town.

Your permission will be highly appreciated. Thanking in anticipation.

Yours faithfully,

Katleho Limakatso

<u>For further information:</u>

<u>Researcher:</u>

Katleho Limakatso: Tel: 078 841 8510

E-mail: lmkmax001@myuct.ac.za

<u>Supervisor:</u>

Associated Prof Romy Parker: Tel: (Work) 021-406 6571

Fax: 021-406 6401

E-mail: romy.parker@uct.ac.za

Chairperson FHS human research ethics committee:

Professor Marc Blockman: Tel: 021-406 6338

Fax: 021-406 6411

E-mail: shuretta.thomas@uct.ac.za

Co-supervisor:

Shamila Manie: Tel: 021-650 1787

E-mail: shamila.manie@uct.ac.za

Appendix M: Exercise program (English)

Left/right judgements phase (week 1-2)

- Sit comfortably with your amputated limb in a relaxed position.
- Open your magazine and begin to circle with a pen all the limbs matching the side of your amputated limb.
- Perform this exercise for 10 minutes of every waking hour.
- Record your participation in your journal.

Imagined movements phase (week 3-4)

- Sit comfortably with your amputated limb in a relaxed position.
- In your magazine, identify a picture of a person with a simple posture of the limb matching your amputated limb.
- Observe and pay careful attention to the limb you identified.
- Imagine moving your limb slowly and smoothly without increasing your pain to the posture presented in the magazine photo.
- Imagine slowly and smoothly returning the limb to the starting point without increasing your pain.
- Find another picture in the magazine. Repeat the exercise.
- Perform this exercise for 10 minutes of every waking hour.
- Record your participation in your journal.

Mirror therapy phase (week 4-6)

- Sit comfortably with your amputated limb in a relaxed position.
- Remove any jewellery or/and cover any tattoos on the opposite limb of the amputated limb.
- Hide your amputated limb behind the mirror and position the unaffected limb in front of the mirror.
- Move both limbs slowly and smoothly while observing the reflection of the unaffected limb in the mirror.
- Perform this exercise for 10 minutes of every waking hour.
- Record your participation in your journal.

NB! If you experience an increase in pain during or after exercise, you are advised to stop the treatment and inform your physiotherapist so that the dosage can be adjusted.

For further information:

Researcher:

Katleho Limakatso: Tel: 078 841 8510

E-mail: lmkmax001@myuct.ac.za

Supervisor:

Associated Prof Romy Parker: Tel: (Work) 021-406 6571

Fax: 021-406 6401

E-mail: romy.parker@uct.ac.za

Chairperson FHS human research ethics committee:

Professor Marc Blockman: Tel: 021-406 6338

Fax: 021-406 6411

E-mail: shuretta.thomas@uct.ac.za

Co-supervisor:

Shamila Manie: Tel: 021-650 1787

E-mail: shamila.manie@uct.ac.za

Appendix N: Home Exercise Journal (Left/right judgements/ Imagined Movements/ Mirror therapy)

DAYS	TIME: 9:00AM- 9:00PM (10 minutes of every waking hour)		
Monday	9:00am-10:00am ☐	10:00pm-11:00pm ☐	11:00pm-12:00pm ☐
	12:00am-1:00pm ☐	1:00pm-2:00pm ☐	2:00-3:00pm ☐
	3:00pm-4:00pm ☐	4:00pm-5:00pm ☐	5:00pm-6:00pm ☐
			Total: /12
Tuesday	9:00am-10:00am ☐	10:00pm-11:00pm ☐	11:00pm-12:00pm ☐
	12:00am-1:00pm ☐	1:00pm-2:00pm ☐	2:00-3:00pm ☐
	3:00pm-4:00pm ☐	4:00pm-5:00pm ☐	5:00pm-6:00pm ☐
			Total: /12
Wednesday	9:00am-10:00am ☐	10:00pm-11:00pm ☐	11:00pm-12:00pm ☐
	12:00am-1:00pm ☐	1:00pm-2:00pm ☐	2:00-3:00pm ☐
	3:00pm-4:00pm ☐	4:00pm-5:00pm ☐	5:00pm-6:00pm ☐
			Total: /12
Thursday	9:00am-10:00am ☐	10:00pm-11:00pm ☐	11:00pm-12:00pm ☐
	12:00am-1:00pm ☐	1:00pm-2:00pm ☐	2:00-3:00pm ☐
	3:00pm-4:00pm ☐	4:00pm-5:00pm ☐	5:00pm-6:00pm ☐

