EFFECTIVENESS OF CERVICAL LATERAL GLIDE MOBILISATION IN THE MANAGEMENT OF CERVICOBRACHIAL PAIN

by

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Abstract

Background

Cervicobrachial pain is a painful condition which, when chronic, might lead to high levels of disability. Limited data from small studies have reported that the lateral glide mobilisation is effective on reducing pain in the short-term. The primary aim of this study was to establish whether the lateral glide mobilisation technique was effective in reducing pain in the long-term.

Methods

Literature reviews on cervicobrachial pain provided the rational to conduct a phase III trial. An audit and a preliminary study were used to inform methods for the trial. A single-centre randomised clinical trial was conducted on participants with chronic cervicobrachial pain. Participants were randomised to receive either the lateral glide with self-management or self-management alone. The trial was powered to detect a between group difference of 20mm on worst pain on a visual analogue scale (VAS) at 52 weeks follow-up.

Results

Ninety-nine participants were recruited to the trial. There was a non-significant between-group difference for mean VAS(worst pain) scores at 52 week follow-up ($p=0.52$; 95% CI -14.72 to 7.44).

Conclusion

The findings from this trial provided no evidence that the lateral glide was more effective than a comparator in the management of chronic cervicobrachial pain in the long-term.

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List of abbreviations

AROM	Active range of movement
CI	Confidence interval
GRADE	Grading of recommendations assessment, development & evaluation
GROC	Global rating of change
MCMD	Minimally clinically meaningful difference
MLM	Multi-level model
NHS	National Health Service
NULI	Neck and upper limb index
n	number
OR	odds ratio
p	probability
PBO	Performance based outcomes
PROM	Patient reported outcome measures
RCT	Randomised controlled trial
RcT	Randomised clinical trial
SD	Standard deviation
SF36 (MCS)	Short-form 36 (Mental component summary)
S-LANSS	Self-report Leeds assessment of neuropathic signs and symptoms
SLR	Systematic literature review
ULNE	Upper limb nerve extensibility test
UK	United Kingdom
VAS	Visual analogue scale

1 INTRODUCTION

Cervicobrachial (neck and arm) pain is a frequently occurring and disabling disorder and has been estimated to account for the majority of patients presenting for treatment with cervical spine disorders (Daffner et al., 2003). When the condition is chronic, it is likely to become a persistent or recurring problem that impacts unfavourably on an individual's mental as well as physical health (Daffner et al., 2003). The most recent study for the natural history of the condition reported reoccurrence rate to be as high as 32% (Radhakrishnan et al. 1994). In addition to the effect on individuals, persistent disablement could lead to high costs for health care systems and society (Karjalainen et al., 2006). Despite its impact, there are no clear guidelines for the management of cervicobrachial pain.

In cervicobrachial pain, pain can be referred to the arm from somatic structures or radiate to the upper limb through neuropathic mechanisms. Numerous classifications have been reported, including cervicobrachial pain syndrome, cervical radiculopathy and neck and arm pain. For the purpose of this study, cervicobrachial pain is defined as the presence of arm pain associated with cervical spine pain (Jull et al., 2008).

1.1 Rationale for the study

Surgical and conservative interventions are used in the management of cervicobrachial pain. Surgery has not been shown to be more effective compared to conservative management and has been reported to carry a 4% complication rate (Fouyas et al., 2002; Carragee et al., 2008). Conservative management has been advocated as the initial treatment of choice for the majority of patients with cervicobrachial pain (Fouyas et al., 2002; Daffner et al., 2003). Exceptions to this are patients with serious local pathology such as fractures, dislocations, myelopathy, infections or tumours that require urgent medical and/or surgical intervention (Carette and Fehlings, 2005).

Conservative management of cervicobrachial pain comprises invasive techniques (such as injection therapy and acupuncture) or non-invasive techniques with physiotherapy, osteopathy and chiropractic being the three most utilised within health care. There is limited evidence to support the use of injection therapy (Peloso et al., 2011) and acupuncture (Trinh et al., 2006). The Task Force on Neck Pain and Associated Disorders published a document in 2008 looking specifically at non-invasive interventions for neck pain, up to 2006. It highlighted that there was inadequate research on cervicobrachial pain for non-invasive interventions and that future research should focus on non-invasive interventions for this patient group (Hurwitz et al, 2008 p.123).

Manual therapy in the form of cervical mobilisation is one non-invasive intervention that is commonly used by physiotherapists, osteopaths and chiropractors. High quality systematic reviews have consistently reported mobilisation to be of value in

the management of cervical spine disorders, such as mechanical neck pain and cervicogenic headache (Gross et al., 2004; Gross et al., 2010; Miller et al., 2010). However, only limited research has been conducted to determine the therapeutic value of mobilisation for patients with cervicobrachial pain (Gross et al., 2004; Gross et al., 2010; Miller et al., 2010; Leininger et al., 2011).

Although a wide variety of mobilisation techniques are used to treat cervical spine dysfunction, it is unknown whether different techniques have varying therapeutic effect. Small scale, short-term studies have identified that the lateral glide mobilisation technique reduces cervicobrachial pain (Allison et al., 2002; Cowell & Phillips., 2002; Coppieters et al., 2003).

The primary research aim for the proposed trial was to identify whether the lateral glide cervical mobilisation was effective in reducing pain levels in the long-term for patients with chronic cervicobrachial pain. Secondary aims were to evaluate any effects the mobilisation had on function and disability. Patient perceived recovery, cost analysis and harm analysis were included in planning of the phase three trial.

1.2 Structure of the thesis

The thesis details processes involved in the development of a clinical trial to evaluate the use of a lateral glide mobilisation in the management of cervicobrachial pain. Methods used to conduct literature reviews are identified, followed by reporting of literature reviews to evaluate classification and epidemiology of cervicobrachial pain, to provide background information (Chapter 2). An in-depth analysis of existing research relating specifically to non-invasive interventions follows. A systematic literature review of non-invasive interventions for cervicobrachial pain was conducted and its findings reported (Chapter 3). The review supported further investigation of the lateral glide technique and different approaches for performing the technique were evaluated to support selection of the most appropriate approach to be used in the main phase III trial. A suitable comparator intervention was also identified with evidence to support its selection (Chapter 4). Planning of the phase III trial was informed by an audit and a preliminary study. Methods used for the phase III trial are identified (Chapter 5) and the results are presented relating to primary and secondary outcome measures (Chapter 6). Trial results and their relationship to previous research are discussed, limitations of the trial are considered and recommendations for future research are identified (Chapter 7). Throughout the thesis, the main trial will be referred to as the 'trial' to effect differentiation from the reporting of other studies.

1.3 Methods used in thesis for evaluation of evidence

Literature reviews (including a systematic review of non- invasive management of cervicobrachial pain) were conducted to support the development of the proposed trial. During the course of the PhD, augmentations to the methods for appraising literature were developed and published in the research literature (Moher et al., 2009; Balshem et al., 2011; Guyatt et al., 2011a; Higgins and Green, 2011). For the presentation of this thesis, evidence has been evaluated using these updated methods to maximise rigour in its evaluation. Information from updated searches was used to provide futher evidence to support methods used and conculsions drawn from the study, and were used to critically evaluate the results of this study in the discussion.

2 AN OVERVIEW OF CERVICOBRACHIAL PAIN

This chapter initially considers the methods used to search and evaluate the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. The chapter then focuses on classifying cervicobrachial pain as a single entity, followed by a critique of frequently reported sub-classification systems. The chapter concludes with a discussion of epidemiology and economic costs of cervicobrachial pain. It considers how cervicobrachial pain affects individuals and the wider effects to health care systems and society.

2.1 Method for the literature search on cervicobrachial pain

Searches were conducted using electronic computerised databases (Cochrane Library, Cochrane central register of controlled trials [CENTRAL], MEDLINE, EMBASE, AMED and CINAHL), from inception to January 2012.

For each database, key terms (cervicobrachial, cervical radiculopathy, neck and arm pain) were identified against classification, epidemiology, prognosis and economic cost. Searches were not limited by study design because it was anticipated that there would be a limited amount of data for some areas such as prognosis and cost. Truncation, exploding, thesaurus mapping and MESH terms were used to fully capture all available evidence (Timmins & McCabe., 2005; Cleary et al., 2009). This approach to searching has been advocated to ensure comprehensive data collection (CRD, 2009).

2.2 Method for the critical evaluation of evidence in the published literature

The GRADE system (Balshem et al., 2011; Guyatt et al., 2011a) was used to rate the quality of evidence reported in retrieved research studies and to determine recommendations about its use. GRADE was chosen because it provided the potential to upgrade or downgrade evidence, allowing a more flexible and sophisticated approach to evaluating the evidence (Balshem et al., 2011; Guyatt et al., 2011a). As with all critical evaluation systems, GRADE is open to subjectivity in use. However, its framework provided a systematic approach to appraising evidence, so that recommendations were determined through a planned method (Balshem et al., 2011; Guyatt et al., 2011a). Over the last decade, several organisations (for example, the World Health Organization, the American College of Physicians and the Cochrane Collaboration) have advocated the use of GRADE over other tools (Guyatt et al., 2008). It has been increasingly recognised, in research literature, as the 'gold standard' for the critical evaluation of evidence (Balshem et al., 2011; Guyatt et al., 2011a).

In general, the GRADE system establishes the quality of evidence and the strength of recommendation across studies, for specific outcomes (Guyatt et al., 2011a). For example, in this thesis, pain as an outcome was analysed separately from function.

A three-part process was used to reach a recommendation:

1. Quality of evidence was determined for eight specified domains.
2. Grade of evidence was determined by how many domains were met.
3. Strength of recommendation was based on the grade together with other determinants, for example risk versus benefit ratio.

2.2.1 Determining quality of evidence in the retrieved literature

Quality was based on eight key domains. Five of the domains could have resulted in downgrading evidence on an outcome: study limitations, inconsistency, indirectness, imprecision and reporting bias (Balshem et al., 2011). Three of the domains could have resulted in upgrading evidence on an outcome: large effect, dose response and consideration for confounders (Balshem et al., 2011).

Fulfilment of each domain was determined by following guidance in the Cochrane Handbook (Schünemann et al., 2011) and the series of publications by Guyatt et al. in the Journal of Clinical Epidemiology (Guyatt et al., 2011b; Guyatt et al., 2011c; Guyatt et al., 2011d; Guyatt et al., 2011e; Guyatt et al., 2011f). Criteria per domain are summarised in Table 2-1.

Table 2-1: Summary of criteria needed to fulfil each domain in GRADE

Domain	Criteria
Study limitations	Limitations are defined in relation to four specific types of bias: *Selection* (Focusing on the evidence of allocation sequence concealment and /or lack of similarity between participants baseline characteristics) *Performance* (Relating to whether blinding of the study participants or personnel has been reported. Or, whether differences between groups in additional care provided e.g. differing amounts of investigations or additional treatment have been identified) *Detection* (Concerning the blinding of outcome assessors and how Between group differences for different outcomes have been been determined) *Attrition* (Describing the proportion of attrition overall and between-groups. High proportion of loss to follow-up can be considered as >20%. An example of uneven loss to follow-up between groups would be 5% in one group compared to 15% in another)
Inconsistency	Inconsistency considers heterogeneity and study outcomes: Heterogeneity between studies might occur if different populations between studies are not comparable. For example, acute v chronic conditions. Inconsistency might be where there are large differences between study outcomes resulting in no clear direction of effect e.g. comparable studies report an intervention to have a positive effect on pain compared to a placebo, whilst others find that the placebo has a preferential pain response to the intervention.
Indirectness	Indirectness relates to external validity: Concerning whether the studies are generalisable, transferable, applicable or directly comparable. For example, the study results might not be generalisable to a UK population if the study was conducted in a third world country.
Imprecision	Imprecision relates to the size of studies, with small studies being subject to higher sampling variation than larger studies and, hence, statistical results are less precise. Imprecision is reflected in confidence intervals, with larger intervals indicating lower precision. In general, more precise results are obtained from studies that have been powered to ensure that adequate numbers of participants are recruited to improve precision.
Publication bias	Publication bias is usually suspected when primary outcomes published in a study protocol are not then published in the results of a completed study, especially when the outcomes published all report a positive result. Findings from research studies that have been funded by industry need to be interpreted with caution, as do outcomes that favour a commercial sponsor
Large effect	Large effect relates to the amount of change seen in outcomes: the quality of evidence can be upgraded by one or two points if large or very large and consistent estimates of treatment effect across studies are reported. Relative risk reduction more than 50% or risk ratio above 2 can be considered to demonstrate a large effect (upgrade by one point). More than 80% or risk ratio above 5 can be considered a very large effect (upgrade by 2 points)
Dose response	Dose response is defined as a correlation between quantity of treatment given and outcomes reported: A good dose response would be where a consistent relationship between an intervention and an outcome is found across similar studies.
Consideration	Confounders are factors that could affect study outcomes:

for confounders	Consideration is given to whether confounders have been identified in RCTs and statistical methods have been used to address confounders in the analyses. For example, older age might have a significant influence on an outcome. If, by chance, the mean age was older in one group compared to another, the results from statistical analyses could be skewed. In this exaxmaple, age could be accounted for using analysis such as ANCOVA.

Footnote: The above criteria were based on Guyatt et al., 2011b; Guyatt et al., 2011c; Guyatt et al., 2011d; Guyatt et al., 2011e; Guyatt et al., 2011f; Schünemann et al., 2011 - Sections 12.2.2 and 12.2.3.

2.2.2 Determining the grade for retrieved studies using GRADE

Using GRADE enabled randomised studies to be downgraded and observational studies to be upgraded, depending on whether the criteria for each domain were met (Balshem et al., 2011). From this, a grade was determined for the overall quality for each outcome. There were four possible grades ranging from 'high' to 'very low' (Table 2-2). GRADE's approach to rating the quality of evidence starts with the study design (randomised or observational study) and evaluates five reasons to possibly rate down the quality of evidence and three to possibly rate up the quality (Balshem et al., 2011 p.404; Guyatt et al., 2011b; Guyatt et al., 2011c; Guyatt et al., 2011d; Guyatt et al., 2011e; Guyatt et al., 2011f). For example, a randomised study might initially start with the highest possible score (4 points), however the score could be downgraded by using the above mentioned reasons. For instance if there were very serious flaws around selection and attrition bias (study limitations) up to two points could be deducted, a further two points could be deductive if there were inconsistent results across the intervention groups (inconsistency). This could potentially leave a study with zero (0 points). Yet, if important covariates had been accounted for in the analysis the score would increase by one point resulting in the overall rating as 'one' (1 point) and the level of evidence would be categorised as 'very low'.

Table 2-2 Method used to establish quality of evidence in GRADE

Study design	Initial quality of a body of evidence	Lower the quality if	Higher the quality if	Quality of a body of evidence
Randomised studies	High ⇒	*Study limitations* -1 Serious -2 Very serious *Inconsistency* -1 Serious -2 Very serious	*Large effect* +1 Large +2 Very Large *Dose response* +1 evidence of a gradient	High (four plus) ⊕⊕⊕⊕ Moderate (three plus) ⊕⊕⊕○
Observational studies	Low ⇒	*Indirectness* -1 Serious -2 Very serious *Imprecision* -1 Serious -2 Very serious *Reporting bias* -1 likely -2 Very likely	*Consideration for confounders* +1 Would reduce a demonstrated effect +1 Would suggest a spurious effect if no effect was observed	Low (two plus) ⊕⊕○○ Very low (one plus) ⊕○○○

[Adapted from GRADE (Balshem et al., 2011, p.404)]

The resultant grades provided an estimated level of confidence about the findings in the available research. This ranged from being defined as very confident that the available research represented the truth (high grade) to very little confidence that the available research was able identify the truth (very low grade) (Balshem et al., 2011) (Table 2-3).

Table 2-3 Interpretation of the grades in the GRADE approach

Grade	Interpretation
High	Very confident of the effect estimate: The estimated effect is close to the true effect.
Moderate	Moderately confident in the effect estimate: The estimated effect is likely to be close to the true effect, but there is a possibility that it is substantially different.
Low	Limited confidence in the effect estimate: The estimated effect might be substantially different from the true effect
Very Low	Very little confidence in the effect estimate: The estimated effect is likely to be substantially different from the true effect.

[Adapted from GRADE (Balshem et al., 2011, p.404)]

2.2.3 Strength of recommendation used in GRADE

Strength of recommendation on a body of research regarding the effectiveness of an intervention was reported as 'high' or 'low'. On their own, high grades did not necessarily imply strong recommendations (Balshem et al., 2011). Other factors that needed to be considered included: risk of harm, patient values, patient preferences and cost (Balshem et al., 2011). This was to ensure that important desirable and undesirable effects of an intervention were considered collectively to reach a recommendation (Guyatt et al., 2008). For example, if a mobilisation (manual therapy) technique used in physiotherapy was consistently reported to reduce pain and was graded to be high (likely to represent a true effect), but, it had been reported as being associated with a high level of harm and the cost to provide it was large, then, the strength of recommendation to integrate this technique into standard practice might be low.

2.2.4 Additional use of GRADE

Prognosis of cervicobrachial pain was included in the study to aid understanding of the natural history of the condition. This was for two reasons: data on the natural

history could be used to compare interventional effects used in the clinical trial and to identify an optimal time for management. For example, if a condition improves spontaneously for most people within the first six weeks of onset, but fails to improve for symptoms extending beyond this time, could imply that delivering intervention to those patients whose condition has lasted beyond the six weeks is appropriate. Since no guidelines were available for the evaluation of prognostic studies, the use of GRADE was queried. Personal correspondence with the guideline developers (Guyatt, 2012) confirmed that "although [GRADE] had not been developed for prognosis it works well with it" (Appendix 1A).

2.3 Classification of cervicobrachial pain

Cervicobrachial pain has been defined as the presence of arm pain associated with cervical spine pain (Jull et al., 2008). This general classification is based on symptom presentation rather than identifying a structural, pathological or physiological cause. It is sometimes impossible to determine the cause of the pain in cervicobrachial pain. Use of a symptom-based approach takes uncertainty into account when diagnosing the potential cause (Summerton, 2006), avoiding the need to use inappropriate diagnostic terms (Summerton, 2006; Thoomes et al., 2012; Zusman, 2012).

"*The clinician should be permitted and encouraged to use appropriate diagnostic names for what he can prove and to avoid diagnostic specifications for entities about which he must guess"(Feinstein, 1968 p.1060)*

Symptom-based classifications have been endorsed by the International Classification of Functioning, Disability and Health (ICF) (WHO, 2002). Sub-classifications (divisions within a classification) have often been used to identify whether patients with different mechanisms of cervicobrachial pain are associated with different responses to distinct intervention approaches (Childs et al., 2004). Hence, a sub-classification system could provide clearer guidance on which patients respond to specific treatments (Childs et al., 2004).

A patho-anatomical sub-classification system has been used frequently in research on cervicobrachial pain. Terms within this system relate to pathological and anatomical causes, for example 'cervical radiculopathy' refers to disease or damage involving spinal nerve roots resulting in radiating arm pain and symptoms (Eubanks, 2010; Karnath, 2012). Despite its frequent use, there was moderate evidence of a poor correlation between abnormal findings on investigations and a patient's subjective symptoms (Max, 2000; Childs et al., 2004) and a poor correlation between patho-anatomical diagnosis and intervention response. It has been questioned whether the identification of a patho-anatomical diagnosis is a meaningful predictor for outcomes in response to interventions in spinal disorders (Trudelle-Jackson et al., 2008; Bertilson et al., 2010).

A second sub-classification system makes use of a pain mechanism (Smart et al., 2008). This approach conceptualises pain as a clinical entity in itself, and provides a comprehensive way of analysing how pain responds to a treatment intervention (Woolf et al., 1998; Smart et al., 2008).

2.3.1 Pain mechanisms in cervicobrachial pain

Musculoskeletal pain can be generated and perpetuated from nociceptive or neurogenic mechanisms (Villemure & Bushnell, 2002; Jones et al., 2003a; Hagberg, 2005; Nijs et al., 2010; Smart et al. 2010; Yi & Zhang, 2011). These mechanisms may occur in isolation or collectively.

Evidence of a nociceptive mechanism in cervicobrachial pain

There is very low evidence that nociceptive structures such as joints, discs, ligaments and muscles are able to refer pain to the neck and arm. A case series by Fukui et al. (1996) reported that cervicobrachial pain could be produced by chemically stimulating the facet joints and reduced by denervation of the joints. No other recent studies have evaluated the potential for facet joints to refer symptoms beyond the level of the shoulder. Small case series have consistently reproduced cervicobrachial pain by chemically stimulating cervical muscles, ligaments and discs (Bogduck & Aprill., 1993; Bogduck, 1995; Simons et al., 1999). None of these studies involved control groups, blinding or statistical analyses and, hence, findings were subject to potentially high bias.

Evidence of a neurogenic mechanism in cervicobrachial pain

Neurogenic pain may be generated by peripheral (peripheral nerve) or central (spinal cord and brain cortex) mechanisms.

Studies on animal models have induced peripheral neuritis and found a causal link, but these findings are not directly transferable to human presentations (Eliav & Tal., 1994; Tal & Eliav., 1996; Study & Kral., 1996; Eliav et al., 1999; Eliav et al., 2001).

No studies have been conducted on human subjects to induce a peripheral neuritis to evaluate whether radiating pain patterns exist in the same way as in animal models.

There was low evidence from one small underpowered study that widespread sensory hypersensitivity occurred in patients with chronic cervicobrachial pain (n=38) compared to asymptomatic subjects ($p<0.01$). The authors concluded that these changes were probably due to alteration in central pain processing (Chien et al., 2008). It was unknown whether alteration to central pain processing was a cause of, or, a consequence of cervicobrachial pain.

Some musculoskeletal conditions have a dominant pain mechanism. For example; current literature in fibromyalgia suggests that the pain predominantly relates to neurogenic supra-spinal mechanism (Petersel et al., 2011; Straud, 2011; Vierck, 2012). This knowledge has influenced current management of fibromyalgia. However, it is unclear to what extent nociceptive structures or neurogenic mechanisms contribute to the development of cervicobrachial pain.

There was some evidence that nociceptive and neurogenic pain mechanisms are interlinked (Quinn et al., 2010) and insufficient evidence to differentiate cervicobrachial pain into distinct sub-categories. Consequently, cervicobrachial pain was considered as a collective term in this thesis.

2.4 Epidemiology of cervicobrachial pain

Epidemiology is the study of patterns and distribution of health or health limiting conditions (Davey Smith, 2001). It is important to understand epidemiological characteristics for different health limiting conditions, such as cervicobrachial pain, to

effectively critique and evaluate research findings (Davey Smith, 2001). For example, the knowledge of prognostic factors in cervicobrachial pain would identify what factors could have the capacity to confound results, therein enabling better critical analysis of existing research, and help inform the design of statistical methods to account for confounding effects in the planning of a clinical trial.