			Total: /12
Friday	9:00am-10:00am ☐	10:00pm-11:00pm ☐	11:00pm-12:00pm ☐
	12:00am-1:00pm ☐	1:00pm-2:00pm ☐	2:00-3:00pm ☐
	3:00pm-4:00pm ☐	4:00pm-5:00pm ☐	5:00pm-6:00pm ☐
			Total: /12
Saturday	9:00am-10:00am ☐	10:00pm-11:00pm ☐	11:00pm-12:00pm ☐
	12:00am-1:00pm ☐	1:00pm-2:00pm ☐	2:00-3:00pm ☐
	3:00pm-4:00pm ☐	4:00pm-5:00pm ☐	5:00pm-6:00pm ☐
			Total: /12
Sunday	9:00am-10:00am ☐	10:00pm-11:00pm ☐	11:00pm-12:00pm ☐
	12:00am-1:00pm ☐	1:00pm-2:00pm ☐	2:00-3:00pm ☐
	3:00pm-4:00pm ☐	4:00pm-5:00pm ☐	5:00pm-6:00pm ☐
			Total: /12

Appendix O: information pack and consent form

Dear Sir/Madam

I am a qualified physiotherapist registered for a masters (MSc) in physiotherapy at the University of Cape Town. I will be working with the physiotherapy outpatients department at your hospital to conduct a research study titled: The effectiveness of graded motor imagery on phantom limb pain and function in upper and lower limb amputees.

Why are we doing this study?

I am writing to invite you to participate in this study. The main reason for this research is to find out whether the treatment called "graded motor imagery" works best to treat phantom limb pain in people who have had an amputation.

What will you need to do?

In this study, you will have an equal chance of being placed into one of two groups. Each group will receive a different type of physiotherapy for a period of six weeks. You will be expected to attend physiotherapy on two separate days in week 1, week 3 and week 5. You will then return at the end 0f week 6 for final assessment. Each session will last for 20 minutes.

The study will take place at your out-patient physiotherapy department. You will be asked to sign an agreement form before taking part. You will then be asked questions to check whether you qualify to take part in the study. If for any reason you do not qualify, you will not be included in this study and your physiotherapy treatment will continue as normal. You will then be assisted with filling some questionnaires which will be made available in English, isiXhosa and Afrikaans. I will then give you an appointment date to begin your treatment.

What risks are involved?

Routine physiotherapy has no risks but you may have a possible increase in pain, muscle stiffness or fatigue. The treatment of graded motor imagery has no risks; it uses imaginary exercises and simple exercises like the ones you would be doing in physiotherapy. However, should you report that your symptoms are getting worse, immediate medical attention will be given to you and you will be referred if necessary.

What benefits are involved?

In this study, you will be educated about phantom limb pain and different ways of how to cope with it daily. In turn, this will improve your goal setting ability, faithfulness to therapy and self-confidence.

What payment will be received?

No payments or benefits will be given to individuals for their participation in this study. However, you will be provided with money to cover your transportation costs for the period of the study, so that your participation in the study does not cost you.

Do I have to take part?

Taking part in the study will not interrupt your normal care at all. Taking part is completely up to you and nothing bad will happen to you if you choose not to participate. If you do choose to take part, you are allowed to pull out at any time and you may choose not to answer certain questions if you don't want to answer them. If you choose to stop coming, it will not affect your normal care at all. Your personal information will not be revealed to anyone without your permission. The results of this study will be stored safely in a password-protected folder. Your name will not be used in publications.

Compensation/Treatment in the event of an injury

Should you choose to participate, please feel free to contact the UCT FHS Human Research Ethics Committee on (021) 406 6338 in case you have any questions about your rights and welfare as a research subject on the study; the researcher, Katleho Limakatso, can be contacted on (078) 8418510. Professor Romy Parker can be contacted on (021) 4066431 to answer any other questions you may have.

Please note that UCT does offer a no-fault insurance that will cover all participants in the event that something may go wrong. This insurance will provide immediate payment of compensation for any trial-related injury in accordance with the Association of the British Pharmaceutical Industry (ABPI) guidelines (1991). These guidelines recommend that UCT, without any legal commitment, should compensate you without you having to prove that UCT is at fault. An injury is considered trial-related if, and to the extent that, it is caused by study activities. You must notify the study investigators immediately of any 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 taking part in the study. Your right in law to claim compensation for injury where you prove negligence is not affected.

Your permission will be highly appreciated.

Yours faithfully,

Katleho Limakatso

CONSENT FORM:

TITLE OF STUDY: THE EFFECTIVENESS OF GRADED MOTOR IMAGERY ON PHANTOM LIMB PAIN AND FUNCTION IN AMPUTEES

I, _____ have read the information sheet. I understand the outline of this study. I do not feel forced to partake in this study and am doing so willingly. I know that I can withdraw from the study anytime and there will not be any penalty for my action.