Specific epidemiological factors relate to:

- Prevalence and incidence rates in a given time
- Risk factors (factors causing an increased risk of developing the condition)
- Associated factors (factors connected with the presence of the condition)
- Prognosis (the natural course of the condition over time)
- Prognostic factors (factors that affect prognosis)

Identifying the prevalence (total number of cases) and/or incidence (number of new cases) provides information on the extent to which cervicobrachial pain occurs in society and justifies the need to research the condition (Carroll et al., 2008). Knowledge of risk and associated factors might be used to establish characteristics of cervicobrachial pain patients (Carroll et al., 2008). Baseline characteristics for known risk and associated factors in interventional studies could be used to determine representativeness of a study cohort, and, hence, generalizability of findings from an interventional study (Burgess et al., 2003; Moher et al., 2010). Prognosis enables an understanding of the natural history of a condition, from which comparisons of outcomes from interventional studies over time can be made (Carroll et al., 2008) and prognostic factors identify confounding variables that might affect outcomes in interventional studies.

2.4.1 Prevalence and incidence of cervicobrachial pain

Collectively, neck pain disorders affect approximately 332 million people, accounting for one fifth of all musculoskeletal conditions worldwise (Bone and Joint Decade, 2012). These figures were based on estimates from the Global Burden of Disease Study 2010 that used survey data from 32,659 people across 5 different countrys (Salomon et al., 2012). There was low evidence from one systematic review (based on reports from 8 separate epidemiology studies between 1987 to 2002; n=15,069) that the global mean lifetime prevalence of neck pain was 48.5% (range 14.2% to 71.0%) (Fejer et al., 2006). Although no numerical value has been reported for the incidence or prevalence of cervicobrachial pain, there was moderate evidence that it is a frequently occurring problem, accounting for the majority of neck pain disorders. For example, in a sample of 1809 patients with neck and arm pain (Daffner et al., 2003) between 1998 and 2001, 533 (30%) patients presented with neck pain in isolation, compared with 1183 (65%) who presented with neck and radicular symptoms. Hence, cervicobrachial pain was more than twice as common as neck pain in isolation. It has been reported to frequently accompany cervicogenic headache (Antonaci et al., 2006, Vincent, 2010). One small study (n=81) reported that 67% of patients with chronic cervicobrachial pain also presented with headache (Persson & Carlsson, 1999). In addition, cervicobrachial pain was reported to feature in 60% of chronic whiplash presentations in a study involving 156 patients (Sterling et al., 2002b). Cervicobrachial pain can be estimated to affect approximately 40% of individuals at some time in their lives.

2.4.2 Risk factors in cervicobrachial pain

Gender, age and smoking have been identified as possible risk factors in the development of cervicobrachial pain (Finocchietti & Trindade1973; Kostova & Koleva 2001; Kaki, 2006).

There was moderate evidence that gender and age were important factors in the development of cervicobrachial pain, with females, aged 40 years or older, being at greatest risk of developing the condition (Finocchietti & Trindade 1973; Kostova & Koleva 2001; Kaki, 2006). Low evidence supported a possible influence of genetic, hormonal and psychosocial factors on pain perception and pain response (LeResche, 1999; LeResche, 2000; Sherman & LeResche, 2006; Keogh, 2006; Wijnhoven et al., 2006; Williams et al., 2010).

There was low evidence that smoking, in some instances, increased the risk of developing cervicobrachial pain. A cross-sectional study on 898 participants (Kosova & Koleva, 2001) reported that males who smoked more than 20 cigarettes per day had a greater incidence of cervicobrachial pain than those who smoked less: 14.8% compared to 3.4% [OR 4.95; 95% CI 1.17 to 19.32]. This finding did not hold for female smokers (Kosova & Koleva, 2001). Smoking is known to reduce circulation generally (Munger & Hawkins, 2004; Scallan et al., 2010) and there was very low evidence that vascular change specific to the nerve roots in the lumbar spine has led to the development of sciatic symptoms (Kobayashi et al., 2005). However, no research has evaluated this association with cervical nerve roots and it was unclear why differences exist between genders. Further studies are needed to establish to what extent and on whom smoking is a risk factor in developing cervicobrachial pain.

2.4.3 Associated factors in cervicobrachial pain

Modern-day lifestyle factors might be better considered as 'associated' rather than 'risk' factors, since it was unclear whether changes in lifestyle cause, or result from, cervicobrachial pain (Carroll et al., 2008). Psychosocial, physical fitness, posture and computer use were identified as possible associated factors.

Moderate evidence existed of an association between psychosocial factors with cervicobrachial pain. An observation study by Daffner et al. (2003) compared the impact of cervicobrachial pain (n=1183) to neck pain alone (n=533). After accounting for age and gender, the study found that patients with cervicobrachial pain had lower levels of mental health and social wellbeing than localised neck pain patients ($p<0.0001$ to $p<0.005$). Although no other studies had evaluated these aspects in cervicobrachial pain, some studies that evaluated psychosocial factors in heterogeneous groups of neck and arm pain syndromes (including cervicobrachial pain) reported similar associations (Curci et al., 1986; Oliveira, 2000; Bongers et al., 2006).

There was low evidence that lack of physical fitness was associated with cervicobrachial pain. One observational study (Krapac et al., 1992) reported that controls (participants without cervicobrachial pain) were more than four times as likely to spend their free time actively involved in activities such as sports and gardening than the participants with cervicobrachial pain ($p<0.001$). Participants with cervicobrachial pain spent a greater proportion of their free time passively, including pursuits such as handicrafts (Krapac et al., 1992). No other cervicobrachial studies have considered this association. However, these results were consistent with other

musculoskeletal studies that have reported associations between increased physical fitness and improved health (Viori, 1995; Miranda et al., 2001; Hayes et al., 2009; Kharuakhorn et al., 2010; Moscato et al., 2010).

One case-controlled study (Krapac et al., 1992) provided very low evidence that people with cervicobrachial pain adopted slouched postures and performed greater repetitive movements at work (tasks not specified) than those without the condition ($p<0.05$). No other evidence was identified in relation to the effect of posture

There was very low evidence that computer use was associated with cervicobrachial pain. It has been suggested that prolonged computer use could be an associated factor in developing cervicobrachial pain (Finocchitti & Trimdade, 1973; Krapac, 1989; Sauter et al., 1991).

Overall, there was very low to moderate evidence of risk and associated factors for cervicobrachial pain (Table 2.4).

2.4.4 Prognosis of cervicobrachial pain

The natural course of any condition determines prognosis (Anderson et al., 1998). There is very low evidence that cervicobrachial pain reduces over time. The largest and most frequently cited study evaluating prognosis in cervicobrachial pain was undertaken in Rochester, Minnesota between 1976 - 1990 (Radhakrishnan et al., 1994). This epidemiological study involved 561 participants over a 13-year period. Although the results indicated that, in 90.5% of cases, symptoms largely resolved with time, all participants received some form of treatment, which could have interfered with the natural course. Radhakrishnan et al. (1994) has been cited in

many publications to support the stance that people with cervicobrachial pain are expected to recover naturally (Wainner & Gill, 2000; Polston, 2007; Eubanks, 2010). However, no well-designed study evaluating natural prognosis has been conducted on cervicobrachial pain to evidence this. Hence, the provision of some form of treatment could play an important part in recovery.

2.4.5 Prognostic factors of cervicobrachial pain

Chronicity (duration of symptoms), psychosocial factors and involvement in litigation have been identified as factors affecting prognosis. There was moderate evidence from a large systematic review (number of included studies = 45) that a longer duration of pain was associated with a worse prognosis in musculoskeletal disorders (Mallen et al., 2007). However, the authors did not report how many weeks or months constituted a 'long duration'. No studies were identified on how chronicity may affect prognosis relating specifically to cervicobrachial pain. A prospective cohort study (n=443) by Bot et al. (2005) reported that duration of neck and shoulder symptoms (including cervicobrachial pain) significantly affected outcomes of pain and disability ($p<=0.005$). Paticipants with baseline durations of one week versus greater than six months had reported recoveries of 60% and 15%, respectively, at one year follow-up (Bot et al., 2005). In the study by Bot et al. (2005), the overall recovery rate was low (32% recovery at one-year follow-up). This contrasted with the findings from Radhakrishnan et al.'s study (1994). One possible explanation was that only 26% of the sample in Radhakrishnan et al.'s study (1994) had chronic symptoms (greater than six weeks duration), compared to 62% of the sample in the study by Bot et al. (2005).

Psychosocial factors have been found to be the most consistent predictor for developing chronic musculoskeletal pain (Oliverira, 2000; Trunks et al., 2008; Lopez et al., 2009; Bergbom et al., 2012; Laisné et al., 2012). There was moderate evidence to support this association in cervicobrachial pain. Specifically, Daffner et al. (2003) (n=1183) reported that poor mental health (using scores from the mental component summary of the Short-Form 36 questionnaire) was associated with increased chronicity (p=0.001). Data from other cervicobrachial pain studies provided further evidence of an association between psychological factors and chronic cervicobrachial pain (Sheather-Reid, 1998; Persson & Lilja, 2001).

There was low evidence that financial compensation, from personal claims, had a negative effect on outcome. A preliminary study (total n=60) (Rasmussen et al., 2001) reported that claimants receiving physiotherapy had poor outcomes, unlike the comparative (non-claimant) group who improved. However, there were significant limitations in this study, including a lack of evaluation for confounding variables (e.g. chronicity and psychosocial factors) and imprecision (e.g. inadequately powered study). A later, appropriately powered study by the same authors (n=202) (Rasmussen et al., 2008), reported that at one-year, the odds ratio for not improving was 17.4 [95%; CI 5.1 to - 60.1] for patients with a claim at baseline (compared with those not claiming), indicating that the claims process had a negative effect on prognosis in cervicobrachial pain. In this later study, chronicity was adjusted for using covariate analysis; however, psychological factors were not, which might have been an important confounder in the outcome (Rohling et al., 1995)

Overall, there was low to moderate evidence to support chronicity, psychosocial factors and involvement in litigation as variables that affected prognosis (Table 2-4).

2.5 Economic costs of cervicobrachial pain

Economic evaluation enabled a fuller appreciation of the financial impact that cervicobrachial pain has had on individuals, health-care systems and society (Korthals-de Bos et al., 2003). Costs were related to work absenteeism and health care costs (Yelin et al. 1995).

2.5.1 Work absenteeism (related to cervicobrachial pain)

No studies were found on work absenteeism related to cervicobrachial pain. A paper by Buckle & Devereux (2002) based on statistics from 40 different resources (including government figures, union bodies and experts) estimated that pain (including cervicobrachial pain) affecting the neck and/or arm collectively accounted for 5.4 million lost working days each year in the United Kingdom (UK). However it was unclear what methods were used to resource data, how any duplication had been addressed and over what time period data were collected. According to figures stated by Buckle & Devereux (2002), an individual would potentially lose one month's earnings per episode of neck and/or arm pain. However, accuracy of these figures was unknown and no recent statistics on work absenteeism were available, hence, it was unclear whether the reported statistics reflected current trends. In addition, no information was available to evaluate whether different types of neck and arm syndromes resulted in differing quantities of work absenteeism.

There was moderate evidence from a cohort study (Hestbaek et al., 2009) that involvement in compensation compounded absenteeism from work. Cervicobrachial pain patients seeking financial compensation (n=137) were four times more likely to be absent from work in the short and long-term compared with those not seeking

compensation (Hestbaek et al., 2009). The estimated odds of patients being absent from work were between 1.71 to 11.51 more likely when they were seeking compensation compared with not seeking compensation (with 95% confidence), at five year follow-up.

To summarise, it is unknown how much work absenteeism could be attributed to cervicobrachial pain. However, based on the study by Hestbaek et al. (2009), people with cervicobrachial pain have a greater amount of sickness absence if they are involved in litigation for that condition.

2.5.2 Health care costs (related to cervicobrachial pain)

There was low evidence that cervicobrachial pain impacted on health care costs. One study (n=3664) found that 58% of patients with chronic cervicobrachial pain reported seeking health care (Huisstede et al., 2008). It has been reported that conservative (non-surgical) intervention is usually sought (Fouyas et al., 2002; Daffner et al., 2003), with non-invasive intervention in the form of physiotherapy frequently being the initial treatment provided (Persson et al., 1997a). No retrieved studies evaluated the costs of physiotherapy. There was moderate evidence that the provision of physiotherapy for neck disorders used a mean of 6.82 sessions (SD 6.55). The wide variation in number of interventions could be due to some physiotherapeutic modalities consisting of brief pain management approaches e.g. self-management, whilst other modalities consisted of a larger quantity of intervention e.g. manual therapy (Hay et al., 2005). Based on the mean figure, estimated total costs per patient with neck pain was £152 per year in 2006 (Manca et al., 2006). It is probable that this represents a much lower figure than would be calculated on current

costing due to rates of inflation over the last decade. As cervicobrachial pain might constitute the majority of neck pain disorders, there is a need for evidence to substantiate the cost-effectiveness of treatment, such as physiotherapy, for this condition.

Overall, there was low to moderate evidence that cervicobrachial pain was associated with moderate economic expenditure, particularly when compensation was involved and the condition was chronic (Table 2-4)

2.5.3 Overall impact of economic costs for cervicobrachial pain

Based on the available evidence, cervicobrachial pain was reported as causing a financial challenge to individuals (Buckle & Devereux (2002), industry (Buckle & Devereux, 2002; Hestbaek et al., 2009) and health care systems (Huisstede et al., 2008). The full extent of the economic burden for this condition is unknown, largely due to the lack of data relating specifically to cervicobrachial pain. Table 2-4 summarises all key factors linked to cervicobrachial pain, including cost.

Table 2-4 Summary of evidence using GRADE for key factors linked to cervicobrachial pain

Grade	Pain mechanism	Incidence	Risk and associated factors	Prognosis	Prognostic factors	Cost
Moderate		Prevalent condition (Persson & Carlsson, 1999; Sterling et al., 2002b; Daffner et al., 2003; Antonaci et al., 2006, Vincent, 2010)	Age (>40 years) (Finocchietti & Trindade1973; Kostova & Koleva 2001; Kaki, 2006) Gender (female) (Finocchietti & Trindade1973; Kostova & Koleva 2001; Kaki, 2006) Psychosocial factors (Daffner et al., 2003)		Chronicity (Bot et al.,2005) Psychosocial factors (Sheather-Reid, 1998; Persson & Lilja, 2001; Daffner et al, 2003)	Involvement in compensation impacts on work absenteeism (Hestback et al., 2009)
Low	Neurogenic (Chien et al., 2008)		Heavy smoker (males) (Kostova & Koleva, 2001)		Financial compensation (Rasmussen et al., 2001; Rasmussen et al., 2008)	Chronic cervicobrachial pain impacts on health care costs (Huisstede et al., 2008; Fouyas et al., 2002; Daffner et al., 2003; Persson et al. 1997)
Very low	Nociception (Fukui et al., 1996; Bogduck & Aprill, 1993; Bogduck, 1995; Simons et al., 1999)		Slouched postures and repetitive activities (Krapac et al, 1992) Computer use (Finocchitti & Trimdade,1973; Krapac,1989; Sauter et al., 1991)	Cervicobrachial pain has a good natural prognosis (Radhakrishnan et al., 1994)		

Footnote: Refer to Table 2-3 for interpretation of the grades

2.6 Summary of cervicobrachial pain

This chapter has highlighted that cervicobrachial pain might derive from multiple mechanisms. Since there was no method for effective differentiation of sub-categories, cervicobrachial pain was considered as a single entity, in this thesis.

Cervicobrachial pain is a prevalent condition which, when chronic, has a significant physical, social and mental impact on the lives of individuals having that condition. Precise costs of the condition to individuals, health care systems and society are unclear.

Despite being a prevalent and disabling painful disorder, there was little evidence to guide the effective management of cervicobrachial pain, particularly, in relation to non-invasive conservative management (Hurwitz et al, 2008). Chapter 3 will report a systematic review of the evaluation of the effectiveness of conservative, non-invasive management approaches for cervicobrachial pain.

3 REVIEWING THE EVIDENCE FOR NON-INVASIVE MANAGEMENT FOR CERVICOBRACHIAL PAIN

3.1 Introduction to reviewing the evidence

Chapter 2 reported that cervicobrachial pain was a prevalent and disabling condition, for which patients usually sought conservative management. In general, there has been a lack of research relating to non-invasive forms of conservative management for this condition (Hurwitz et al, 2008).

An initial systematic review of relevant literature (SR) was conducted in 2006 to critically appraise evidence on the effectiveness of non-invasive interventions for cervicobrachial pain. The systematic approach was selected because SRs were, and still are, widely accepted as the "gold standard" for reviewing research literature (Egger et al., 2003; Centre for Reviews and Dissemination, 2008, Centre for Evidence Based Medicine, 2009; Moher et al., 2009). Findings from the SR were used to support the research question addressed in this thesis and development of the trial design (including interventions).

The SR was repeated in 2010 using augmented guidelines for its conduct (Maher et al., 2003; Foley et al., 2006) with a view to publish findings. This second review revealed the lack of a SR on non-invasive management of cervicobrachial pain. Five systematic reviews on non-invasive interventions for generalised neck pain were retrieved, but none of these analysed cervicobrachial pain as a sub-group, hence limiting interpretation of their findings for that condition (Kay et al., 2005; Haraldsson

et al., 2008; Graham et al. 2009; Haines et al., 2010; Gross et al., 2010). The second SR was published in 2011 (Salt et al., 2011; Appendix A).

For the purpose of this thesis, the review was updated for the third time (at the end of January 2012) to include consideration of relevant new studies on effectiveness of non-invasive interventions for cervicobrachial pain and their findings. This chapter presents the methodology and findings of the most recent SR (January 2012).

3.2 Rationale for and aim of the systematic review

Whilst there are many ways to conduct a literature review (Dixon-Woods et al., 2005), narrative and systematic review methods are the most frequently used (Goldsmith et al., 2007). A narrative method adopts a holistic approach to analysing research and, consequently, its findings could be subject to a higher level of bias (Bryman, 2012). Systematic reviews are more focused and structured, using methods that optimise the chance of finding relevant studies and aim to minimise bias at each stage in the process (Moher et al., 2009). It has been argued that stronger conclusions may be drawn from a SR, making this approach one of the highest levels to evidence practice and to identify gaps in a body of research (Green et al., 2011)

The aim of the SR was to identify what, if any, evidence existed to support effectiveness of non-invasive approaches in the management of cervicobrachial pain. To address this aim, studies of interest needed to consider effectiveness of a non-invasive approach compared to a control or placebo, or to another comparative non-invasive approach. Between-group differences (in well designed and conducted studies) would enable meaningful comparisons to be made across the intervention

effects (Lubke et al., 2003). By definition, since pain was the key feature of cervicobrachial pain, the primary outcome to establish effectiveness of management needed to relate to a change in pain. As cervicobrachial pain has been associated with an increased level of disability (Daffner et al., 2003), secondary outcomes needed to relate to disability, including the loss of function. Additional outcomes of interest were risk of harm, cost and patient preference or patient perceived value of intervention to establish the overall strength of recommendations made (Balshem et al., 2011).

3.2.1 Rationale for updating systematic review from previous published article

The SR was updated in 2012. The update was based on the published version (conducted in 2010 and published in 2011 [Salt et al, 2011; Appendix A)]. Changes from the published version included an updated search to 31st January 2012 and the use of different methods to analyse the retrieved literature – principally that the Cochrane 'risk of bias tool' was used in preference to the PEDro scale to evaluate methodological quality (internal validity), and GRADE was used instead of the Oxford Centre for Evidence-Based Medicine Levels of Evidence (to establish the quality of retrieved evidence and to determine the level of recommendation).

Justification for these changes was based on growth in the research literature supporting use of Cochrane's risk of bias to assess internal validity (Higgins et al., 2011) rather than a scoring system, such as PEDro (Rushton et al., 2011). The rationale for the recommendation was based on the fact that many items in scoring systems are not related to internal validity (Higgins et al., 2011). This criticism

applied to three of the ten items on the PEDro scale ('intention to treat analyses', 'between-group statistical comparisons' and 'point measures and measures of variability') which related to precision of results and not to internal validity. Additionally, the quality of PEDro as a tool has been criticised for not considering all important aspects (for example, it does not include *a priori* specification of primary outcomes or consideration of inter-group imbalances in attrition rates on the primary outcome) limiting its validity (Rushton et al., 2011).

The decision to use GRADE (rather than the Oxford approach) to determine the quality of evidence was based on arguments presented in the growing literature on different approaches to conduct critical appraisals (Balshem et al., 2011; Guyatt et al., 2011a) and publication of more user friendly guidelines on its application that made its use more accessible (Guyatt et al., 2011b; Guyatt et al., 2011c; Guyatt et al., 2011d; Guyatt et al., 2011e; Guyatt et al., 2011f;). In summary, GRADE provided a stronger framework, as reported in Chapter 2.

3.2.2 Method used on updated systematic review

The Cochrane Tool was used to critically appraise design features influencing internal validity of studies that were included in the review (Higgins et al., 2011). Design features that influence external validity were critiqued using the last section of the Critical Appraisal Skills Programme (CASP) tool for reporting RCTs (accessible at www.casp-uk.net). Findings from these critical evaluations were used to support decisions about the quality of the reported evidence using GRADE. This review has been reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-analyses: PRISMA (Moher et al., 2009), to ensure that it has followed a

standardised structure and provided a comprehensive coverage of key information. PRISMA comprises a check-list (accessible at http://www.prisma-statement.org/) for key features to be reported in systematic reviews and advocates the use of a flow diagram to clarify review stages. Guidance on how to use the checklist effectively was taken from Liberati et al. (2009), which details the level of information required per feature.

Eligibility criteria used in the systematic review on non-invasive therapy for cervicobrachial pain

Studies

Only randomised controlled studies were included (Lubke et al., 2003; Lefebvre et al., 2011). It has been demonstrated that inclusion of non-randomised studies in a review could lead to considerable bias, compromising estimates of intervention effect (Lubke et al., 2003; Lefebvre et al., 2011). No restrictions were placed on language or publication date, to ensure that the review was comprehensive (Centre for Reviews and Dissemination, 2009; Morrison et al., 2009).

Participants

Adults with cervicobrachial pain aged 16 years or over, of either gender, were included. Most spines would have reached skeletal maturity by the age of 16 years (O'Neil, 2003). Younger participants were not included because there was no evidence to support the assumption that non-invasive therapy techniques had the same effect on the developing spine as on fully developed ones (Hestbaek & Stochkendahl, 2010).

Participants were required to have cervicobrachial pain, defined as the presence of arm pain associated with cervical spine pain (Jull et al., 2008). Studies that involved participants with cervicobrachial pain as part of a larger study on generic neck pain were included if an analysis was reported on that specific sub-group. This decision was made to avoid increased heterogeneity in the sample to be analysed.

Participants with cervical myelopathy, tumour, rheumatic disease or central neurological disorder (e.g. multiple sclerosis) were excluded, because management approaches would be considerably different in these cases (Jull et al., 2008).