Signed: (write name and surname)

Participant: _____ Date and Place:

Researcher: _____ Date and Place:

Witness (if necessary): _____ Date and Place:

For further information:

Researcher:

Katleho Maxwell Limakatso: Tel: 078 841 8510

E-mail: lmkmax001@myuct.ac.za

Supervisor:

Associated Prof Romy Parker: Tel: (Work) 021-406 6571

Fax: 021-406 6401

E-mail: romy.parker@uct.ac.za

Chairperson FHS human research ethics committee:

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Fax: 021-406 6411

E-mail: shuretta.thomas@uct.ac.za

Co-supervisor:

Shamila Manie: Tel: 021-650 1787

E-mail: shamila.manie@uct.ac.za

Appendix P: Detailed results of the EuroQoL EQ-5D-5L

	Total (n)	Experimental Group (n)	Control Group (n)	Significance Test
Mobility: Baseline				$\chi^2 = 8.88$; p= 0.06
No problems	9	5	4	
Slight problems	2	0	2	
Moderate problems	2	2	0	
Severe problems	5	4	1	
Unable to walk	3	0	3	
Mobility: 6-weeks				$\chi^2 = 6.7$; p= 0.16
No problems	13	8	5	
Slight problems	1	0	1	
Moderate problems	2	2	0	
Severe problems	2	1	1	
Unable to walk	3	0	3	
Mobility: 3-months follow up				$\chi^2 = 9.8$; p= 0.04 *
No problems	7	2	5	
Slight problems	7	6	1	
Moderate problems	2	2	0	
Severe problems	2	1	1	
Unable to walk	3	0	3	
Self-care: Baseline				$\chi^2 = 0.01$; p= 0.99
No problems	16	8	8	
Slight problems	2	1	1	
Moderate problems	2	1	1	
Severe problems	1	1	0	
Unable to wash or dress	0	0	0	
Self-care: 6-weeks				$\chi^2 = 0.01$; p= 0.99
No problems	17	9	8	
Slight problems	2	1	1	

Moderate problems	2	1	1	
Severe problems	0	0	0	
Unable to wash or dress	0	0	0	
Self-care: 3-months follow up				$\chi^2 = 0.69$; p= 0.71
No problems	15	7	8	
Slight problems	3	2	1	
Moderate problems	3	2	1	
Severe problems	0	0	0	
Unable to wash or dress	0	0	0	
Activity: Baseline				$\chi^2 = 3.25$; p= 0.52
No problems	7	4	3	
Slight problems	7	4	3	
Moderate problems	4	2	2	
Severe problems	1	1	0	
Unable to do usual activities	2	0	2	
Activity: 6-weeks				$\chi^2 = 4.96$; p= 0.29
No problems	9	6	3	
Slight problems	6	2	4	
Moderate problems	2	2	0	
Severe problems	3	1	2	
Unable to do usual activities	1	0	1	
Activity: 3-months follow up				$\chi^2 = 4.3$; p= 0.37
No problems	6	3	3	
Slight problems	8	4	4	
Moderate problems	3	3	0	
Severe problems	3	1	2	
Unable to do usual activities	1	0	1	
Pain: Baseline				$\chi^2 = 6$; p= 0.2
No problems	3	2	1	
Slight problems	8	3	5	

Moderate problems	3	3	0	
Severe problems	5	3	2	
Extreme pain	2	0	2	
Pain: 6-weeks				$\chi^2 = 5.9$; p= 0.11
No problems	9	7	2	
Slight problems	9	4	5	
Moderate problems	1	0	1	
Severe problems	2	0	2	
Extreme pain	0	0	0	
Pain: 3-months follow up				$\chi^2 = 4.8$; p= 0.19
No problems	8	6	2	
Slight problems	8	3	5	
Moderate problems	3	2	1	
Severe problems	2	0	2	
Extreme pain	0	0	0	
Anxiety: Baseline				$\chi^2 = 5$; p= 0.29
No problems	9	3	6	
Slight problems	6	5	1	
Moderate problems	3	2	1	
Severe problems	1	0	1	
Extreme anxiety/ depression	1	0	1	
Anxiety: 6-weeks				$\chi^2 = 5.1$; p= 0.08
No problems	12	8	4	
Slight problems	5	2	3	
Moderate problems	3	0	3	
Severe problems	0	0	0	
Extreme anxiety/ depression	0	0	0	
Anxiety: 3 months follow up				$\chi^2 = 4$; p= 0.19
No problems	10	6	4	
Slight problems	7	4	3	
Moderate problems	3	0	3	

Severe problems	0	0	0
Extreme anxiety/ depression	0	0	0