Interventions

Specific non-invasive management included manual therapy, exercise, traction, behavioural therapy and electrotherapy. These interventions had been consistently reported in the literature as a means of managing neck pain (Kay et al., 2005; Childs et al., 2008; Haraldsson et al., 2008; Hurwitz et al. 2008; Graham et al. 2009; Gross et al., 2009; Haines et al., 2009; Gross et al., 2010). The search strategy also included non-specific treatment terms, such as, physiotherapy or chiropractic, to encompass as many non-invasive interventions as possible. Invasive modalities such as surgery, epidurals and acupuncture were excluded unless they were used as a comparator in a study. Other acceptable comparators included placebo treatments or no-treatment control groups. When this was not possible, one non-invasive intervention was compared to another.

Outcome measures

Studies were included if they contained at least one outcome measure for pain, since pain response to intervention was the primary objective of the review. Secondary outcome measures included reports on function and disability, since these have been recognised as co-morbidity factors affecting people with cervicobrachial pain (Daffner et al., 2003). Separate publications on the same study were included when different, but relevant, outcomes were reported.

Information sources

The search strategy encompassed a wide range of information sources (summarised below), including published and unpublished data to reduce the potential for publication bias (Centre for Reviews and Dissemination, 2009).

- Electronic search on computerised databases from inception to January 2012: Cochrane central register of controlled trials (CENTRAL), MEDLINE, EMBASE, AMED, CINAHL and the Physiotherapy Evidence Database (PEDro).

- Citation search: from articles identifying cervicobrachial pain.

- Special interest groups: the Musculoskeletal Association of Chartered Physiotherapists (MACP), the International Federation of Orthopaedic Manipulative Therapists, the British Osteopathic Association, and the United Chiropractic Association (UCA) were contacted by email asking if they were aware of any unpublished data on the subject area. The MACP and the UCA forwarded the email to their members.

Search strategy

A range of key words was specified under population, intervention and design methods (van Tulder, 2003) (Table 3-1).

Table 3-1 Key terms in search used for systematic literature review

Population	Intervention	Design methods
Cervicobrachial, cervical radiculopathy, cervical neuralgia, neck and arm pain, trapezius myalgia	Management, therapeutics (including: electro, hydro, cryo and heat), physical therapy, osteopathy, chiropractic, exercise, patient education and advice, behavioural therapy, manipulation, mobilisation, massage, traction	Random allocation, randomised controlled trial

All terms were exploded in each database, where possible. In addition, thesaurus mapping and truncation were used. These methods enabled an automatic expansion on key terms to identify papers that might be relevant, but not include a key term. For example, a relevant study might have been identified under a term 'physical therapy' rather than 'physiotherapy'. Searching databases this way had been advocated to ensure comprehensive data collection (CRD, 2009; Rafols et al., 2010). Details of the Medline search can be found in Appendix B.

Study selection and appraisal

Two reviewers, both subject specialists (one of whom was the Principal Investigator), independently searched the information sources against the eligibility criteria (reported earlier). Edwards et al. (2002) recommended the use of two reviewers over one to enable full identification of all eligible studies (Edwards et al., 2002). The two subject reviewers independently assessed methodological quality for each included

study using The Cochrane 'risk of bias' tool (Higgins et al., 2011). Disagreement was resolved by consensus using a third reviewer (a research methodologist). Attempts were made to contact authors of articles for additional information when both reviewers agreed that there was a lack of information on which to judge compliance with the eligibility criteria.

Strength of agreements between reviewers regarding study selection and methodological quality were evaluated using values of Cohen's Kappa (Cohen, 1960). Interpretation of Kappa values was based on standards proposed by Landis and Koch (1977) with 0 representing poor agreement in the worst scenario, through to .81 to 1 representing almost perfect agreement in the best scenario (Table 3-2).

Table 3-2 Standards for strength of agreement using kappa coefficient for study selection in systematic review

Kappa value	Interpretation of agreement
0	None
0.01 to 0.20	Slight
0.21 to 0.40	Fair
0.41 to 0.60	Moderate
0.61 to 0.80	Substantial
0.81 to 1	Almost perfect

[Adapted from Landis & Koch, 1977, p.165]

The use of Kappa has been criticised as having a lack of interpretability when compared with other measures of concordance, such as percentage agreement (McHugh, 2012). However, unlike percentage agreement, Cohen's Kappa takes into account the level of agreement that occurs by chance (Sim & Wright, 2005) and is

considered to be the gold-standard for establishing inter-assessor agreement (Strijbos et al., 2006). Hence, it was the preferred choice to measure inter-reviewer agreement in this study.

A data extraction table was compiled to summarise participant characteristics, interventions and results for all studies included in the review. Detailing these study characteristics has been advocated as being important to enable a more comprehensive understanding of the data to support the review process (Liberati et al., 2009).

Planned method of review analysis

The primary analysis evaluated the effects of non-invasive therapy on pain (the primary outcome measure). Secondary analyses evaluated the effects on function and disability as pain frequently leads to limitations in physical and social capability (Winance, 2006).

Meta-analyses were used to pool results across studies. This method of pooling data has been recommended to reduce error of interpretation, especially for small studies, and to produce higher precision when estimating overall intervention effects (CRD, 2009; Morrison et al., 2009; Higgins and Green, 2011, section 9.1.4; Bryman, 2012). In this review, meta-analyses were conducted on comparable outcome measures across studies that reported interventions and comparators of a similar nature, and with the same or similar timing of assessments. Comparable outcome measures were defined as different instruments that were developed to measure the same underlying construct, for example, the visual pain analogue scale and the numerical pain analogue scale (Hjermstad et al., 2011). To avoid selection bias, two reviewers

(the principal investigator and a methodological expert) independently identified combinations of studies and comparable outcome measures that were considered to be appropriate for quantitative synthesis.

Direct pooling of the data across the different studies was inappropriate due to inter-study variations on outcome measures, and details of the interventions and comparators. Hence, a random-effects meta-analysis was conducted on standardised differences in mean values (Centre for Reviews and Dissemination (CRD), 2009; Deeks et al., 2011). Effect sizes and 95% confidence intervals were computed using DerSimonian-Laird random-effects (CRD, 2009; DerSimonian & Laird, 1986). This method has been advocated for random-effects meta-analysis because it has higher power than other random-effects models (Kontopantelis & Reeves, 2012). Cochrane's Q statistic was computed to assess the effect of heterogeneity on intervention results for each meta-analysis (CRD, 2009). The Q statistic had been criticised as having low power for pooled analysis of small and/or few studies and overestimation of effects in large and/or multiple studies (Deeks et al., 2011). However, it is the most frequently used test and, providing the limitations are recognised, is useful when interpreting the results of meta-analysis (Biggerstaff & Jackson, 2008). Results from the meta-analysis were also presented in a Forest plot, to provide a clear and concise summary of findings across studies (Schriger et al. 2010). All analyses were performed using StatsDirect software (StatsDirect, 2009).

Qualitative analyses, using the GRADE approach, were conducted on outcomes that did not satisfy requirements for the conduct of meta-analyses. Quality of evidence was rated on a four point scale: 'high', 'moderate', 'low' and 'very low' (Table 2-3) for

pain, function and disability. In addition, analysis of risk of harm, cost and perceived value/preference of intervention (which have been recognised as important factors to determine strength of recommendation (Balshem et al., 2011)) were evaluated to complete a comprehensive analysis and to establish strength of recommendation per intervention. Strength of recommendation was determined as 'high' or 'low' (Section 2.2.3).

3.2.3 Findings from the systematic review

Study selection

Figure 3-1 summarises the article selection process. Following review of titles and abstracts, 21 articles were identified and full papers obtained. Ten articles were excluded: 8 did not meet the 'cervicobrachial' definition, 1 was a commentary and 1 did not measure pain. No relevant unpublished studies were found.

Substantial to perfect inter-reviewer agreement (Landis & Koch, 1977) was achieved for the selection of studies to be included in the review, with Kappa values of 0.96 (SE=0.04; $p<0.0005$; $n=50$; SE=standard error) using titles, and perfect agreement using abstracts and full texts.

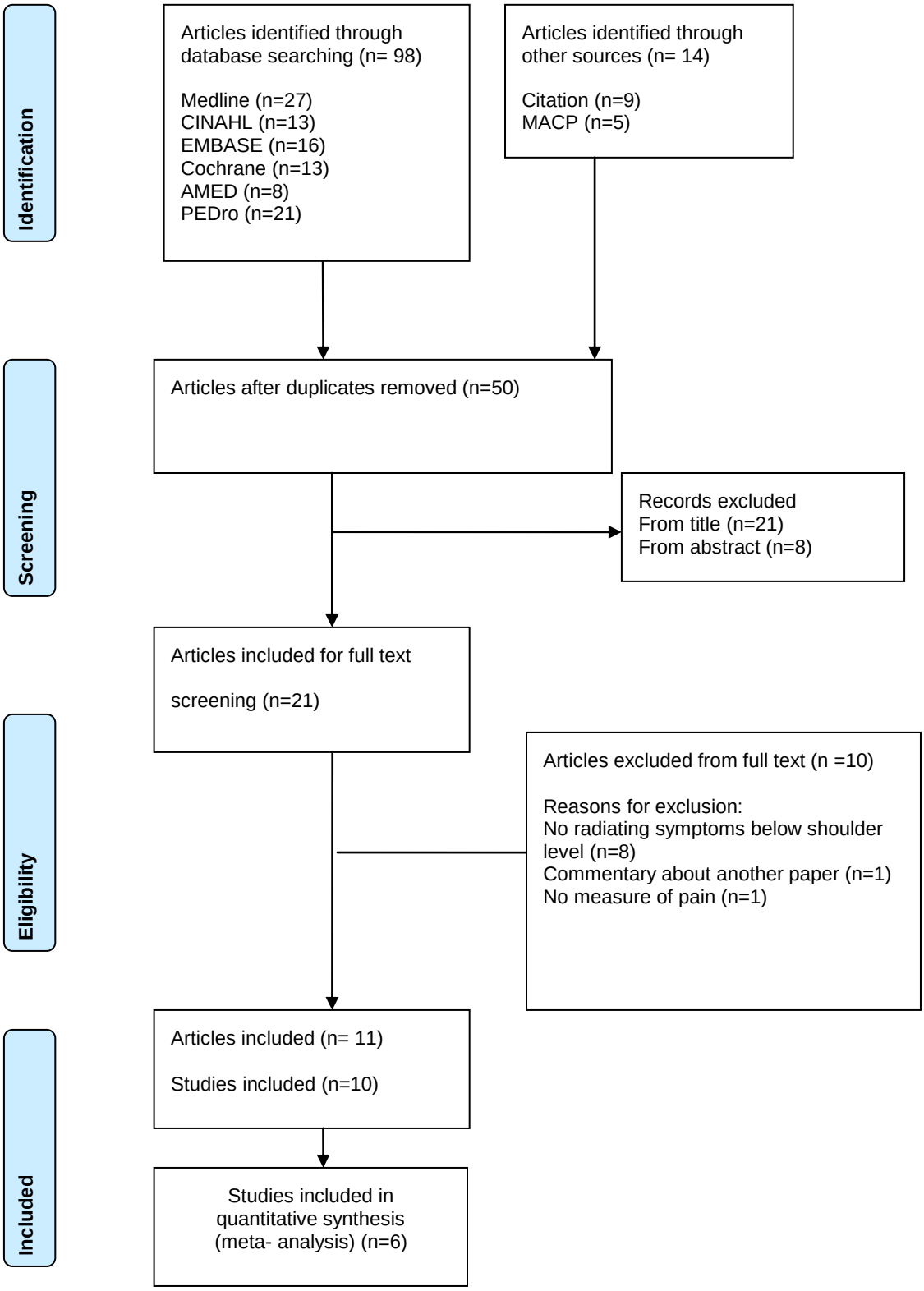


Figure 3-1 Systematic review study selection flow diagram [**Based on Moher et al., 2009]**

Risk of bias within studies selected for the systematic review

Perfect inter-rater agreement was obtained in ratings across all eight 'risk of bias' items, for all eleven studies (Kappa=1.00, SE=0.00). There was an increase in level of agreement using the Cochrane risk of bias approach compared to scoring with PEDro – as used in the previous published review (Salt et al., 2011). Unlike PEDro, the Cochrane 'risk of bias' included an 'unclear risk of bias' option and that might account for the higher rate of agreement between reviewers.

Overall, the quality of studies included in the review was poor. None of the studies met all eight criteria for low risk of bias (Figure 3-2). The number of criteria fulfilled, ranged from six indicating low risk of bias (Bernaards et al., 2007) down to two indicating high risk of bias (Klaber Moffett et al., 1990; Allison et al., 2002; Kuijper et al., 2009; Ragonese, 2009). The variability of the Cochrane scores revealed an inconsistence across studies' internal validity. These findings were in contrast to the PEDro scores in the previous published review (Salt et al., 2011), where all studies scored 6 or above, indicating a consistently high quality of internal validity (Foley et al., 2006). This discrepancy supports previous arguments (Rushton et al., 2011) that the choice of tool could affect the interpretation of quality of evidence found in published research and, hence, the strength of recommendations made on the basis of findings.

Study	Random sequence allocation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personal (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (short-term attrition bias)	Incomplete outcome data (long-term attrition bias)	Selective reporting (reporting bias)	Other bias
Allison et al.(2002)	+	?	-	+	?	?	?	?
Bernaards et al. (2007)	+	+	-	-	+	+	+	+
Coppieters et al. (2003)	+	+	-	+	+	NA	?	?
Howe et al. (1983)	+	+	-	+	?	?	-	-
Klaber Moffett et al.(1990)	?	?	+	+	?	?	?	?
Kuijper et al. (2009)	+	+	-	?	?	?	?	-
Persson et al. (1997)	+	+	-	-	+	-	?	-
Persson & Lilja (2001)	+	+	-	-	+	-	?	-
Ragonese (2009)	+	+	-	?	?	?	?	-
Walker et al. (2008)	+	+	-	+	+	+	?	-
Young et al. (2009)	+	+	-	+	+	+	?	-

Key: **+**=low risk of bias; **?**=unclear risk of bias; **-** = high risk of bias; NA= not applicable

Figure 3-2: Summary of risk of bias for studies used in literature review (n=11 articles)
[Based on plots in Higgins et al., 2011]

Risk of bias across studies used in the review

Methodological weaknesses identified across the 11 studies included a lack of blinding of participants and study bias (Figure 3-3). Blinding of participants was only achieved in one study (Klaber Moffett et al., 1990). This was not unexpected as there are inherent difficulties with complete-blinding in many non-pharmaceutical treatment modalities (Boutron et al., 2008*;* Moher et al., 2010*)*. Other study bias related to intrinsic issues around the provision of intervention. For example, Howe et al., (1983), permitted injections to some of the participants to allow 'manipulation to be carried out' (Howe et al., 1983 p.575), yet injections are an intervention in their own right. In this instance, it was unclear whether positive effects were as a result of the intervention under investigation (i.e.the manipulation), or due to the provision of the injection. Confounders such as this could bias study results.

Selective reporting had the highest level of 'unclear' risk of bias. One study fulfilled the criterion by publishing a full proposal, outlining methods, prior to the review (Bernaards et al., 2007). However, for the majority, there was insufficient information to enable judgement to be made. According to the Cochrane Handbook, this finding was not unexpected (Higgins et al., 2011).

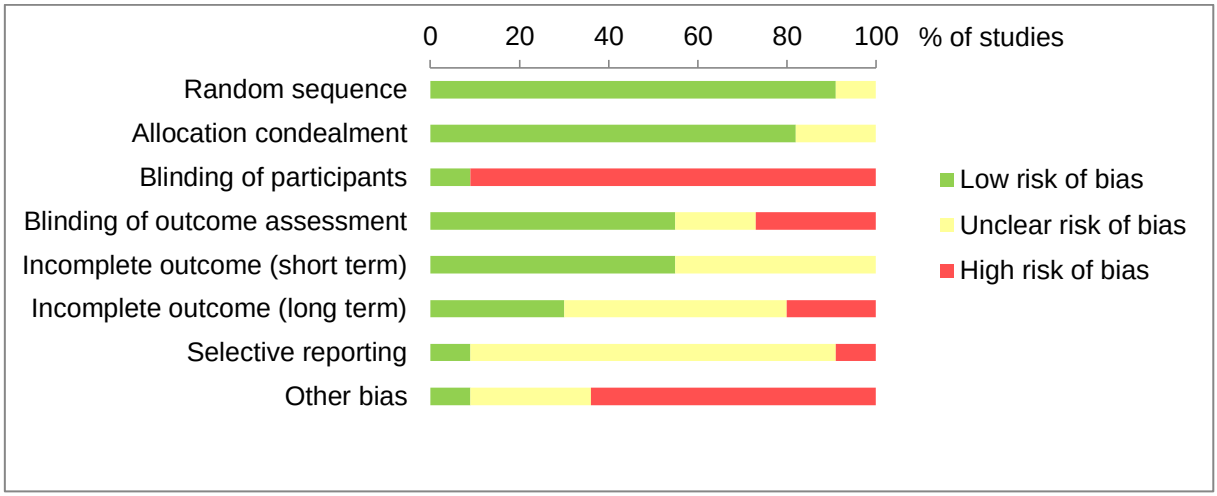


Figure 3-3: Risk of bias (n=11studies) across the 11 included articles
[Based on risk of bias chart in Higgins et al., 2011]

Systematic review's study characteristics

Descriptive data for the ten studies (11 articles) included in the review are summarised in Table 3-3.

Methods

All ten studies were undertaken in a clinical setting and were randomised intervention studies. Of these, one used a 'no-intervention' control in a cross-over study design (Allison et al., 2002); one used pain medication across groups to act as a control for the manipulation intervention (Howe et al., 1983), and, two used a placebo intervention as the control (Klaber Moffett et al.,1990; Young et al.,2009). The remaining studies used comparative interventions ranging from no-specific treatment e.g. advice to stay active (Kuijper et al., 2009) to a specific therapeutic intervention e.g. therapeutic ultrasound (Coppieters et al., 2003).

Table 3-3 Characteristics of studies included in the systematic review

Study	Study design	Participants	Participant classification	Symptom duration	Interventions & assessment points	Outcome measures	Results
Allison et al. (2002) Australia	RCT with crossover design 3 groups: A: Neural PT with exercise; n=10 B: Articular PT with exercise; n=10 C: No treatment; n=10	n=30 Mean age 54 F=20	**Cervico-brachial pain syndrome** Cervicobrachial pain with positive brachial plexus tension test.	Chronic >3/12 Mean 36/12	A: Cervical lateral glide, shoulder girdle oscillation, muscle re-education and home exercise. B: Glenohumeral and thoracic mobilisation, and home exercise. Treatment is given over an 8/52 period. Quantity of treatment not specified. Assessment at baseline, 4/52 and 8/52.	**Pain:** VAS pain, SF McGill. **Function/disability**: NPQ.	**Pain:** Statistically significant between-group differences in improvement of mean VAS pain for A compared to B at 8/52 (p=0.03). No statistically significant between-group differences on SF McGill (p=0.15). **Function/disability:** No statistically significant differences between groups at any assessment period.
Bernaards et al. (2007) Netherlands	RcT 3 groups: A: Work related behavioural change group; n=152 B: Work and exercise related behavioural change group; n=156 C: Usual care; n=158	n=466 Mean age 44 F=207	**Neck and upper limb symptoms** Pain, tingles or stiffness in the neck, shoulders, arms, wrists and/or hands. No local somatic disease such as tennis elbow or carpel tunnel syndrome.	Chronic IQR 14-16 months	A: Behavioural changes with regard to posture, workplace adjustment, breaks and coping with high work demands. B: As for group A. In addition, behavioural changes with regard to engagement in moderate to heavy intensity physical activities. Physical exercise was not part of the intervention. Groups A and B receive 6 meetings over 6 months. Assessment at baseline, 6/12 and one year.	**Pain:** NPRS **Function/disability**: DWS (numerical scale).	**Pain:** No statistically significant between-group differences at 6 months. Statistically significant between-group differences for reduced mean pain score for A compared with C at 12 months (p<0.05). **Function/disability:** No statistically significant differences in changes over time across groups or between-groups at 6 or 12 months regarding disability at work.

Coppieters et al (2003) Australia	RcT 2 groups: A: Cervical mobilisation (lateral glide); n=10 B: Therapeutic ultrasound; n=10	n=20 Age range 35- 63 Mean age 48. F=16	**Neurogenic cervicobrachial pain** An active and passive movement dysfunction related to non-compliance of the median nerve and adverse response to median nerve palpation. Positive NTPT.	Sub-acute and chronic Range 2/52 – 6/12.	A: Single session of lateral glide mobilisation to the cervical spine B: Single session of therapeutic ultrasound to most painful area. Assessment at baseline and immediately following treatment in response to the NTPT.	**Pain:** NPRS	**Pain:** No between-group differences were reported. Statistically significant immediate improvement in mean pain reduction pre compared to post treatment for A ($p<0.005$), but not for B ($p=0.28$).
Howe et al (1983) UK	RCT 2 groups: A: Cervical manipulation and medication; n=26 B: Medication; n=26	n=52 Age range 16-65. F=31	**Neck and upper limb symptoms** Pain in the neck, arm or hand related to a lesion in the cervical spine. No other causes of pain in the shoulder or arm. Reduced cervical intervertebral joint movement or palpable asymmetry.	Mixed Range of duration. Details not provided	A: Quick Thrust manipulation +/- injection and treated with NSAID (azapropazone) B: NSAID alone. Quantity of treatment not recorded. Assessment at baseline, immediately following treatment, 1/52 and 3/52.	**Pain:** Measures identified as 'absent', 'same', 'better' or 'worse' for pain in the neck, shoulder and arm/hand.	**Pain:** Statistically significant between-group differences for immediate improvement in pain in neck ($p<0.005$) and shoulder ($p=0.02$) for A compared to B. Differences are not sustained at one and three week follow-up post-treatment. No statistically significant differences between-groups for pain in the arm/hand.
Klaber Moffett & Hughes (1990) UK	RCT 2 groups: A: Sustained Traction; n=44 B: Placebo traction; n=50	n=94 Age range 39–60. F=58	**Neck and arm pain** Symptoms in the arm clinically indicative of a radiculopathy or brachialgia stemming from the neck.	Chronic >3/12 Mean 33/52.	A: Up to 12 sessions of sustained weighted traction (between 6-18 pounds) over four weeks. B: Up to 12 sessions of placebo traction (2 pounds) over four weeks Neck school education (one hour session) given to both groups. Assessment at baseline, immediately after treatment and 3/12 following treatment.	**Pain**: VAS pain **Function/disability:** VAS social dysfunction scale and one individually chosen activity of daily living. GHQ and STAI.	**Pain:** No statistically significant between-group differences for mean VAS pain at any assessment period. **Function/disability:** No statistically significant between-group differences for mean VAS social, activity of daily living, GHQ or STAI at any assessment period.

Kuijper et al (2009) Netherlands	RcT 3 groups: A: Semi-hard collar; n=69 B: PT; n=70 C: No specific treatment; n=66	n=205 Mean age 47 F=101	**Cervical radiculopathy** Radiation of arm pain distal to elbow. Provocation of arm pain by at least one neck movement. Sensory and motor change in one or more adjacent dermatome / myotome. Diminished reflexes on ipsilateral side.	Acute/sub-acute Mean 3/52	A: Semi-hard collar day use for up to 6/52. B: PT with a focus on mobilising and stabilising the cervical spine was given twice weekly for 6/52. C: Advice to continue normal daily activities. Assessment at baseline, 3/52, 6/52 and 6/12.	**Pain:** Two VAS pain scales – neck pain and arm pain **Function/disability:** NDI score	**Pain:** Statistically significant between-group differences for mean improvement in pain for A compared to C and for neck pain (p<0.00) and arm pain (p=0.00) during the first 6 weeks post-intervention. Statistically significant between-group differences for mean improvement in B compared to C for neck pain (p=0.00) and arm pain (p=0.00) for the first 6 weeks post-intervention. No statistically significant between-group differences for mean improvement in pain between A and B for the first 6 weeks post-intervention. No statistically significant between-group differences At 6 months, between any groups. **Function/disability:** Statistically significant between-group differences for mean improvement in disability for A compared to C (p=0.02) for the first 6 weeks post-intervention. No statistically significant between-group differences for any other time scale or between any other groups.

Persson et al (1997) & Persson and Lilja (2001) Sweden	RcT 3 groups A: Surgery; n=27 B: Rigid collar; n=27 C: PT; n=27	n=81 Age range 28-64. F=37	**Cervical radiculopathy** Clinical and radiologic findings (plane X-rays and magnetic resonance tomography) indicating nerve root compression corresponding to the distribution of pain.	Chronic Range 5/12-120/12 (mean = 53/12)	B: Rigid collar for daytime use and soft collar for night for 3 months. C: General PT up to 15 treatment sessions over 3 months. Modalities include TENS, heat, US, cold, massage, traction, mobilisation, exercises, stretches, aerobic exercise, rest, relaxation and advice on ergonomics, posture and co-ordinated exercise. Most commonly used treatments were traction, mobilisation and heat. Assessment at baseline, 15/52 & one year.	**Pain:** Two VAS pain scales - 'present pain' and 'worst pain over the last week' **Function/disability:** SIP, MACL, HAD, CS, and DRI..	**Pain:** No statistically significant between-group differences in mean pain scores between B and C at any assessment point. **Function/disability:** Statistically significant between-group differences for reduced disability in mean SIP score for C compared to B ($p<0.05$) at 15 weeks, but not at one year. Statistically significant between-group difference in improvement in mean function/ reduction in disability in some but not all of the DRI for C compared to B ($p=<0.05$) at 15 weeks. No between-group statistical differences between B and C for any other scale at any of the assessment points.

Ragonese (2009) USA	RcT 3 groups: A: Manual PT; n=10 B: Exercise PT; n=10 C: Combined manual and exercise PT; n=10	n=30 Age range or mean not stated. F=19	**Cervical radiculopathy** Definition: neck and/or upper extremity symptoms. Presence of either a positive spurlings test or cervical distraction test or ipsilateral cervical rotation less than 60° or brachial plexus tension test.	Not stated	A: Cervical lateral glide and thoracic mobilisations and neural dynamic techniques for the median nerve. B: Deep neck flexor, lower and middle trapezius and serratus anterior strengthening (supervised) C: combined approaches of A and B Treatment given three times a week for 3/52 for each intervention group. Assessment at baseline, 1/52, 2/52 and 3/52	**Pain:** NPRS **Function/disability:** NDI.	**Pain:** Statistically significant between-group differences for reduced mean pain for C compared to A and B ($p<0.01$) at 3 week follow-up. **Function/disability:** Statistically significant between-group differences for improved function for C compared to A and B ($p<0.05$) at three week follow-up.
Walker et al (2008) USA	RcT 2 groups: A: Manual therapy and exercise; n=31 B: Minimal intervention; n=27	n=58 (a sub-group from 98 patients with general neck pain). Mean age 48. Gender specific to subgroup not known.	**Neck and upper limb symptoms** Mechanical neck pain with neck and unilateral upper extremity symptoms	Mean in days: A: 1082 B: 521	A: Any manual therapy technique commonly used in clinical practice (mobilisation, manipulation, muscle energy and stretching techniques) and home exercise programme directed at stabilising and mobilising the cervical spines. Most commonly used technique(s) not specified. B: Advice from GP on posture, continuation of normal daily activities and neck movement, and medication. Placebo therapeutic ultrasound to the neck and home exercise programme directed at mobilising the neck (provided by physical therapists). Six sessions of treatment over three weeks for both groups. Assessment at baseline, 3/52, 6/52 and one year.	**Pain:** VAS pain scale for upper limb pain **Function/disability:** NDI	**Pain:** No statistically significant between-group difference in mean pain at any assessment point. A has a statistically significant reduction in pain from baseline at each follow-up. B did not have a statistically significant reduction in pain compared to baseline beyond 3/52. **Function:** No results were reported specific to sub-group of patients with upper limb symptoms with regard to NDI.

Young et al (2009) USA	RCT 2 groups: A: Intermittent traction; n=45 B: Placebo traction; n=36	n=81 Age range 18-70 Mean age 47 F=55	**Cervical radiculopathy** Unilateral upper-extremity pain, paraesthesia and numbness. 3 out of 4 positive tests for the following: 1. Spurling test 2. distraction test 3. brachial plexus tension test 4. ipsilateral neck rotation <60°	Mixed < 3/12 = 42 >3/12 = 39	A: Intermittent mechanical traction from approx. 20 pounds to 35 pounds. B: Placebo mechanical traction using 5 pounds or less. Both groups received postural education, manual therapy and exercises directed to the cervical spine and scapula. Treatment given on average 7 occasions over an average of 4.2 weeks. Assessment at baseline, 2/52 and 4/52	**Pain:** NPRS **Function/disability:** NDI and PSFS.	**Pain:** No statistically significant between-group difference on mean NRPS at 2/52 or 4/52 follow-up. **Function/disability:** No statistically significant between-group difference on mean NDI or PSFS at 2/52 or 4/52 follow-up.

Key: CS= Coping Strategies Questionnaire; DWS= Disability at Work Score; DRI= Disability Rating Index; F= female; GHQ= General Health Questionnaire; GROC= Global Rating of Change scale; HADs= Hospital and Depression scale; MACL= Mood Adjective Check List; NDI= Neck Disability Index; NPRS= Numeric Pain Rating Scale; NPQ= Northwick Park Questionnaire; NTPT= Neural Tissue Provocation Test; NSAID= Non-steroidal anti-inflammatory drug; PSFS= Patient Specific Functional Scale; PT= Physiotherapy; RCT= Randomised controlled trial; RcT= Randomised clinical trial; SF McGill= Short-form McGill Questionnaire; SIP= Sickness Impact Profile; STAI= State Trait Anxiety Inventory; VAS= Visual Analogue Scale.

Short-term post-intervention assessment (defined as the first assessment point following completion of intervention) ranged from immediately following intervention (Howe et al., 1983; Klaber Moffett et al., 1990; Coppieters et al., 2003) to 15 weeks post intervention (Persson et al., 1997, 2001). Follow-up assessments varied considerably: one study had no follow-up assessment (Coppieters et al., 2003), whilst others evaluated outcome measures up to one year post intervention (Persson et al., 1997,2001; Bernaards et al., 2007; Walker et al., 2008).

Quantity of intervention ranged from a single session of treatment (Howe et al., 1983; Coppieters et al., 2003) to 24 sessions (Persson et al., 1997, 2001). Intensity and duration of intervention were also variable, from one treatment in isolation (Coppieters et al., 2003) to 3 treatment sessions a week (Klaber Moffett et al., 1990; Ragonese et al., 2009) and extending over a period of 6 months (Bernaards et al., 2007). It is not clear whether this considerable variability in quantity of treatment reflects a true account of variability in the clinical provision on non-invasive management for this condition.

Participants

The ten studies in the review randomised 1036 participants. From available data, there was a broad age range from 16 to 70 years, with marginally more females than males. There was a variable duration of symptoms, but insufficient data to detail the range. Diagnostic methods differed across studies. The majority of studies stated selection criteria on symptom type and pattern of radiation or referral.

Interventions

Interventions fell into five distinct groups: general physiotherapy, traction, manual therapy, exercise therapy and behavioural therapy.

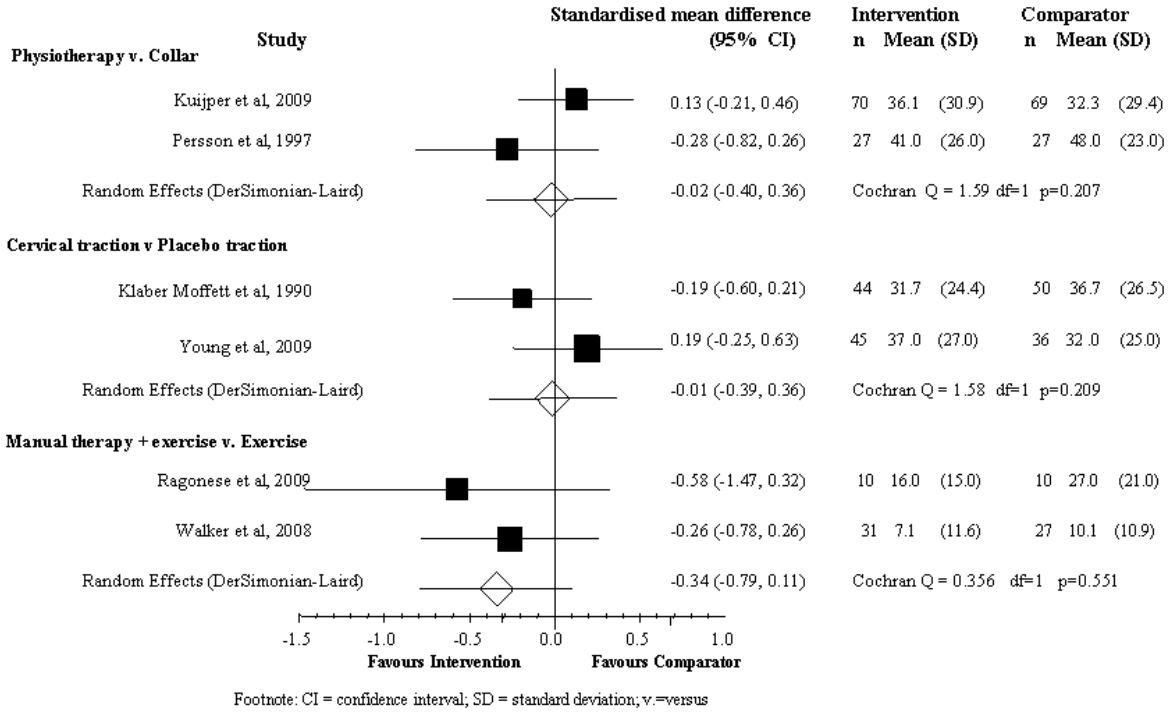
Outcomes

All studies reported pain as an outcome. Five studies used the visual analogue scale (VAS) and four used the numeric pain rating scale (NPRS) as an outcome measure. Howe at al. (1983) used a four category descriptive pain outcome measure. There was some variability in time frames, which ranged from evaluating 'current pain' (Persson et al., 1997, 2001) to 'worst pain in the last four weeks' (Bernaards et al., 2007). There were different areas for pain representation including: 'neck, shoulder, arm pain' (Persson et al., 1997, 2001), 'pain in either neck or arm' (Coppieters et al., 2003), and separate outcome measures to represent pain in the neck and pain in the arm (Kuijper et al., 2009). Allison et al. (2002) used the Short-form McGill questionnaire in addition to a VAS. Howe et al. (1983) used a pain scale that comprised of four descriptive items.

Functional and disability outcome measures were used by eight of the ten studies. The Neck Disability Index (NDI) was used in four studies. Otherwise, there was considerable variation in constructs measured – including a focus on work related aspects (Bernaards et al., 2007), specific problems to an individual (Young et al., 2009) and psychological and psychosocial aspects of function and disability (Persson and Lilja, 2001).

Meta-analyses of review results on post-interventional pain outcomes

Three meta-analyses were conducted to consider the effects of treatments on short-term (post-intervention) pain outcome (Figure 3-4). There were no other comparable outcomes, time points or interventions across the studies included in the review.



Footnote: CI = confidence interval; SD = standard deviation; v.=versus

Figure 3-4: Forest plot of pain (intervention v. comparator) – short-term post-interventional outcomes with meta-analyses

Overall, there was no evidence that general physiotherapy (including electrotherapy, manual therapy, exercise, heat, relaxation and/or advice), or traction reduced pain in the short-term compared to comparators. There was a trend towards a favourable response to manual therapy and exercise but this did not reach statistical significance (DerSimonian-Laird pooled effect size = -0.34; 95%CI -0.79 to 0.11).

Synthesis of systematic review results

This systematic review found inconclusive evidence for non-invasive intervention in the management of cervicobrachial pain. Evidence was assessed from 10 randomised clinical studies (1036 participants) and conducted across 5 countries. Different non-invasive interventions were evaluated in terms of their effects on pain, disability and function for participants with cervicobrachial pain. There was excellent between-reviewer agreement on study selection (Kappa 0.96) and perfect between-reviewer agreement on methodological quality (Kappa 1). Overall quality per outcome across studies was variable, ranging from high (for evaluation of function and disability in response to traction) to very low (for evaluation of function and disability in response to general physiotherapy and manual and exercise therapy) (Table 3-4).

Table 3-4: GRADE evidence profile of studies in review [Outline adapted from Guyatt et al., 2011a]

TYPE OF THERAPY Outcome	Number of studies/ participants (Design)	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Effect size	Dose response	Confounders	Quality
GENERAL PT **Pain** **Function** **Disability**	Two studies (RCT) Participants (n=286)	All outcomes: Very serious limitations (-2)	Function/ disability: (-1)	No serious indirectness for all outcomes	No serious imprecision	None detected	Small	No evidence any outcome	Limited consideration across outcomes	**Pain:** *Low* **Function & disability:** *Very low*
TRACTION **Pain** **Function** **Disability**	Two studies (RCT) Participants (n=175)	All outcomes: Serious limitations (-1)	Pain: Serious limitations (-1) Function/ disability: consistent findings	No serious indirectness for all outcomes	No serious imprecision	None detected	Small	No evidence of high dose response on any outcome	Some consideration across outcomes (+1)	***Pain:** *Moderate* **Function & disability:** *High*
MANUAL THERAPY & EXERCISE **Pain** **Function** **Disability**	Five studies (RCT) Participants (n= 190)	All outcomes: Serious limitation (-1)	Pain: Consistent findings Function/ Disability: Serious limitations (-1)	No serious indirectness for all outcomes	Serious imprecision (-1)	None detected	Small	No evidence of high dose response on any outcome	Limited consideration across outcomes	**Pain:** *Low* **Function & Disability:** *Very low*
BEHAVIOURAL THERAPY **Pain** **Function** **Disability**	One study (RCT) (n=466)	All outcomes: Serious limitation (-1)	Not applicable (no other studies to compare)	Unclear what 'usual care' referred to (-1)	No serious imprecision	None detected	Small	No evidence of high dose response on any outcome	Some consideration across outcomes (+1)	**Pain, function and disability:** *Moderate*

Footnote: Refer to Table 2-2 Method used to establish quality of evidence in GRADE in GRADE [Outline adapted from Guyatt et al., 2011a]

General Physiotherapy

Meta-analyses showed that general physiotherapy was no more beneficial than comparators in reducing pain in the short-term (95% CI -0.40 to 0.36) (Figure 3-4). There was a difference in trends between the two studies evaluated, with one favouring the comparator (Kuijper et al., 2009) and the other favouring the intervention (Persson et al., 1997, 2001). Both studies used similar comparative interventions (use of collar). There was some heterogeneity between the two studies (Cochran Q=1.59, df=1; p=0.21) that might be explained by these opposing trends. This finding did not change in the long-term evaluation of pain, where there was low evidence that general physiotherapy was no more beneficial than comparators (Persson et al., 1997, 2001; Kuijper et al., 2009).

General physiotherapy was no more beneficial than comparators in improving function (very low evidence): Persson and Lilja (2001) reported that participants who received physiotherapy performed significantly better ($p<0.05$) on three of the twelve aspects of the Disability Rating Index (walking, sitting for a long time and heavy work) in the short-term (at fifteen weeks) compared to those wearing a collar (Persson and Lilja, 2001). They reported that sitting for a 'long time' (duration was not specified) remained improved at one year ($p<0.05$). Kuijper et al. (2009) found a non-significant improvement in the Neck Disability Index (NDI) for participants who received physiotherapy compared to a 'no-specific treatment' comparator ($p=0.09$).

General physiotherapy was no more beneficial than comparators in reducing disability (very low evidence): Persson et al. (1997) reported that participants who received physiotherapy had improved scores on the Sickness Impact Profile (SIP)

compared to collar use in the short-term ($p<0.05$), but not at one year ($p>0.05$) (Persson et al., 1997). Findings indicated no evidence that general physiotherapy improved psychological or psychosocial wellbeing in the short or long-term ($p>0.05$) (Persson et al., 2001).

Traction

A meta-analysis showed that cervical traction was no more beneficial than comparators in reducing pain in the short-term (95% CI -0.39 to 0.36). There was a difference in trends between the two studies evaluated, with one favouring the comparator (Young et al.2009) and the other favouring the intervention (Klaber Moffett et al., 1990). Both comparative interventions used placebo traction. There was potential for pain reduction in the short-term using traction in a sustained, rather than intermittent, form (Klaber Moffett et al., 1990), but it did not reach a statistically significant effect (95% CI -0.60 to 0.21). This finding did not change in the long-term evaluation of pain, where there was moderate evidence that cervical traction was no more beneficial than comparators (Klaber Moffett et al., 1990; Young et al., 2009).

Cervical traction was no more beneficial than sham or placebo in improving function and reducing disability at any time point (high evidence) (Klaber Moffett et al., 1990; Young et al., 2009).

Manual Therapy and exercise

The meta-analysis showed a trend that manual therapy and exercise was favourable in reducing pain in the short-term (Figure 3-4) but this did not reach a statistical significance (95%CI -0.79 to 0.11). Both Walker et al. (2008) and Ragonese (2009)

found a reduction in pain at three weeks post-intervention following the commencement of manual therapy and exercise. Statistically significant between-group differences were only found in Ragonese's study ($p<0.01$), but not in Walker et al.'s (2008) study ($p=0.21$). This finding did not change in the long-term follow-up evaluation of pain, where there was low evidence that manual therapy plus exercise was no more beneficial than comparators in changing pain (Ragonese, 2009; Walker et al. 2008).

Some studies focused on evaluating specific forms of manual therapy. Allison et al. (2002) found statistically significant improvements in pain at 8 weeks, for participants receiving neural-biased manual therapy (cervical lateral glide and shoulder girdle oscillation) compared to those receiving articular-biased treatments (glenohumeral and thoracic mobilisation) ($p=0.03$). Coppieters et al. (2003) assessed the effectiveness of the lateral glide specifically. They found, unlike the ultrasound comparator, the lateral glide intervention resulted in a statistically significant improved pain response to a 'neural tissue provocation test' for the upper limb immediately post intervention ($p<0.0003$), however no between-group differences were evaluated; therefore interpretation for effectiveness was limited. Howe et al. (1983) found cervical manipulation significantly reduced neck pain immediately post-intervention compared to control ($p<0.001$). However, there were variable responses to upper limb pain ($p<0.02$ in the shoulder; $p=1.97$ in the arm/hand). No statistically significant improvements were found at one week follow-up (Howe et al., 1983). Two participants in the manipulation group also had facet joint injections (lidocaine and hydrocortisone) to "allow the manipulation to be carried out". It was not reported

whether the participants who received injections made any statistically significant improvement compared to those who did not.

There was very low evidence that manual therapy and exercise improved function and reduced disability. Ragonese (2009) reported a statistically significant improvement at three week follow-up on the Neck Disability Index scores for participants who received manual therapy and exercise compared to those who received either manual therapy or exercise. In contrast, Allison et al. (2002) reported no statistically significant improvements on the Northwick Park Questionnaire at the same follow-up point for those who received manual therapy compared to comparators. None of the other studies on manual therapy and exercise evaluated function or disability for cervicobrachial pain (Howe et al., 1983; Coppieters et al., 2003; Walker et al., 2008).

Behavioural Therapy

There was 'moderate' evidence that behavioural therapy was more beneficial than comparators in reducing pain. Bernaards et al. (2007) evaluated whether behavioural changes towards working style with or without engagement in physical tasks was more effective than 'usual care'. The level and type of intervention in 'usual care' was not specified. There were no statistically significant between-group differences on any measure in the short-term (post-intervention). At one year follow-up, there were statistically significant between-group differences for pain ($p<0.05$), favouring the group receiving the working style behavioural change (without the physical task engagement) compared to those receiving 'usual care'.

Adverse events relating to harm were not reported. Participants who received behavioural therapy were less likely to utilise additional health care for their symptoms compared to 'usual care' ($P<0.01$) over a six month duration, signifying cost-effectiveness.

Discussion of systematic review findings

To establish strength of recommendation, the level of evidence should be considered alongside other factors, including risk of harm, patient values, patient preferences and cost (Balshem et al., 2011).

Of the selected studies included in the systematic review, only one study evaluated financial expenditure relating to health care costs in response to behavioural intervention (Bernaards et al., 2007). None of the studies reported on adverse events or risk of harm. Two of the studies assessed participants' values in the form of self-reported recovery in response to behavioural therapy and cervical traction (Bernaards et al., 2007; Young et al., 2009).

General Physiotherapy

From the available evidence, general physiotherapy had a low level of recommendation to support its use in cervicobrachial pain; however this recommendation was based on limited evidence.

Meta-analyses indicated that general physiotherapy provided no additional reduction of pain in the short-term. There were consistent findings that general physiotherapy was no more effective in reducing pain than the use of a collar or 'no specific treatment' at long-term follow-up. There was conflicting evidence that general

physiotherapy reduced disability or improved function. There was no evidence of cost-effectiveness, risk of harm or any data to establish if participants valued one intervention in preference to another.

From limited evidence, it would appear that the composite nature of generalised physiotherapy (including electrotherapy, traction, manual therapy and exercise) is no more effective that comparators.

Traction

Traction had a low level of recommendation to support its use in cervicobrachial pain.

Meta-analyses indicated that cervical traction provided no additional benefit than placebo in reducing pain in the short-term. There were consistent findings that cervical traction was no more effective in reducing pain in the long-term or, reducing disability and improving function in the short-term or long-term than placebo traction. There was limited evidence, from one study, that intermittent traction did not improve participant self-reported recovery compared to sham or placebo in the short-term ($p=0.74$) or long-term ($p=0.58$) (Young et al., 2009). There was no evidence to support or refute traction as a cost-effective modality and no data to evaluate any risk of harm associated with traction.

Manual therapy and exercise

Manual therapy and exercise had a low level of recommendation to support its use in cervicobrachial pain. Meta-analyses indicated a trend for manual therapy and exercise to be beneficial in reducing pain in the short-term, but this did not reach statistical significance.

There was conflicting evidence that manual therapy and exercise was advantageous in long-term pain reduction as well as on disability and function in the short and long-term. No evidence evaluated risk of harm for manual therapy and exercise in cervicobrachial pain. One study evaluated the effects of manual therapy and exercise on cost-effectiveness and participant self-reported recovery (Walker et al., 2008) but there was no sub-group analysis for the cervicobrachial pain participants, therefore, interpretation was limited.

Behavioural therapy

Behavioural therapy had a low level of recommendation to support its use in cervicobrachial pain.

According to one study (Bernaards et al., 2007), behavioural therapy improved pain in the long-term compared to 'usual care'. This study showed potentially moderate benefit, but it was recognised that further studies were needed to confirm this. Without having clear details on what treatment the 'usual care' group received, it was difficult to comment on how this treatment effect occurred. It was, also, unclear why this effect was evident at the one-year follow-up and not at short-term follow-up.

There was moderate evidence that behavioural therapy did not improve function or disability. There was moderate evidence that behavioural therapy was a cost-effective modality, as participants who received behavioural therapy were reported as less likely, over a six month duration, to use additional health care for their symptoms compared to the 'usual care' comparator ($P<0.01$). Adverse events relating to harm were not reported.

3.2.4 Comparisons with other reviews

A previous review on neck pain reported insufficient evidence for manual therapy for neck disorders with radicular findings (Gross et al., 2004). There was some evidence from this review to support a positive influence of manual therapy and exercise on cervicobrachial pain in the short-term, although it was acknowledged that this evidence was weak. Some recent systematic reviews have evaluated the effects of manual therapy on cervicobrachial pain (Boyles et al., 2011; Leininger et al., 2011). Similar conclusions were reported.

3.2.5 Limitations of the systematic literature review

This review was based on all the available literature at the time of conducting the searches (from start to January 2012). Published and unpublished sources were searched. However, a potential weakness, as for most reviews, was the risk of incomplete retrieval of relevant literature.

Cervicobrachial pain is a heterogeneous term and, consequently, there was variation in participants' criteria across studies. Some studies aimed to identify cervical radiculopathy specifically. Identifying patho-anatomical causes, such as cervical radiculopathy (disease pertaining to the nerve root), has not been found to be effective in identifying conditions that will or will not respond to therapy (Section 2.3).

There was variability in the outcome measures, with a lack of consistency in assessment time frames and how scales were used (Section 3.2.3 – outcomes).

Frequency, intensity and duration of reported interventions varied considerably. Pooling results in meta-analyses was, therefore, limited. Future studies should focus

on identifying cost-effective, clinically appropriate, low-risk interventions. In many studies included in this review, there was some reduction in pain and recovery of function, irrespective of treatment received. However, all studies used some form of intervention in the comparator groups; therefore, the data from this review does not further the understanding of the natural course of the condition.

Three studies reported patient values and preferences in the form of global rating of change scores (Bernaards et al., 2007; Walker et al., 2008; Young et al., 2009). Global ratings of change scores have been recommended as a valid way to represent patient values (Kamper et al., 2009). There was inconsistency in which scales were used: Bernaards et al. (2007) used a seven-point scale, Young et al. (2009) a thirteen-point score and Walker et al. (2008) a fifteen-point scale. However, it has been reported that scales between 7-point and 15-points are equally responsive (Lauridsen et al., 2007), enabling cross-analysis between study results.

None of the studies reported harms; therefore the level of risk associated with each treatment modality was unknown. The reporting of adverse events has been advocated (Ioannldis et al., 2004), but, it would appear from this review that it is not yet common practice.

3.3 Conclusions from evidence of non-invasive management for cervicobrachial pain

There was insufficient information to make recommendations regarding the management of cervicobrachial pain.

There was low evidence for the effectiveness of non-invasive management of cervicobrachial pain. Potential benefits were indicated in the provision of manual therapy and exercise and behavioural change approaches to reduce pain (Table 3-5)

Table 3-5 Grade of evidence to support effectiveness of non-invasive interventions in cervicobrachial pain

Grade	Intervention
Moderate	Behavioural therapy (long-term pain reduction) (Bernaards et al., 2007)
Low	Manual therapy (short and long-term pain reduction) (Howe et al., 1983; Allison et al., 2002; Coppieters et al., 2003; Walker et al., 2008; Ragonese et al., 2009)
Very Low	Manual therapy (improvement in function and disability) (Ragonese et al., 2009)

Footnote: Refer to Table 2-3 for interpretation of grades

General physiotherapy and traction were no more effective than comparators in reducing pain. Effects of non-invasive management on function and disability were mixed.

3.4 Identification of need to conduct research trial on the lateral glide mobilisation

Limited evidence from this review indicated that the provision of manual therapy and exercise and a behavioural change approach might be a cost-effective approach to

reduce pain in the management of cervicobrachial pain in the short- and long-term. The future role of manual therapy in health care was identified, in 2007, as an important area to research (Smith, 2007; Vernon & Humphreys, 2007). Manual therapy encompasses a wide range of techniques including joint mobilisation or manipulation, myofascial techniques, acupressure and massage. Some techniques might provide enhanced therapeutic effect compared to others. The need to evaluate effectiveness of specific manual therapy techniques for specific conditions has been reported (Hoving et al., 2001; Smith, 2007; Millar et al., 2010). From the findings of this review, it was unknown whether any specific treatment techniques or approaches influenced outcome on pain, function or disability for cervicobrachial pain. The most consistently used manual therapy approach reported in studies included in the review was the lateral glide mobilisation technique. The lateral glide technique (which involves an oscillation of one vertebra on another) has been advocated for management of cervicobrachial pain in clinical texts (Jull et al., 2008). No high quality clinical studies have evaluated the effectiveness of the lateral glide mobilisation specifically in the management of cervicobrachial pain, either in the short or long-term.

3.5 Summary of non-invasive management of cervicobrachial pain

Cervicobrachial pain is largely managed conservatively. There continues to be a lack of research substantiating what interventions constitute best practice. The provision of manual therapy with exercise has a low level of evidence to support its use in reducing pain. The lateral glide has been the most consistently reported specific

manual therapy technique used in past research, however there is very low evidence to support its use as a specific manual therapy intervention for cervicobrachial pain in the immediate-term and no evidence to support its use as a specific manual therapy intervention in the short or long-term. The next chapter will consider the lateral glide as an intervention, and evaluate how this technique might create a hypoalgesic (pain relieving) effect.

4 AN OVERVIEW OF EXISTING NON-INVASIVE INTERVENTIONS FOR CERVICOBRACHIAL PAIN

4.1 Introduction to existing interventions

Chapter 3 identified evidence that the lateral glide mobilisation might be an effective intervention for patients with cervicobrachial pain. This chapter reports a critical evaluation of how the lateral glide could have an effect on pain and appraises the different approaches to performing a lateral glide. Justification is presented for selection of the approach that was used in a randomised controlled trial to assess its effectiveness (reported in Chapter 5).

The second part of the chapter appraises methods that could be used to evaluate the effectiveness of the lateral glide on cervicobrachial pain. The use of a self-management approach as the comparator treatment is discussed and the development of a new, bio-psychosocial self-management tool is reported.

4.2 The lateral glide mobilisation

The lateral glide technique was originally described by Elvey (1986) as a manual treatment, involving a small oscillatory movement, applied to the neck with an element of traction. In modern texts, the lateral glide is still considered to be a technique that might induce pain relief and lead to improvements in disability and, potentially, be useful in the management of cervicobrachial pain (Jull et al., 2008).

4.2.1 The lateral glide's effect on pain

There was moderate evidence that cervical joint mobilisation has an immediate effect on reducing pain in neck and upper limb musculoskeletal conditions. A systematic review by Schmid et al. (2008) reported that cervical mobilisation could reduce pain by approximately 20% more than control approaches. Eight of the 15 studies in Schmid et al.'s (2008) review used the lateral glide technique. Consistent findings from studies have supported that the lateral glide has a hypoalgesic (pain reducing) effect beyond comparators (therapeutic ultrasound), placebos (manual contact intervention) and controls (no intervention) on at least one pain outcome measure (Table 4-1). However, there were some inconsistencies between pain outcome measures, for example, statistically significant effects on VAS (pain) and on pressure pain thresholds were identified in some, but not all studies. This inconsistency might be due to the heterogeneity of participants across the studies, or a lack of power to detect change within studies.

Table 4-1 Effectiveness of the lateral glide mobilisation on pain

Study	Participants	Comparator, control or placebo	Pain Outcome measure	Results
Coppieters et al., (2003)* RCT	n=20 sub-acute and chronic neurogenic cervicobrachial pain	Therapeutic ultrasound (comparator)	Numerical pain rating score in response to the ULNE	No between-group differences reported. Significant immediate improvement in mean pain reduction pre compared to post treatment for mobilisation group ($p<0.00$), but not for ultrasound group ($p=0.29$).
McClatchie et al., (2009) RCT	n=21 Chronic shoulder pain	Manual contact, without mobilisation (placebo)	VAS pain	Significant between-group differences favouring the mobilisation group ($p =<0.00$).
Sterling et al., (2010) RCT	n=39 Chronic whiplash associated disorder	Manual contact without mobilisation (placebo)	NFR; VAS pain; PPT; TPT	Significant between-group differences favouring the mobilisation group for NFR ($p=0.04$). Did not reach statistical significance for VAS, PPT or TPT.
Vincenzino et al., (1996) RCT	n=15 Lateral epicondyalgia	Manual contact without mobilisation (placebo) and no contact (control)	PPT; VAS pain	Significant between-group differences favouring the mobilisation group for PPT ($p<0.01$). Did not reach statistical significance for VAS
Vincenzino et al., (1998) RCT	n=24 Chronic lateral epidondyalgia	Manual contact without mobilisation (placebo) and no contact (control)	PFGS; PPT; TPT; ULNE	Significant between-group differences favouring the mobilisation group for PPT, ULNE, PFGS ($p>0.05$). Did not reach statistical significance for TPT

Key: n= number; NFR = Nociceptive flexion reflex threshold; PFGS = Pain free grip strength; PPT = Pressure Pain Threshold; RCT= Randomised controlled trial; TPT= Thermal Pain Threshold; ULNE=Upper Limb Nerve Extensibility test; VAS=Visual Analogue Scale;
*= Study on cervicobrachial pain subjects

4.2.2 Theory of how the lateral glide's effect on pain might be achieved

It has been reported that a hypoalgesic effect (from a lateral glide) occurs in response to the mechanical stimulation of the cervical afferents in the joints, muscles, ligaments and nerves (Elvey, 1986; Coppieters et al., 2003; Jull et al., 2008). This stimulation is reported in the literature to affect pain perception by altering the processing of pain at spinal cord and cortical levels (Schmid et al., 2008; Bialosky et al., 2009). Evidence to support how the lateral glide can achieve a hypoalgesic effect has been focused on two key mechanisms

- Produce a mechanical effect
- Affect pain mechanisms

Evidence of a mechanical effect

There was low level evidence that the lateral glide creates a mechanical effect, but very low evidence that this mechanical effect occurs at the level of the cervical vertebrae. Vincenzino et al. (1999) reported that application of the lateral glide technique to the fifth on the sixth cervical vertebra consistently produced a mechanical displacement of the vertebra with C5 to T1 having the largest lateral displacement of 3cm (95% CI 2.74 to 3.94). Although this study had serious limitations (including a very small number of participants: n=8; and questionable reliability for use of reflective tape as markers over anatomical landmarks during the ultrasonic imaging) these were the only data available to evidence a mechanical effect for the lateral glide technique (Figure 4-1).

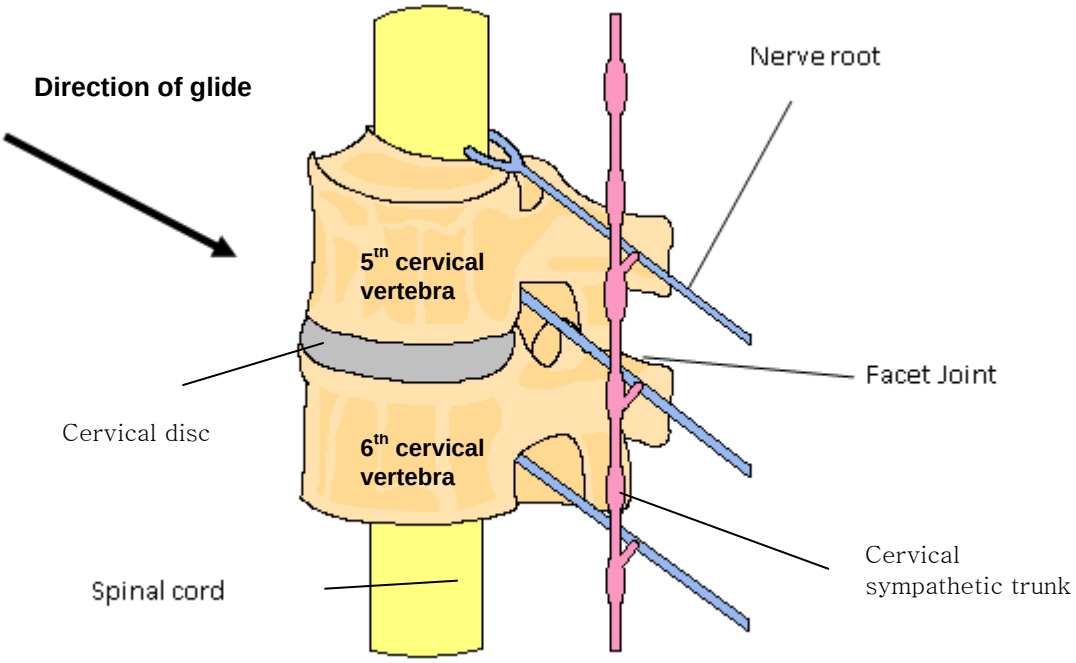


Figure 4-1: Direction of glide applied to the 5th vertebra.

Other studies have consistently found that mobilisation (in the form of a posterior/anterior glide) to the cervical spine produces little to no movement of the vertebrae, but can produce consistent changes in the soft tissue area local to the application of the technique (McGregor et al., 2001; McGretor et al., 2005; Lee et al., 2005). It has been hypothesised that any therapeutic benefit could be the result of the soft tissue deformation rather than any mechanical effect at the level of the joint (McGregor et al., 2005).

Evidence of an effect on pain mechanisms

There was a moderate level of evidence that the lateral glide could modulate pain mechanisms. A randomised controlled study (n= 39) reported that application of the lateral glide to the fifth on sixth vertebrae resulted in changes to a spinal reflex, indicating a change in spinal cord hyper excitability (Sterling et al., 2010) (Figure 4-2). This was the only study that had evaluated changes at spinal cord level. Other studies evaluated changes within the sympathetic nervous system in response to the lateral glide.

There was moderate evidence that sympathetic change was associated with alterations in activity in the periaqueductal grey region (PAG) of the midbrain, an area of the brain believed important in pain modulation via the descending inhibitory pathways (Schmid et al., 2008). Animal and human studies have consistently reported concurrent changes in pain, brain activity and sympathetic output (Gebber et al., 1999; Green et al., 2006; Dean, 2011). Clinical studies used change in sympathetic output (including thermal skin changes and blood flow change) to demonstrate that lateral glide mobilisation affected descending cortical control. However, findings were inconsistent across studies. Most studies supported a positive association (Vincenzino et al., 1995; Vincenzino et al., 1998); however one study found a mixed response (Vincenzino et al., 1994).

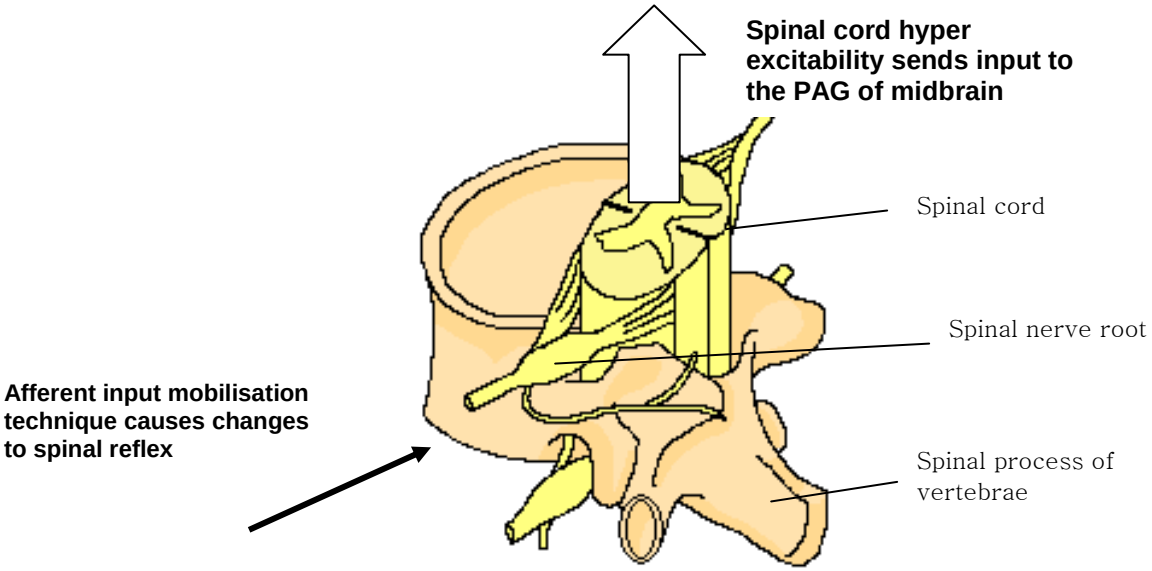


Figure 4-2: Effects of the lateral glide on the spinal cord
Key: PAG= periaqueductal grey region

To summarise, there was moderate evidence that the lateral glide had a hypoalgesic effect. There was very low evidence that the effect was caused by mechanical stimulation and moderate evidence that this resulted in altered pain processing (Table 4-2). It is important to recognise that these effects have been observed on a heterogeneous group of subjects (only one of the studies was on cervicobrachial pain patients) and that effects have been evaluated only in the immediate term. It was unknown whether the physiological effects of the lateral glide extended into short, medium or long-term.

Table 4-2 Grades of effectiveness for the lateral glide mobilisation

Grade	Evidence
Moderate	The lateral glide had an immediate pain reducing effect (Schmid et al., 2008) Pain was reduced by modulation to pain processes (Vincenzino et al., 1995; 1998; Sterling et al., 2010)
Very Low	The lateral glide created a mechanical effect to the internal tissues in the cervical spine (Vincenzino et al., 1999)

Footnote: Refer to Table 2-3 for interpretation of grades

4.2.3 Different approaches when using the lateral glide mobilisation

Standardising a mobilisation technique is controversial. Early narrative work of Elvey (1986) specifically advocated using the lateral glide at the most symptomatic vertebral level. However, there was a low level of evidence that equivalent effects result from manual therapy delivered to either a symptomatic or non-symptomatic level (Cleland et al., 2005; Aquino et al., 2009). It has been recommended that, in research, techniques should be specific and reproducible to enable findings to inform practice (Jull et al., 2008).

Different approaches have been reported for administering the lateral glide (Table 4-3).

Table 4-3 Different approaches used by studies using the lateral glide mobilisation

Study	Technique named	Direction of glide	Level of glide	Grade and duration of glide	Position
Allison et al., (2002)* RCT	Lateral glide technique	Gentle, slow controlled lateral glide, away from the side of pain	Level not specified.	Slow oscillations into resistance but not pain. Duration not specified.	Supine lying. Hand resting on chest or abdomen. Shoulder supported over the acromial region. Head and neck supported.
Coppieters et al., (2003)* RCT	Lateral glide technique	A lateral translatory movement away from the involved side while minimising gross cervical side flexion or rotation.	One or more motion segments C5, C6, C7	Grade and duration not specified. (Reference made to Vincenzino et al, 1999)	Supine lying. Shoulder girdle depressed. Occiput and neck cradled. Arm either resting on abdomen or in more abducted positions (depending on patient's level of pain)
Cowell and Phillips (2002)* SCS	Lateral glide technique	A lateral glide mobilisation, directing the glide to the opposite side of the pain	C5/6	Oscillatory mobilisation. Grade and duration not specified.	Supine lying. Hand resting on abdomen and then progressing into a more abducted and extended position.
Elvey (1986) DP	Lateral glide technique	Lateral gliding, directing the glide to the opposite side of the pain	Dependent on level of nerve root	Oscillatory manner. Duration and grade not specified.	Supine lying. Hand resting on thorax, by side or in outstretched position. Shoulder girdle is lightly fixed. Gentle cervical traction may be applied.
McClatchie et al., (2009) RCT	Lateral glide mobilisation	Mobilisation was directed towards the same side of the symptoms	C5, C6, C7	Grade IV+. 120 seconds at each level.	In sitting with back supported and head in neutral, hands on lap.

Ragonese (2009)***** RCT	Lateral glide mobilisation	Lateral glide towards the side of the symptoms	C2, C3, C4C5, C6, C7	Oscillatory. Grade III or IV for approximately 30-45 seconds at each level.	Supine position. Head and neck cradled.
Saranga et al., (2003) RCT	Lateral glide technique	The cervical lateral glide technique (Maitland, 1986) was performed on the contralateral side and directed *towards* the side of the arm being investigated	C5/6	Grade III. 60 second mobilisations (x3) with one minute interval in between.	Supine lying. Head and neck were kept in a neutral position.
Sterling et al., (2010) RCT	Cervical lateral glide	Cervical lateral glide directed away from the nominated side of pain.	C5/6	Grade not specified. 60 second mobilisations (x3) with one minute interval in between.	Supine lying. Whole hand contact with the neck.
Vincenzino et al., (1994,1995, 1996, 1998,1999) RCTs	Lateral glide technique	Directed contra laterally to the affected upper limb. The therapist specially emphasised the lateral translatory motion away, while minimising gross rotation and side flexion.	C5/6	Oscillatory grade III glide. 30 second mobilisations (x3) with one minute interval in between.	Supine lying. Arm in varying positions of shoulder abduction, medial rotation and elbow extension. Shoulder girdle depressed. Occiput and neck cradled.

Key: C= cervical vertebra; C5/6= 5^{th} on 6^{th} cervical vertebra; DP=descriptive paper; grade III=large amplitude into resistance; grade IV+=small amplitude end range movement; RCT=Randomised Controlled Trial; SCS=Single Case Study; *Studies on cervicobrachial pain subjects

No standard approach to delivering the lateral glide was identified. Different approaches related to the direction of glide, the level to which the glide was applied, intervention parameters (the quantity and depth of oscillation used), the therapist's hand position (push or pull techniques) and, the positions in which the patient was positioned when receiving the glide (supine or sitting).

Direction of glide

The most consistently used direction of the technique involved an oscillatory glide away from the side of symptoms (Elvey, 1986; Vincinzino et al., 1994,1995,1996,1998, 1999; Allison et al., 2002; Cowell & Phillips, 2002; Coppieters et al., 2003; Sterling et al., 2010). Studies that used the lateral glide directed away from the side of symptoms have consistently reported a reduction in pain on at least one outcome measuring pain (Vincinzino et al., 1995, 1996, 1998; Allison et al., 2002; Cowell & Phillips, 2002; Coppieters et al., 2003; Sterling et al., 2010).

Level of glide

Mobilising the fifth relative to the sixth cervical vertebrae was the most consistently used level for applying the lateral glide (Vincenzino et al., 1995, 1996, 1998, 1999; Cowell & Phillips, 2002; Coppieters et al., 2003; Saranga et al., 2003; McClatchie et al., 2009; Sterling et al., 2010). There was limited justification for using this level. The reason for using this level was unclear. A low level of evidence indicated that the largest amplitude of mid to lower cervical spine motion occurred between the fifth and sixth vertebrae in normal movement (Bogduck & Mercer, 2000; Wu, 2010), therefore it might be possible that mobilisation to this level had the greatest impact on

mechanoreceptor stimulation. It has been theorised that an increased afferent input from mechanoreceptor stimulation might result in greater changes to spinal cord hyper excitability leading to an increased stimulation of the PAG resulting in an increased descending cortical control pain inhibition (Schmid et al., 2008).

Intervention parameters

Most of the earlier work relating to the lateral glide technique did not specify duration or depth of mobilisation. These parameters have been specified in more recent publications, but have been variable. Vincenzino et al. (1996, 1998, and 1999) used 30 second mobilisations at grade III (large amplitude, through range oscillations); while McClatchie et al. (2009) used 120 seconds at grade IV (small amplitude, end range oscillations). There were no explanations to justify dose of treatment and no clear indications whether fewer or more mobilisations affected outcomes. The mean duration of treatment, across studies, was 60 seconds and the most frequently used grade of mobilisation was grade III.

Therapist's hand position

There was some inconsistency in the placement of the therapist's hands on the patient. Some studies described the therapist as supporting the head and neck (at the level to be treated) with the hand delivering the mobilisation to deliver a pulling-type of mobilisation to the neck (Vincenzino et al., 1995, 1996, 1998; Cowell & Phillips, 2002; Coppieters et al., 2003). Sterling et al. (2010) modified this approach to support the head with one hand and apply the glide with the other hand, thereby creating a more pushing-type mobilisation. Sterling et al. (2010) hypothesised that the placement and pressure of the whole hand contacting the symptomatic side had

the potential to add therapeutic advantage in terms of pain modulation. This could be due to the increased stimulation of mechanoreceptors in the anterior and lateral cervical muscles, which are known to be densely populated with muscle spindles (Boyd Clarke et al., 2002), as well as a greater stimulation of the cutaneous afferents in the skin (Sterling et al., 2010). The increased stimulation could create a larger effect on the central pain mediating mechanisms (Section 4.2.2).

Positioning of patient

In all but one of the studies that evaluated lateral glide (Saranga et al., 2003), the technique was performed on patients in the supine lying position. Some studies positioned the patient's arms in more abducted (out to the side) positions (Vincenzino et al., 1995, 1996, 1998), whilst others rested the patients arm on their abdomen (Allison et al., 2002; Cowell and Phillips, 2002). One study had the arm either on the abdomen or in more abducted positions, depending on the patient's level of pain (Coppieters et al., 2003). It has been reported that sustained stretch positions to mechanically sensitised nerve tissue (such as an abducted arm position) should be avoided due to the vascular compromise to the nerve tissue (Julius et al., 2004).

4.2.4 Methods to evaluate the lateral glide mobilisation on cervicobrachial pain in clinical studies

Clinical studies that evaluated medium-term and long-term effects of intervention on cervicobrachial pain used the lateral glide in conjunction with other manual therapy (Allison et al., 2002; Ragonese et al., 2009). Since the glide technique was part of a package of treatment involving other manual therapy approaches, the effect of the lateral glide was completely confounded with any effect of that 'package'.

Consequently, no conclusions about effectiveness of the lateral glide may be drawn using findings from these studies.

To evaluate effectiveness of the lateral glide, a control, placebo treatment or comparative intervention could be used. The advantage of a no-treatment control is reported to eliminate most extraneous variables that could confound results of a study (Sim & Wright, 2000); however there were ethical issues of withholding treatment particularly when a study was to take place over a long period of time (De Deyn, 2000). Placebo interventions were considered, including a 'sham' mobilisation whereby the physiotherapist could support the neck and head as if to deliver the lateral glide, but not add the mobilisation. However, it has been stated that placebos are ineffective when they are distinguishable, in any way (which would be the situation in the proposed trial) (Hróbjartsson & Boutron, 2011). This could explain the differences across some of the results that used placebo to evaluate the effectiveness of the lateral glide on the immediate effects of pain (Table 4-1). An alternative was to provide a comparative intervention. A comparative intervention that could be used across both trial groups would effectively act as a 'control' to the lateral glide mobilisation.

There was moderate evidence that self-management enables patients to understand and manage their condition, sustaining health in a cost-effective way (Hurwitz et al., 2008; Patel et al., 2009). Self-management was considered a viable across-group intervention. Given that the systematic review in Chapter 3 highlighted that manual therapy and exercise and behavioural change might be an effective means for

managing cervicobrachial pain, it was considered appropriate to use an 'exercise with behavioural change' approach as the basis for self-management.

Comparative interventions: self-management approaches

The systematic review in Chapter 3 found moderate evidence that behavioural change intervention was effective in reducing pain in the long-term for patients with cervicobrachial pain (Bernnards et al., 2007). Bernnards et al. (2007) delivered behavioural change as a group-based intervention. Group-based interventions have been used in other cervicobrachial studies, for example, Klaber-Moffett et al. (1990) used a group-based education session in their study. However, it was unclear whether a group-based approach is preferable to a one-to-one approach. A potential disadvantage of group intervention is that it needs adequate numbers of patients per group to be a realistic option. Hence, it was anticipated that the provision of group intervention for cervicobrachial pain might not be viable. Alternatives were to use audio-visual aids or an information booklet.

A literature search was conducted from inception to December 2006, to establish what patient information sources were already available. The search used electronic databases and key words (Section 2.1) as well as general search engines (Google and Yahoo). The search found a DVD 'Treat your own neck and arm pain' (2004). This DVD focused on an exercise approach, with little consideration given to behavioural therapy. The search was widened to include all neck pain categories. Two booklets: 'Treat your own neck' (McKenzie, 1983) and 'The Neck Book' (Waddell et al, 2004) were identified. The 'Treat your own neck' book follows an exercise and advice approach. Whilst it provided some information on cervicobrachial symptoms,

little attention is given to behavioural modification. This reflected that little was known about the value of psychosocial aspects relating to neck pain around the time the DVD was produced and the booklet written. 'The Neck Book' was clearly written and encompassed some aspects of behavioural therapy, exercises and advice; however the information was generic to neck pain and had few references to arm symptoms. For cervicobrachial pain sufferers, a significant proportion (50%) of pain relates to the arm (Daffner et al., 2003). None of the information sources were considered appropriate for the management of cervicobrachial pain.

Development of a self-management booklet

There was a low level of evidence, from a number of small studies that written information is an effective means of delivering information (Jull et al., 2008; Haines et al., 2010; Jack et al, 2010). The author decided to produce a booklet for the purpose of use in the trial that encompassed three key sections: behavioural change, home exercise and advice.

Behavioural changes related to posture, workplace, breaks and coping, which was consistent with the study by Bernaards et al. (2007). The coping component adopted a cognitive behavioural approach where the patient worked with the therapist to identify problems and seek solutions. This approach had been documented to be important in managing pain (Morley et al., 1999; McCracken & Turk, 2002; Bosy et al., 2009; Hansen et al. 2011).

The home exercise component was more difficult to determine as it was unknown which exercises were the best to combine with manual therapy. Studies in the systematic review that included home exercise in conjunction with mobilisation used

cervical and shoulder range of motion and cervical stabilising exercises (Allison et al. 2002; Walker et al. 2008).

Advice was frequently reported as a means to manage cervical conditions. Advice on staying active, relaxation and self-help strategies was based on limited findings from small, low quality cervicobrachial studies (Kogstad, 1978; Krapac et al, 1992).

The design of the 'Self-treatment for neck and arm pain' booklet was developed in accordance with guidelines from the Department of Health (2003). Diagrams used from copyrighted texts were granted permission for use. The production and funding of the booklet was agreed at the Trust at the main trial site. The process of developing the booklet involved three stages. In the first stage, the booklet was reviewed by two academic researchers and two clinical specialist physiotherapists who advised about content and layout. In the second stage, a convenience sample of patients with cervicobrachial pain in a clinical setting (n=10) provided verbal and written feedback on their own experience of using the booklet (Table 4-4).

Table 4-4 Feedback from patents about the self-management booklet

Positive comments	Comments requiring change
Easy to follow, self-explanatory	Take out the bit about going to the gym – I find it off-putting
Clear and concise	
Everything in the leaflet is bang-on	Can I use an ice pack instead of heat as I find ice helps me more?
I'm not having any problems using it at all	
I found the leaflet easy to use	
This book explained why I experience neck and shoulder pain	

Recommendations largely related to alterations in grammar and layout. In addition, the section on using heat was changed to using heat and cold and the 'use of a gym' was replaced by 'other forms of exercise to improve fitness'. This process informed the third and final stage. This was piloted in the preliminary study, detailed in Chapter 5 (Section 5.17.5). The development for this booklet was supported by the Hospital Trust at the main trial site, and has since been adopted by the Trust as part of standard practice in the management of cervicobrachial pain.

4.3 Summary for existing interventions for cervicobrachial pain

There was moderate evidence to support that the lateral glide could have an immediate hypoalgesic effect on pain. It was acknowledged that the majority of supporting evidence came from studies on patients with musculoskeletal conditions other than cervicobrachial pain. However, all studies were on subjects who had pain either in the neck or arm region making it plausible that these findings might be transferable to patients with cervicobrachial pain.

A comparative intervention was required to evaluate the effectiveness of the lateral glide. The self-management approach was identified as the most suitable comparator. There were concerns that delivering the self-management intervention in a group setting was not feasible. Existing audio-visual and written tools were not assessed to be suitable. This led to the development of a new self-management booklet, based on current evidence at the time of designing it.

Chapter 5 will discuss how the intervention modalities identified in this chapter are integrated into a randomised clinical trial to evaluate the effectiveness of the lateral glide mobilisation on cervicobrachial pain. (Appendix E)

5 DESIGN AND METHODS FOR THE CLINICAL TRIAL

5.1 Methods used in clinical trial

Chapter 3 identified a need to assess the effectiveness of lateral glide mobilisation for patients with cervicobrachial pain. This chapter details the methods used in a clinical trial to investigate effectiveness of the lateral glide mobilisation in the management of cervicobrachial pain.

An overview of different methods that were considered and a rationale for the selected approach are presented, together with an account of preparatory studies (including an audit of an NHS Hospital Trust in the West Midlands and a preliminary study) that were used to inform the final design and methods for the main trial. The design and methods are reported in line with guidance from the Consolidated Standards of Reporting Trials (CONSORT) statement (Schulz et al, 2010), to ensure coverage of all relevant information.

5.2 Trial objectives

The aim of this trial was to investigate whether a self-management intervention with lateral glide mobilisation was more effective than a self-management intervention on its own for participants with cervicobrachial pain.

The primary objective was:

To establish the long-term effectiveness of the lateral glide mobilisation in reducing pain, for patients with cervicobrachial pain.

Secondary objectives were:

i) To assess the short-term effectiveness and longitudinal effectiveness (over 12 months) of the lateral glide mobilisation to reduce pain.

ii) To assess the longitudinal effectivenss (over 12 months) of the lateral glide mobilisation to improve function and disability.

iii) To evaluate short-term cost-effectiveness of the lateral glide in terms of work absenteeism and utilisation of physiotherapy resources.

iv) To identify short-term risk of harm associated with the lateral glide mobilisation.

v) To explore whether participants with a dominant neuropathic mechanism of pain respond differently from the lateral glide than those without a neuropathic mechanism in the short-term.

vi) To explore whether participant preference was associated with outcome in the short-term.

5.3 Trial design

A prospective, randomised controlled trial (RCT) was conducted, with participants randomised to one of two groups: a lateral glide and self-management intervention (Mobilisation group) or self-management intervention alone (Comparator group). The primary outcome measure was change in perceived pain as indicated using a visual analogue scale, with a clinically meaningful difference taken as 20mm. Assessments were made on four occasions (at baseline prior to intervention and at 6, 26 and 52 weeks post the first intervention session). The 52 week follow-up was the primary end point to establish the long-term effect on the primary outcome (pain). The design included key features such as allocation concealment, blinding of assessors, and randomisation of participants to groups (Schulz et al., 2010). The key stages of the trial are summarised in Figure 5-1.

A prospective RCT was selected for the trial design to establish a cause-effect relationship of lateral glide mobilisation on cervicobrachial pain (Sibbald & Roland, 1998) whilst minimising the potential influence of bias and chance (Sim & Wright, 2000). Participants in the Comparator group received the self-management intervention alone. Participants assigned to the Mobilisation group received the self-management intervention and the lateral glide intervention. This design enabled between-group differences to be attributed to the addition of the lateral glide mobilisation in the Mobilisation group. Self-management has been demonstrated to be an appropriate intervention for cervicobrachial pain, making it a suitable comparative intervention in this trial (Section 4.2.4).

The selected design can be described as a pragmatic trial (Hotopf, 2002; Patsopoulos, 2011). Pragmatic trials have been reported to be a realistic compromise between observation studies (which have good external validity and poor internal validity) and conventional RCTs (which have good internal validity and poor generalisability) (Hotopf, 2002, Godwin et al., 2003; Patsopoulos, 2011). They are an appropriate design to assess intervention for use within a clinical setting (Wakefield, 2000) and are able to provide convincing evidence to practising clinicians (Wakefield, 2000; Godwin et al., 2003; Howick, 2009; Patsopoulos, 2011; Tonelli, 2012).

A preliminary study was conducted to evaluate the selected methods and to identify changes that could improve the quality of the main trial (Lancaster et al., 2004; Loscalzo, 2009; Aran et al., 2010; Cocks & Torgerson, 2013). Details of the preliminary study are reported in Section 5.17. Data from the preliminary study informed a power calculation to determine the sample size that was required for the main trial, to ensure adequate precision of the estimated treatment effect for the primary outcome measure (Lancaster et al., 2004; Carroll et al., 2008; Cocks & Torgerson, 2013).

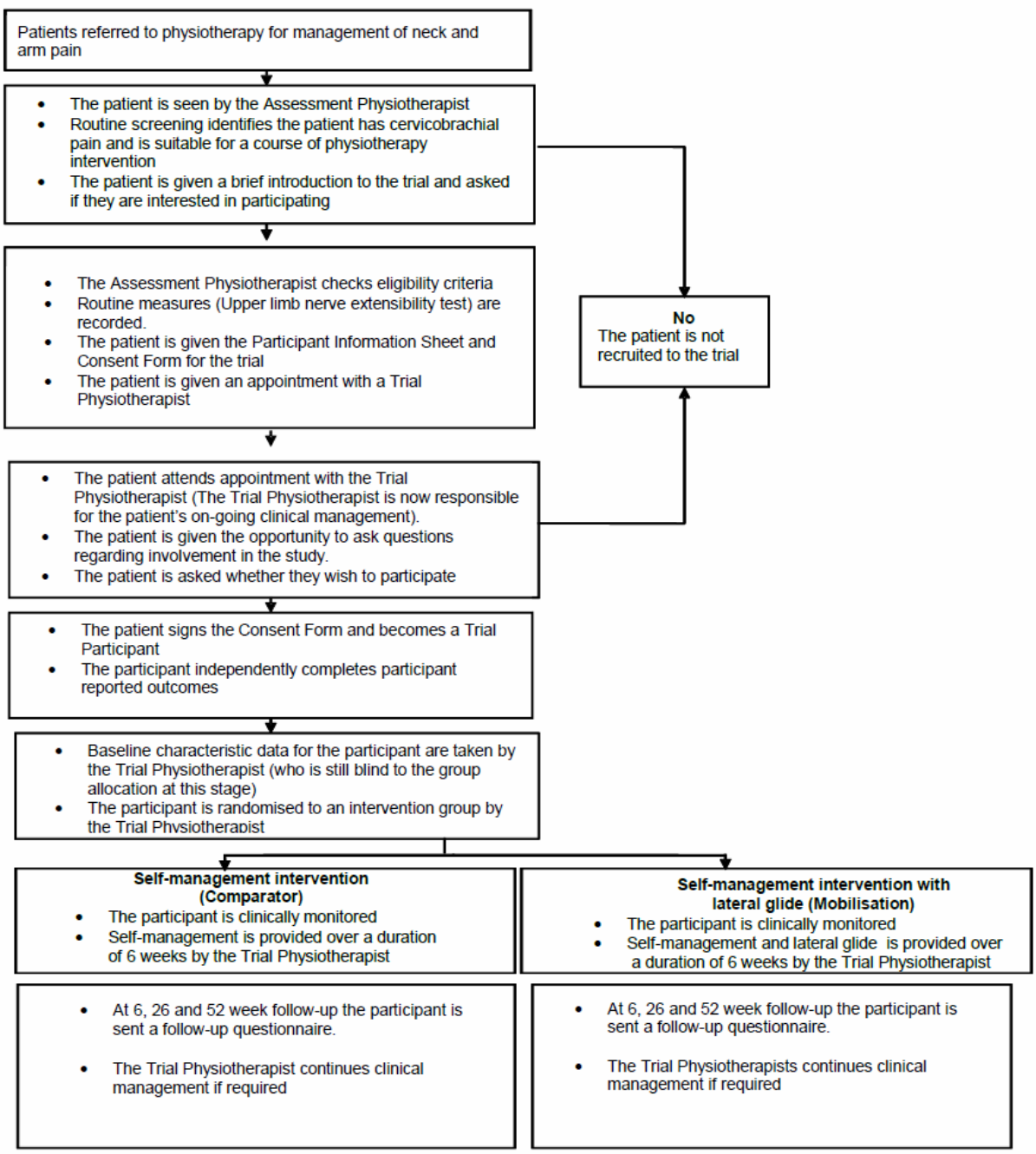


Figure 5-1: Key stages in the trial to assess effectiveness of the lateral glide with self-management compared to Self-management alone

5.4 Trial participants

All prospective participants were assessed by an Assessment Physiotherapist. In this trial, Assessment Physiotherapists were advanced musculoskeletal physiotherapists (band 7 or 8) working in the National Health Service. Physiotherapists working at these grades are recognised as having highly developed assessment skills (NHS staff council, 2010), hence, ensuring that participants were screened against trial criteria as effectively as possible e.g. to eliminate co-existing pathology such as shoulder impingement. An Assessment Physiotherapist verbally informed potential participants that a clinical trial was being conducted to evaluate two comparative approaches of physiotherapy for neck and arm pain and ascertained whether they would be interested in participating. Those who were interested were screened by one of the Assessment Physiotherapists, using the following eligibility criteria.

5.4.1 Trial eligibility criteria

Potential participants were screened for eligibility against a set of eligibility criteria (Table 5-1).

Table 5-1 Participant eligibility criteria for trial

Inclusion	Exclusion
Aged 18 – 65 years experiencing cervicobrachial pain (San Román et al., 2002; O'Neil, 2003; Hestbaek & Stochkendahl, 2010)	Bilateral arm symptoms
Symptoms for greater than six weeks (Daffner et al., 2003)	Symptoms indicative of serious pathology (red flags): History of cancer, unexplained weight loss (4.5-6.8kg within two weeks or less), severe unremitting night pain, general malaise and constant unvarying pain (Goodman & Snyder, 2000; Carette & Fehildings, 2005; Moffett & McLead, 2006)
Adequate knowledge of English language	
Verbally consented to consider being involved in the trial and attend review appointments (Woolard et al., 2004)	Symptoms of vascular thoracic outlet syndrome (Bearn et al., 1993; Fassiadis et al., 2005; Fiorentini et al., 2005; Elman & Kahn, 2006)
	Co-existing musculoskeletal upper limb pathology (Lauder, 2002; Polston, 2007; Cannon, 2007)
	Systemic condition affecting nerve or joint function e.g. rheumatoid arthritis, multiple sclerosis (Williams et al, 2003; Goldenberg, 2010)
	Previous surgically invasive techniques to the neck (Fouyas et al., 2002; Carragee, 2008)
	Receiving (or planned to receive) alternative interventions for cervicobrachial pain
	Involved in litigation associated with cervicobrachial pain (Rasmussen et al., 2001; Rasmussen et al., 2008)
	Already involved in a research studies (Ulrich et al, 2005)

Rationale for the eligibility criteria is reported below. The criteria were restricted to those supported by clear evidence, since too many criteria could affect generalisability of a trial's findings (Van Spall et al., 2007; Moher et al., 2010).

Trial inclusion criteria:

Cervicobrachial pain

The main inclusion criterion was cervicobrachial pain defined as arm pain associated with cervical spine pain (Jull et al., 2008). The additional requirement of a positive upper limb nerve extensibility test was considered because all previous cervicobrachial pain studies using the lateral glide mobilisation had included nerve extensibility as a prerequisite (Allison et al., 2002; Cowell & Phillips., 2002; Coppieters et al., 2003; Ragonese, 2009). However, this trial aimed to include somatic referred, as well as, neurogenic radiating causes of the problem, as it was considered possible that somatic referred pain could be affected by mobilisation. This has since been supported in a publication by Jull et al. (2008). Hence, a positive upper limb extensibility test was not included as an inclusion criterion, but was recorded so that association between a positive test and outcome on pain could be explored.

Age

Eligible age range was specified as 18 to 65 years, inclusive. The lower age limit ensured that patients entering the trial had reached skeletal maturity (San Román et al., 2002; O'Neil, 2003). This was important since it was unknown whether manual therapy techniques on developing spines had the same outcome as on fully developed ones (O'Neil, 2003; Hestbaek & Stochkendahl, 2010). The upper age limit of 65 was selected because, in people over this age, there was low evidence that pain could be processed differently due to reduced psychosocial and physical pain modulation (Riley et al., 2000; Karp et al., 2008). Alterations in pain processing could

potentially affect response to trial intervention, particularly as the lateral glide is thought to affect pain through neurophysiological modulation and physical effect (Section 4.2.2). Most published clinical studies on cervicobrachial pain, at the time of planning the trial and more recently, had not included patients over the age of 65 (Howe et al, 1983; Klaber Moffett et al., 1990; Persson et al., 1997/2001; Allison et al., 2002; Coppieters et al., 2003; Bernaards et al., 2007; Walker et al., 2008).

Symptom duration

Patients were eligible if they had experienced symptoms for more than six weeks. There was a low level of evidence in the published literature that patients with symptoms of less than six weeks had a naturally good prognosis (Daffner et al., 2003; Vos et al., 2008; Kuijper et al., 2009), perhaps due to natural recovery occurring within this time (Boswell et al., 2007). There was a low level of evidence that cervicobrachial pain persisting for longer than six weeks had a less favourable prognosis (Daffner et al., 2003).

It was considered more appropriate to evaluate the effectiveness of the lateral glide when it was provided at a time when natural recovery was less likely to occur. Excluding acute presentations was consistent with several previous studies evaluating the lateral glide technique for cervicobrachial pain (Allison et al., 2002; Cowell and Phillips, 2002; Coppieters et al., 2003).

Language

All participants needed to have adequate understanding of written and spoken English to enable their comprehension of the Self-management Booklet and completion of the self-reported participant outcome measures.

Compliance

Patients were explicitly informed that the trial would continue for one year. They were included if they demonstrated a willingness to attend all follow-up assessments. The importance of information gathered at follow-up appointments was carefully explained to potential participants, since this approach had been reported to reduce attrition rate at follow-up (Woolard et al., 2004).

Trial Exclusion criteria:

Serious pathology.

It has been recognised that patients with serious pathology require urgent medical attention and, therefore, are usually unsuitable for physiotherapy intervention (Greenhalgh & Selfe, 2006). Although rare, some serious pathology may present with cervicobrachial pain, including Pancoast tumour (Vargo & Flood, 1990; Owen & Ameen, 1993), spinal metastasis (Vecht, 1990) and Cervical Potts disease (a form of tuberculosis) (Achouri et al., 1997). 'Red flags' comprise a collection of progressive symptoms that help to identify serious pathology of the spine (Goodman & Snyder, 2000; Carette & Fehildings, 2005; Moffett & McLead, 2006). They include a history of cancer, unexplained dramatic weight loss, severe unremitting night pain, constant unvarying pain and general ill health (Vecht 1990; Owen & Ameen, 1993; Goodman

& Snyder, 2000; Carette & Fehlings, 2005; Moffett & McLean, 2006; Binder, 2007; Nordin et al, 2008; Greenhalgh & Selfe, 2010). These criteria were used to exclude patients who could be exposed to increased risk if they were involved in the trial.

Bilateral arm symptoms

The lateral glide technique is a unilateral technique described as gliding away from the side of pain (Hall & Elvey, 1999; Vincenzino et al, 1994, 1995, 1998, 1999; Allison et al, 2002; Cowell & Phillips, 2002; Sterling et al, 2010). Hence, participants needed to have symptoms in one arm only. Patients with bilateral symptoms were not recruited to the trial.

Symptoms strongly suggestive of thoracic outlet syndrome

There was evidence to suggest that thoracic outlet syndrome was associated with an increased risk of thromboembolism (Bearn et al., 1993; Fassiadis et al., 2005; Fiorentini et al., 2005; Elman & Kahn, 2006) and that this was more likely to be associated with the vascular rather than neurogenic forms of the condition (Fugate et al., 2009). Consequently, Assessment Physiotherapists were informed to exclude patients with cervicobrachial pain that presented with signs and symptoms of vascular compromise. It was recognised that a level of vascular monitoring would have been required for these patients that was not within the scope of the trial protocol. It would also have been a confounding variable to include these patients.

Co-existing musculoskeletal upper limb pathology

Narrative texts have reported an association between cervicobrachial pain and co-existing upper limb pathology (Lauder, 2002; Polston, 2007). There was low evidence

from one prospective observational study (Cannon, 2007; n=191) that patients with cervicobrachial pain frequently have co-existing upper limb pathology. Shoulder impingement has been reported to be the most frequent co-existing condition with cervicobrachial pain ($p<0.001$) (Cannon, 2007). Clinically, multiple musculoskeletal conditions are managed collectively through numerous physiotherapy modalities, of which the lateral glide could be one. Adding additional treatment to address other pathology would have had the potential to confound results from the trial. Withholding additional treatment for a co-existing pathology would have been unethical (De Deyn, 2000). For these reasons, patients with known co-existing pathologies were excluded from the trial.

Systemic conditions affecting nerve or joint function.

Conditions such as multiple sclerosis or rheumatoid arthritis are progressive pathological disorders that impact on pain, physical and mental health (Williams et al, 2003; Goldenberg, 2010). Hence, including these conditions could have had a negative impact on outcome and confounded results.

Previous cervical spine surgery.

Surgery structurally alters cervical mechanics and has the potential to interfere with normal anatomical and physiological processes (Fouyas et al., 2002; Carragee, 2008). The lateral glide technique is thought to affect pain by affecting cervical mechanics and changing pain by influencing physiological processes (see Section 4.2.2).

Alternative management

Other interventions to manage cervicobrachial pain could have affected outcome and confounded results from the proposed trial. Patients were excluded when there was a known plan for alternative intervention e.g. surgery or injections.

Involvement in litigation issues regarding cervicobrachial pain.

There was moderate evidence that involvement in litigation has compounding effects on prognosis and outcome in conservative management of cervicobrachial pain (Rasmussen et al., 2001; Rasmussen et al., 2008) (Section 2.4.5). Hence, patients involved in litigation were excluded from the trial.

Current involvement in another clinical study.

Additional commitments are often required by patients who are involved in clinical studies. It was considered important not to cause additional burden for individuals who were already participating in a research study elsewhere (Ulrich et al, 2005). Hence, potential candidates who were involved in other clinical studies were excluded.

5.4.2 Consenting process used in clinical trial

A patient with cervicobrachial pain and who matched the eligibility criteria (i.e. a potential trial participant) was informed about the trial by an Assessment Physiotherapist. The information provided by Assessment Physiotherapists was standardised to reduce the potential for bias during this information giving process (Buckley et al., 2007; Junghans & Jones, 2007). The information covered what

participation would involve (including a description of the two interventions), data collection time frames, the number of follow-up appointments required, the consenting process, and the option to withdraw at any time without any consequences for their treatment.

A potential participant who was interested in taking part was given detailed, written information about the trial (Appendix C) by the Assessment Physiotherapist.

A physiotherapy appointment was made with a Trial Physiotherapist, who would be providing the intervention. Trial Physiotherapists were band 6 clinical musculoskeletal physiotherapists. Band 6 physiotherapists are considered to have the necessary skills to deliver manual and self-management interventions effectively (NHS staff council, 2010). When a potential participant attended the first appointment with the Trial Physiotherapist, the Trial Physiotherapist ascertained whether the potential participant remained interested in being involved in the trial and/or required further clarification about participation. This was achieved by inviting the potential participant to ask questions and providing further clarification to them, as required. The aim of this process was to ensure each participant had been fully informed, as far as possible, prior to commencing the trial (Knifed et al., 2007; Singh, 2008). Arguably, the process of seeking consent could have influenced the way that a potential participant responded to intervention (Sim & Wright, 2000). However, to fulfil ethical requirements, individuals have the right to be fully informed before making a decision about participation (Nuremberg Code, 1949).

Patients who declined to participate in the trial continued to receive their physiotherapy care (from the Trial Physiotherapist) as per standard practice. Patients

wishing to be involved in the trial signed a consent form (Appendix C) and became a trial participant.

To address consistency, all Trial Physiotherapists were trained on the consenting process by the Principal Investigator. This was in line with the Good Clinical Research Practice Guidelines (2002).

5.5 Ethical approval and registration for preliminary study and main trial

Obtaining ethical approval prior to commencing a clinical research study is a legal requirement in the United Kingdom for all studies that involve human subjects (Central Office for Research Ethics Committees (COREC), 2000; National Research Ethics Service (NRES), 2009). Formal approval is designed to protect the rights, safety and dignity of research participants (COREC, 2000; National Patient Safety Agency, 2009). Before commencement of both the preliminary study and the main trial, approval was obtained from South Staffordshire Local Research Ethics Committee: preliminary study reference number (06/Q2602/50); main trial reference number (09/H1203/45) (Appendix D).

The preliminary study and the main trial were registered, independently, with "Current Controlled Trials" (http://www.controlled-trial.com): preliminary study (ISRCTN87397856); main trial (ISRCTN62431186). Trial registration was important to enable transparency of the planned methods from the outset (Riis, 2000; Moher et al., 2010). The World Health Organisation has stated that "the registration of all

interventional trials is a scientific, ethical and moral responsibility" (www.who.int/ictrp/en; Accessed 14 July 2009).

5.6 Funding for main trial

An application for Elsevier Research Award was successful, and an award of £2000 was given by the Manipulation Association of Chartered Physiotherapists (now the Musculoskeletal Association of Chartered Physiotherapists) in December 2009 for the costs of the cervicobrachial pain trial.

5.7 Settings and locations of trial

The trial was located in the United Kingdom (UK). Involvement in research has been recognised as important to the National Health Service (NHS) as it drives innovation and develops high standards of patient care (National Institute for Health Research, 2013). The NHS, therefore, was an appropriate setting in which to conduct the trial.

5.8 Trial interventions

The primary aim of the trial was to evaluate effectiveness of the lateral glide mobilisation. Both groups in the trial received a self-management intervention and one group also received lateral glide mobilisation.

Participants were randomised to one of two groups that were identified as:

- Self-management only (Comparator)
- Lateral glide mobilisation with self-management (Mobilisation)

Interventions (as per randomised group) were provided for up to a maximum of six weeks (the intervention period), regardless of group allocation. Intervention

commenced at the first visit to the Trial Physiotherapist. It was difficult to determine the optimum dose (number and frequency) of self-management or mobilisation interventions in this trial. No consistent dose of treatment for either intervention had been identified in previous cervicobrachial pain studies (Section 3.2.3). An electronic literature search (using methods described in Section 2.1) from inception to January 2009 identified no literature to identify an optimum dose of non-invasive intervention for cervicobrachial pain. Information was also limited for neck pain generally. Mean values reported for the optimum number of interventions to achieve clinical effectiveness in neck pain ranged from 2.78 (SD 4.55) (Klaber-Moffett et al., 2005) to 6.4 (SD 5.4) (Skargren et al., 1998). There were no reported figures for frequency of interventions (chiropractic and physiotherapy treatment). A pragmatic approach was adopted for this trial, with the Trial Physiotherapist and participant jointly determining the amount of intervention, as per standard practice in the participating sites involved in the clinical trial.

5.8.1 Self-management intervention

Participants in both intervention groups received a self-management booklet, specifically developed for the trial, as described in Section 4.2.4 (Appendix E).

A Trial Physiotherapist discussed each section of the booklet with a participant to ensure understanding of the booklet's content (RAND group, 2007). The participant was taught the exercises and given opportunity to practise them under supervision of the Trial Physiotherapist. The Trial Physiotherapists were requested to spend a consistent time on the booklet with each participant. This was important to ensure, as far as possible, that provision of self-management was delivered equally across

trial groups, so that any between-group differences could be attributed to the lateral glide mobilisation.

5.8.2 Lateral glide intervention

In addition to the self-management intervention, the Mobilisation group received lateral glide mobilisations. Justification that the lateral glide could be considered a legitimate approach was given in Section 4.2.

The lateral glide mobilisations were performed with the patient in a supine position, with the glide directed away from the side of pain, for duration of 60 seconds and for three repetitions (Figure 5-2). A grade III mobilisation was used to aid consistency in the delivery of the technique. The rationale for choosing this dose was to align with evidence in previous research (Section 4.2.3). Each participant was treated by the same Trial Physiotherapist on each treatment session to align with standard practice at the participating site in the trial.

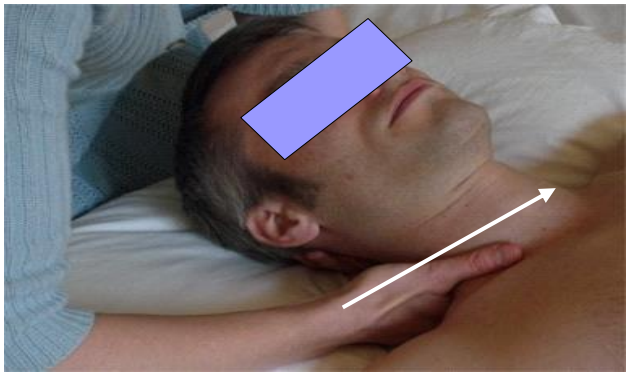


Figure 5-2: Lateral glide mobilisation technique for right cervicobrachial pain

Footnote: The arrow shows the direction of movement

5.8.3 Intervention period used in trial

The intervention period was defined as the first six weeks following commencement of intervention. Participants who elected to return for subsequent appointments during this period were given the opportunity to check aspects of the self-management booklet (to ensure that the exercises and advice had been correctly interpreted) and, if assigned to the Mobilisation group, to continue with the lateral glide mobilisation intervention. When the participant, in conjunction with the Trial Physiotherapist, decided that no further appointments were necessary, the participant was placed on an 'open' appointment until the first follow-up appointment (six week follow-up). An open appointment enabled a participant to return for further intervention (as per randomised protocol) during the intervention period (i.e. up to the sixth week post baseline). The Trial Physiotherapists were informed not to add additional treatment modalities during the intervention period (Section 5.8) because such addition might confound any effect of the lateral glide therapy, thereby, reducing the power to detect its short-term effect. As the trial treatment did not extend beyond the intervention period (six weeks post baseline), it was considered unethical to discourage any additional treatment beyond this point. It was accepted, therefore, that additional treatment beyond the short-term (six week follow-up) was permitted as this was standard practice at the participating trial site. Additional treatment was recorded at follow-up appointments as involving 'more physiotherapy/osteopathy etc.', 'acupuncture', 'injections to the cervical spine', 'cervical spine surgery' or 'a combination of treatment'. Consideration was given to recording the quantity of additional treatment; however, some additional treatment could have been provided off-site making it difficult to obtain reliable information.

5.8.4 Trial Physiotherapists

The Trial Physiotherapists delivering the intervention were Band 6 musculoskeletal physiotherapists. A Band 6 physiotherapist is considered to have sufficient skills to deliver manual and self-management interventions effectively (NHS staff council, 2010). Trial Physiotherapists were not masked to allocation (this was not feasible due to the nature of the interventions) which might have led to performance bias (Geddes, 2009). This has been recognised as a frequent issue in pragmatic studies (Godwin et al., 2003). To reduce performance bias as much as possible, Trial Physiotherapists were screened out of the trial if they declared a strong preference on how cervicobrachial pain should be managed. Minor preferences were recorded at the start of the trial. Preferences at the end of the trial were recorded to determine whether the therapists had changed their opinions over the duration of their involvement in the trial.

5.8.5 Standardisation of intervention for the Trial Physiotherapists

A half-day training session was provided to all Trial Physiotherapists, during which they were given a copy of the trial protocol (Appendix F), instructed on the use of the self-management booklet and taught the lateral glide technique, and asked not to add additional interventions during the intervention period. The Principal Investigator taught the lateral glide treatment to all Trial Physiotherapists, to ensure consistency of training. Each Trial Physiotherapist practised the technique until the Principal Investigator assessed that they could demonstrate a standardised application of the technique.

The half-day training session on the manual therapy technique and behavioural intervention was shorter than training sessions reported in other research studies (Curtis et al., 2000; Lamb et al., 2010). The reason was that the lateral glide mobilisation was a single technique and the behavioural intervention (in the self-management booklet) was within the scope of standard physiotherapy practice (Thacker & Gifford, 2005). In contrast, in the study by Curtis et al. (2000), generalist physicians (who would not usually deliver manual therapy) were trained to deliver mobilisation techniques and, in the study by Lamb et al. (2010), nurses, physiotherapists and psychologists were trained to provide six sessions of group cognitive behavioural therapy using a range of techniques (e.g. guided discovery) that would have been unfamiliar to some of these professionals.

Six-monthly update training sessions were repeated for the Trial Physiotherapists during the recruitment phase, to ensure that standardisation of intervention was maintained. No guidance was found recommending the frequency of repeat training sessions. It was decided that six months was practicable to fit with the time requirements of the participating therapists.

5.9 Assessment periods during the trial

Assessment for the main trial was at baseline and at follow-up intervals 6, 26 and 52 weeks from baseline. A questionnaire was sent to patients comprising outcome measures at each follow-up time point. A postal method of data collection was selected over an appointment as it had been reported that participants with symptom resolution were less likely to attend follow-up appointments (Dawson et al., 2010).

The initial follow-up at six weeks represented the short-term post-intervention effects. Six weeks was selected to represent the end of the intervention period, based on participants receiving up to six, weekly appointments. Six or fewer appointments had been identified in the literature as the mean number of appointments needed to achieve clinical effectiveness in neck pain (Klaber-Moffett et al., 2005; Skargren et al., 1998).

The 26 week follow-up represented a mid-point review that evaluated change between the short-term and long-term outcomes, to provide more detailed, longitudinal information on intervention effects. The 52 week follow-up was the primary end point in this trial, in-line with other cervicobrachial studies (Walker et al., 2008; Ragonese et al., 2009) – enabling a comparison of findings. Long-term outcomes have also been reported as being important to justify the efficacy of treatment modalities used in neck pain (Hurwitz et al., 2008) and for chronic musculoskeletal conditions (Derry et al., 2012). The effects of manual therapy on cervicobrachial pain in the short (6 weeks) and long-term (52 weeks) also reflects assessments of clinical interest in previous studies (Persson et al., 2001; Bernaards et al., 2007; Walker et al., 2008; Kuijper et al. 2009).

5.10 Baseline measurements of trial participants

Baseline measures on participant characteristics were recorded at the start of the trial. This established how representative the study cohort was, to determine generalisability (Burgess et al., 2003; Moher et al., 2010).

5.10.1 Demographic baseline data

Key demographic data included age and gender. These variables had previously been identified (with a moderate level of evidence) to predispose or be associated with the development of cervicobrachial pain (Finocchietti & Trindade,1973; Kostova & Koleva, 2001; Kaki, 2006). Additional information included smoking status and occupational status, which have been associated (a low/ very low level of evidence) with cervicobrachial pain were collected (Finocchietti & Trindade, 1973; Krapac, 1989; Sauter et al., 1991; Kostova & Koleva, 2001). Details on absence from work due to cervicobrachial pain were included as a baseline measure for cost analysis.

5.10.2 Clinical baseline data

Key clinical data included pain scores (using a VAS scale), as the primary outcome measure (Section 5.11.1). Psychosocial well-being (SF36, mental component) and level of chronicity both had a moderate level of evidence to support their association with prognosis (Sheather-Reid, 1998; Persson & Lilja, 2001; Daffner et al, 2003, Bot et al. 2005) and, therefore, were important to assess at baseline. Any history of whiplash associated disorder (WAD) and the distribution and type of symptoms were also assessed because of their potential relevance when interpreting results from the trial.

5.10.3 Identification of participants with a dominant neuropathic pain state and mechanical nerve sensitivity

A secondary objective of this trial was to explore whether a neuropathic pain state or mechanical nerve sensitivity affected outcome on pain response to intervention. Identification of neuropathic pain was made using the The Self-report Leeds Assessment of Neuropathic Signs and Symptoms (S-LANSS) questionnaire

(Bennett, 2001; Bennett et al., 2005; Bennett et al., 2006; Jensen, 2006), while nerve mechanosensitivity was identified using the upper limb nerve extensibility test (ULNE) (Wainner et al., 2003).

The Self-report Leeds Assessment of Neuropathic Signs and Symptoms (S-LANSS) questionnaire was developed to identify neuropathic dominant pain states (Bennett, 2001), and its scores range from 0 to 24, with a score of 12 or more represented a "probable" neurogenic cause (Bennett, 2001; Bennett et al., 2005; Bennett et al., 2006; Jensen, 2006). There was a low level of evidence that S-LANSS had better reliability than other pain assessment tools, such as the Neuropathic Pain Scale, to identify patients with chronic neuropathic pain (Jensen, 2006).

The upper limb nerve extensibility test (ULNE) is a physical measure used to identify whether patients with cervicobrachial pain have mechanical nerve sensitivity (Figure 5-3). This test has been used as a prerequisite in studies investigating manual therapy intervention on neurogenic cervicobrachial pain (Allison et al., 2002; Cowell & Phillips., 2002; Coppieters et al., 2003; Ragonese, 2009). In this trial, participants with both neurogenic (i.e. those with a positive ULNE test and scores on S-LANSS of 12 or higher) and somatic cervicobrachial pain were included to provide a comparison of findings across these two sub-groups and a comparison of findings for the neurogenic sub-group with those from previous studies on that sub-group.

Figure 5-3: Picture to show the application of the upper limb nerve extensibility test (ULNE)

There was low evidence to support the accuracy of ULNE for diagnosing neuropathic cervicobrachial pain (Rubinstein et al., 2007). The test was defined as positive when symptoms were reproducible or when there was a reduction in elbow extension by greater than 10° compared to the asymptomatic side (Wainner et al., 2003). The approach described by Wainner et al. (2003) (resulting in either a positive or negative test) has greater reliability and smaller measurement error than using a goniometer to measure range of elbow extension, as used previously (Coppieters et al., 2003).

Standardisation of how Assessment Therapists applied the Upper limb nerve extensibility test

The ULNE was a physical baseline measure (unlike other baseline measures in the trial), consequently, training was conducted to ensure that the ULNE was used and interpreted in a consistent way. The Principal Investigator taught Assessment Physiotherapists how to perform and interpret the test (i.e. what would constitute a positive test) for use in the trial. Assessment Physiotherapists practised the technique until they were able to demonstrate its application and could verbally

support what they would classify as a positive test. The method of applying the test was written on the assessment sheet as a reminder to all Assessment Physiotherapists on how to conduct the test. Follow-up training was done at six monthly intervals during the course of the trial.

5.10.4 Identification of patient preference for trial intervention

A secondary objective in this trial was to explore whether patient preference affected outcome on pain response to intervention. It was recognised that participants with a preference for one of the interventions might bias the trial positively if they believed that they had received the more effective treatment, or negatively if they believed that they had received the less effective treatment (Brewin and Bradley 1989; Klaber-Moffett et al., 1999; Klaber-Moffett et al. 2005; Adamson et al., 2008). Asking for patient preference at baseline enabled post trial consideration to be made on whether preference was associated with change on the primary outcome measure (Adamson et al., 2008). This approach has been used in previous RCTs within physiotherapy research (Klaber-Moffett et al., 1999; Klaber-Moffett et al. 2005).

5.11 Outcome measures used in trial

Selection of appropriate outcome measures was based on recommendations from the International Classification of Functioning, Disability and Health (ICF) framework (World Health Organisation, 2002) and supported by the CONSORT group (Moher et al., 2010).

5.11.1 Primary outcome measure - Pain

VAS

The primary outcome measure was pain perception measured on a visual analogue scale (VAS). Pain is the key feature of cervicobrachial pain (Jull et al., 2008). A high level of pain perception leads to increased disability and reduced function, having an adverse effect on health and wellbeing (Daffner et al., 2003). Consequently, pain has been the single most consistently used outcome across all studies evaluating effectiveness of intervention on cervicobrachial pain.

Pain is an inherently subjective measure. Self-report outcome measures have been considered a clinically relevant and reliable means for assessing pain perception (Dworkin et al., 2005; Dawson et al., 2010) and have been used consistently in previous studies to establish effectiveness of interventions to manage cervicobrachial pain (Howe et al., 1983; Klaber Moffett et al., 1990; Persson et al., 1997; Persson & Lilja, 2001; Allison et al., 2002; Coppieters et al., 2003; Bernaards et al., 2007;Walker et al., 2008; Kuijper et al., 2009; Ragonese, 2009, Young et al., 2009). The visual analogue scale (VAS, using a 10 centimetre line, scaled 0 -100) was selected as the primary outcome measure in this trial. This intensity scale has been used frequently to assess pain perception in research studies (Dworkin et al., 2005). Numerical and verbal rating scales were considered, however, it has been reported that previous responses on these scales are easier to remember than on a VAS and, therefore, could have had a greater potential for recall bias across time points (Petrou et al., 2002; Dodonco McDonald, 2008). Hence, a visual analogue scale was used in this trial.

The visual analogue scale for pain VAS (pain) has good reported construct validity for this patient population when compared to the McGill questionnaire (van Kleef 1996; Allison et al., 2002) and responsiveness to change in pain to interventions for cervicobrachial pain at six weeks ($p<0.01$) (Walker et al., 2008; Kuijuper et al., 2009), and at one year ($p=0.000$) (Walker et al., 2008).

This trial used two visual analogue scales. Each scale comprised a 100mm horizontal line marked “no pain” at 0 and “worst pain imaginable” at 100 (hence, higher scores related to higher pain perception). Participants were asked to mark a cross on each scale to indicate the intensity of their pain. One scale represented worst pain in their neck and arm, and a second scale represented average pain in their neck and arm. Both scales were representative of pain over the preceding week. There was low evidence to support using ‘worst’ and ‘average’ pain on VAS over a proceeding week (Persson et al., 1997; 2001; Allison et al., 2002; Bolton et al., 2010). In addition, VAS pain scales have been used in this way by other cervicobrachial studies (Persson et al., 1997; 2001; Allison et al., 2002).

Global rating of change score

The Global Rating of Change score (GROC) provided an overall perception of change in pain, ranging from -6 (a great deal worse from baseline) to +6 (a great deal better from baseline); with 0 indicating no change (Jaeschke et al., 1989; Michener et al. 2013). GROC provided information relating to patient self-perceived change in pain, therein indicating a participant’s value of interventional effect. This has been reported to be an important consideration when interpreting study findings (Balsham et al., 2011; Guyatt et al., 2011a). Other versions of global rating of change scores

were considered, including those with fewer and more points; however the 13-point scale has been validated for use in upper limb disorders, has established clinically meaningful differences for this population (Jaeschke et al., 1989; Mitchener et al. 2013).

Assessment of pain medication in conjunction with VAS and GROC completed a comprehensive evaluation of change in pain (Doleys & Doherty, 2000). Pain medication used a self-complete descriptive scale at follow-up to identify any change requirements to pain medication. Other methods for assessment were considered, including the ranking of pain medication according to the 'pain ladder' (Lawrie & Simpson, 2006; Sarzi-Puttini et al., 2012), but, adjuvant analgesics such as tricyclic medications, that might be given for patients with chronic cervicobrachial pain (Furlan et al., 2006), are not part of the ladder (World Health Organisation, 2008), potentially leading to some ambiguity.

5.11.2 Secondary outcome measures

Secondary outcomes were measured under three constructs:

- Function and disability
- Harm
- Costs

Outcome measures on function & disability

Neck pain is considered the second highest cause of disability in the world from all musculoskeletal conditions (Bone and Joint Decade, 2012). There was moderate evidence, in the literature that cervicobrachial pain could negatively impact on

function and disability (Daffner et al., 2003). Function can be affected by personal factors whereas disability has a more encompassing affect from environmental factors (World Health Organisation, 2002). Function and disability can be assessed using condition-specific or generic outcome measures. Condition-specific measures provide more detailed information on limitations particular to that condition, whereas generic outcome measures can evaluate the effect of an intervention on overall well-being (Guyatt et al., 1999, Guyatt, 2002). Both specific and generic outcome measures were used in this trial.

The Neck and Upper Limb Index (NULI) (Stock et al., 2003) was selected as the condition-specific outcome measure to evaluate function and disability. This was chosen because it was the only tool that evaluated symptoms in the neck and arm, collectively, making the content validity high for patients with cervicobrachial pain (Stock et al., 2003; Jull et al., 2008). Additionally, the NULI evaluated psychosocial, occupation and sleep-disturbance to incorporate multiple aspects of function and disability.

The NULI comprised twenty questions, divided into four sub-scales: physical activities, work, psychosocial factors, and, sleep. Scores range from 0 to 100, with high scores indicating worse function/disability. It was developed for patients with conditions affecting both the neck and arm (Stock et al., 2003) and was reported to have high levels of reliability and validity in a patient population with cervicobrachial pain referred for physiotherapy (Stock et al., 2003). Additionally, it has been reported to have good construct validity when compared to the SF36 and high sensitivity to change (Stock et al., 2003).

The RAND Short-form 36 (SF-36) version 2 was selected as the generic outcome measure to evaluate function and disability. The SF-36 has been reported as having good construct validity and better responsiveness to change when compared to the Euroqol and Nottingham Health Profile (McDowell & Newell 1996; Oga et al., 2003).

The SF-36 comprised 36 items, subdivided into 8 dimensions: physical function, role limitation, bodily pain, general health perception, mental health, social function, emotional role and vitality (Jenkinson et al., 1999). In addition, it has been validated for use as two main sub-scales: the mental component scale (MCS) and the physical component scale (PCS). Each sub-scale is scaled from 0 to 100, with higher scores representing good health (Jenkinson et al., 1999). Version 2 (1996) of the scale was selected for use in this trial due to its improved measurement properties and established norm-based scoring (Jenkinson et al., 1999; Ware, 2002). UK norm-based scoring was standardised to have a mean of 50 (SD =10) across each sub-scale (Jenkinson et al., 1999). Hence, a group mean score of 50 or less could be interpreted as being below the average health of the population (Jenkinson et al., 1999). The same figure has been found for US population norms (Ware, 2002).

The MCS component of the SF-36 included questions relating to mental health, social function, emotional role and vitality (Jenkinson et al., 1999). There was moderate evidence from a study by Daffner et al. (2003) that the MCS component was sensitive in detecting reduced scores in patients with cervicobrachial pain (mean score= 45), and, when adjusted for age and gender, the reduction from norm-based scores was significantly lower than for neck or arm symptoms in isolation. The same

study (Daffner et al., 2003) reported that chronicity of symptoms had a larger impact on the MCS than the PCS. Hence, only the MCS sub-scale was included in the trial.

Outcome measure on harm

'Harm' has been defined as the 'the totality of possible adverse consequences of an intervention' (Ioannidis et al., 2004. p782). For this trial, levels of harm were categorised based on the Common Terminology Criteria for Adverse Events (2006) (Table 5-2).

Table 5-2: Criteria for 'risk of harm'

Criteria	Description
Mild (low) harm	Any temporary minor negative treatment responses that are recorded on the comments sheet by the Trial Physiotherapists and collated during the intervention period (Appendix G).
Moderate harm	Participants who withdraw/ are withdrawn from the study as a direct result of the intervention they received, but have not been subject to any serious or permanent harm. Reasons for discontinuation (when possible) are established by the Trial Physiotherapist, Assessment Physiotherapist or Principal Investigator.
Severe (high) harm	This is recorded on a separate document by the Trial Physiotherapist and is defined as the participant suffering serious injury, major permanent harm or unexpected death in response to the intervention during the course of intervention (Appendix H).

[Based on Common Terminology Criteria for Adverse Events v3.0, (Cancer Therapy Evaluation Programme, 2006]

The risk of harm was evaluated against any benefit (compared to the primary outcome measure) per intervention group (Ioannidis et al., 2004). This perspective was taken to broaden interpretation of the results from clinical outcome measures.

Outcome measures on cost

Chronic musculoskeletal pain has been reported to be a significant burden to the UK economy (Phillips et al., 2008) and it has been recommended that studies evaluating chronic musculoskeletal pain include an evaluation of cost (Lewis et al., 2007). In this trial, work-absenteeism was used to evaluate socio-economic costs (Phillips et al., 2008). Resource use (quantity of physiotherapy interventions) was used to evaluate cost-effectiveness of the interventions (Cooper et al., 2005; Balshem et al., 2011; Brunetti et al., 2013). Work-absenteeism was recorded as 'time off work in the preceding month' at each time point (Waddell & Waddell, 2000; Phillips et al., 2008).

Resource use was recorded as the quantity of intervention per participant during the intervention period (up to the 6 week follow-up). Physiotherapy utilisation cost was expressed as the mean number of physiotherapy appointments needed per group and calculated in terms of mean monetary value of unit costs for therapist time (Waddell & Waddell, 2000; Phillips et al., 2008).

The total cost for participants' use of physiotherapy across the whole trial period was not analysed, since no data were collected on visits to physiotherapists (or other musculoskeletal practitioners) external to the trial. Participants were asked whether they had received any further treatment following the intervention period; however it was anticipated that participants would be unable to accurately recall the number of interventions they had received across a longer duration such as between weeks 26 and 52 (Paulhus, 1991; Dodorico McDonald 2008).

5.12 Clinically meaningful difference on the primary outcome measure

The minimal clinically meaningful difference has been defined as the smallest difference that patients and clinicians recognise as a worthwhile change (Maughan & Lewis, 2010). The minimal clinically meaningful difference on VAS pain was taken as 20mm (on a 0 to 100mm scale) (Hayes & Wooley, 2000; Dworkin et al., 2008; Vernan & Humphreys, 2008), and, therefore, it was important to be able to detect a difference or change of 20mm or more as statistically significant in the proposed trial (Hayes & Wooley, 2000). More recent non-invasive cervicobrachial pain studies (Walker et al. 2008; Kuijuper et al. 2009) used a value of 12mm to identify meaningful differences across groups. However, the justification for 12mm was based on findings from studies in emergency medicine which focused on important differences over time rather than establishing between-group differences. It was questionable whether using the figures for difference in pain across time in the acute medicine setting was transferable to be used for between-group differences on interventional studies for chronic pain (Dworkin et al., 2008).

5.13 Randomisation strategy used in trial

Randomisation procedures were used to reduce the risk of bias by balancing potential confounders (variables that could influence results) between groups and, therein, improved the quality of the trial (Krnz et al., 2007). Initially web-based and telephone randomisation systems were considered as these had been reported as superior methods to ensure allocation concealment (Viera & Bangdiwala, 2007). However, due to the lack of resources available for this trial, neither of these methods

was viable. Instead, a computer number table generator was used to determine the sequence of treatment allocation. This method of allocation has been recognised as acceptable and effective (Schulz & Grimes, 2002a; Kelley et al., 2003).

5.13.1 Sequence generation used in trial

An independent researcher generated the random order list. There was a moderate level of evidence that higher scores on VAS pain at baseline needed to be reduced by a larger amount to detect a change meaningful for a participant (Bird and Dickson, 2001; Tubach et al., 2004; Emshoff et al., 2011). Stratified randomisation procedures were used to balance baseline pain severity scores across the two intervention groups, within each of three classifications of baseline pain: low= 0-25 on VAS scale, moderate= 26-74 on VAS scale and high= 75-100 on VAS scale. The independent researcher generated the random order within each classification of baseline pain using a minimisation procedure that allowed for a maximum difference of 3 participants across intervention groups, within each pain stratum, to prevent sample size imbalance (Schulz & Grimes, 2002a). This approach ensured similarity between intervention groups in terms of initial presenting pain scores and group sizes at the beginning of the trial (Sim & Wright, 2000).

5.13.2 Allocation concealment in trial

Treatment allocation was printed on slips of paper and placed in sealed opaque envelopes, by an independent researcher. The envelopes were numbered sequentially to ensure that the Trial Physiotherapists opened them in the correct order, and, thereby, adhered to the planned randomisation.

The above approaches to sequence generation and allocation concealment endeavoured to avoid selection bias (Hernán et al., 2004; Higgins et al., 2011).

5.13.3 Implementation of trial

Participants were recruited by trained Assessment Physiotherapists and treatment allocation was revealed to participants by trained Trial Physiotherapists (Figure 5-1) (Sections 5.8.5 and 5.10.3).

5.14 Blinding strategy

The Assessment Physiotherapists were blind to group allocation, enabling unbiased recruitment of participants.

It was impossible to blind the participants and the Trial Physiotherapists to treatment allocation. There is a high level of evidence from multiple systematic reviews (Sculz et al., 1995; Juni et al., 2001; Balk et al., 2002) that failure to blind participants and intervention providers may exaggerate effect-estimate by up to 25% (18-39%) (Sculz et al., 1995; Juni et al., 2001; Balk et al., 2002; Hróbjartsson & Boutron, 2011). It was not feasible to blind the Trial Physiotherapists because they were the providers of the intervention. Ways to blind participants were considered: for example, a placebo intervention could have involved the Trial Physiotherapist supporting the neck and head as if to deliver the lateral glide, but not add the mobilisation. However, it has been reported that placebos are ineffective if they can be distinguished from the intervention, as would be the likely situation here (participants are likely to distinguish an oscillatory pressure from a non-oscillatory pressure) (Schulz & Grimes, 2002b; Hróbjartsson & Boutron, 2011). Consequently, participants

were not blinded to intervention and the consequential risk of bias was noted as a potential weakness in the trial.

5.15 Data processing

The data were input into SPSS (version 19), by a research assistant who had no other role in the trial. Data with regards to the group (i.e. intervention) were recorded using a code (0 and 1), to ensure that the Principal Investigator, who analysed the data, remained blind to group allocation and to enable unbiased judgement of the conclusions drawn (Schulz & Grimes, 2002b; Karanicolas et al., 2010). The intervention groups were revealed to the Principal Investigator only after completion of all statistical tests and consideration of the results (Schulz & Grimes, 2002b; Karanicolas et al., 2010).

5.16 Audit of throughput of chronic cervicobrachial patients to inform trial

No information was available to determine key characteristics of the target population, such as the prevalence of cervicobrachial pain (Section 2.4.1) and the number of patients with this condition who presented with chronic manifestations. Consequently, an audit was conducted to determine whether a sufficient number of patients were likely to be available to potentially participate in a trial, and to inform the potential rate of recruitment.

The audit was conducted in the acute hospital where the Principal Investigator worked, in the West Midlands. It was based on electronic referral data from the year 2005 (the earliest point at which electronic data were available) to 2006.

The audit revealed that 126 patients with chronic cervicobrachial pain had been referred to the physiotherapy department at the site during 2005, with a mean referral rate of 10.5 (SD 5) patients per month (minimum n=4; maximum n=23). This condition accounted for 5% of the total musculoskeletal referrals to the site, during 2005. However, there was a concern that a downward trend occurred during this period (Figure 5-4). Therefore, the audit of referrals was extended to December 2007(Figure 5-6), which led up to, and continued during the duration of the preliminary study (Section 5.17.2).

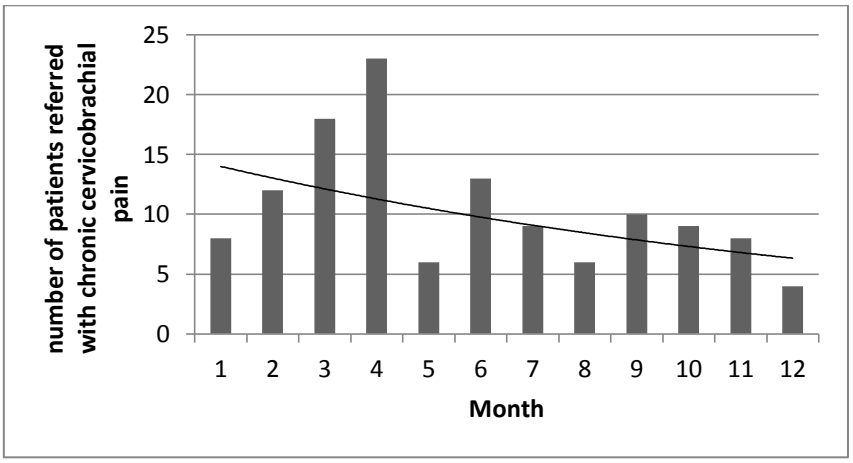


Figure 5-4: Number of patients with chronic cervicobrachial pain referred to trial site in 2005 (with trend line)

5.17 Preliminary study to inform trial

A preliminary study provided further information to inform planning of the main randomised controlled trial (Lancaster et al., 2004). The preliminary study was located in a physiotherapy department in an acute hospital in the West Midlands. Data from the 2005 audit indicated that the selected physiotherapy department had sufficient patient referrals to recruit to the preliminary study (Section 5.16) and that a

minimum of 30 participants (Lancaster et al., 2004) could be recruited to the study over a period of six months.

Aims of the preliminary study were to evaluate the following, in preparation for the main trial:

- Participant flow
- Recruitment rate
- Randomisation strategy
- Appropriateness of outcome measures
- Acceptability of interventions and outcome measures
- Contribute to establishing a sample size for the main RCT

(Lancaster et al., 2004; Arain et al., 2010; Thabane et al., 2010).

Use of preliminary studies was in concordance with recent recommendations from the National Institute for Health Research (NIHR) (2012).

5.17.1 Participant flow during preliminary study

Participant flow was evaluated up to the first follow-up (6 weeks post-intervention). Running the preliminary study to include follow-up at one year (as planned for the main trial) was considered, however this was impractical due to time constraints.

Assessment Physiotherapists identified a total of 50 patients with cervicobrachial pain who were suitable for physiotherapy. Thirty-two patients were ineligible to participate due to co-existing upper limb pathology (n=14), multiple reasons (from criteria) (n=8), bilateral symptoms (n=3), red flags (n=3), planned surgery (n=1), co-

existing rheumatic condition (n=1), being involved in litigation (n=1) and, age (n=1). (Figure 5-5).

Eligible participants (n=18) gave informed consent and were randomised to receive lateral glide mobilisation and self-management (n=8; Mobilisation group) or self-management alone (n=10; Comparator group).

Eight (80%) participants in the Comparator group and 7 (87%) in the Mobilisation group completed assessments at follow-up (6 weeks) (Figure 5-5). All returned questionnaires had been fully completed.

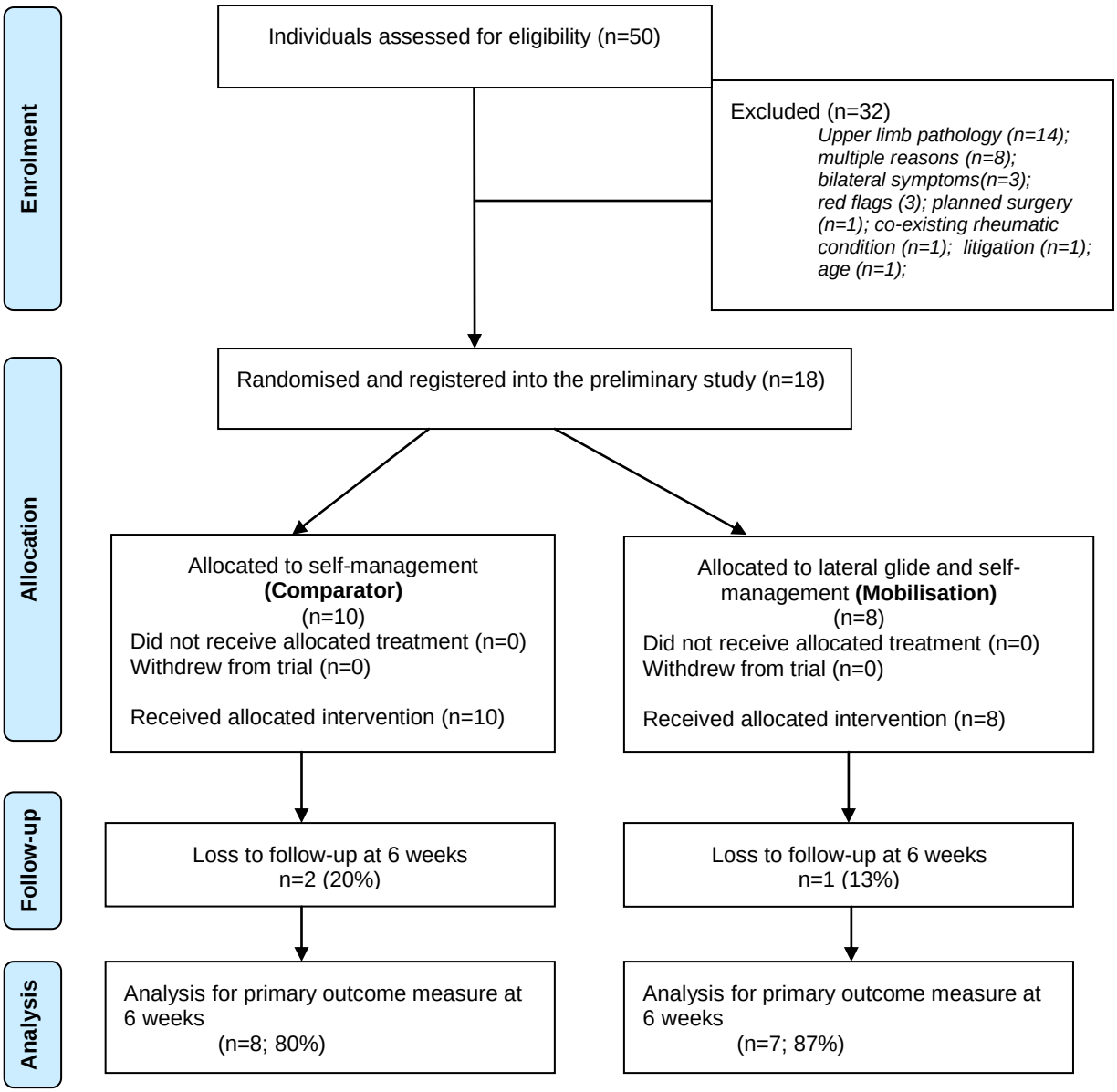


Figure 5-5: Participant flowchart of the preliminary study (adapted from Moher et al., 2010)

Three participants did not return their questionnaires, two from the Comparator group and one from the Mobilisation group, resulting in an overall loss to follow-up of 17%. A loss greater than a 20% has been reported to be an unacceptable level of attrition (Sackett et al., 2000; Schulz & Grimes, 2002c). The preliminary follow-up rate was only just within this parameter; therefore, a strategy was required to ensure a better level of follow-up in the main trial.

5.17.2 Recruitment during preliminary study

Eighteen participants were recruited from January 2007 to April 2008. This was less than the expected number of 30 (based on data from the 2005 audit), despite the expected time-frame being increased.

As planned, auditing referral rate for patients with chronic cervicobrachial pain was continued, leading up to and during the preliminary study (2007). Overall, the mean number of referrals per year for chronic cervicobrachial pain was 74, however as 2005 had an atypical referral pattern (the unexplained high referral rate peeking in April 2005; n=23), the mean was re-calculated based on data from 2006 and 2007. The revised mean referral rate was 48 per year (Figure 5-6), which accounted for 2% of all musculoskeletal referrals to the preliminary study site. This number was below that estimated from previous data (Section 2.4.1).

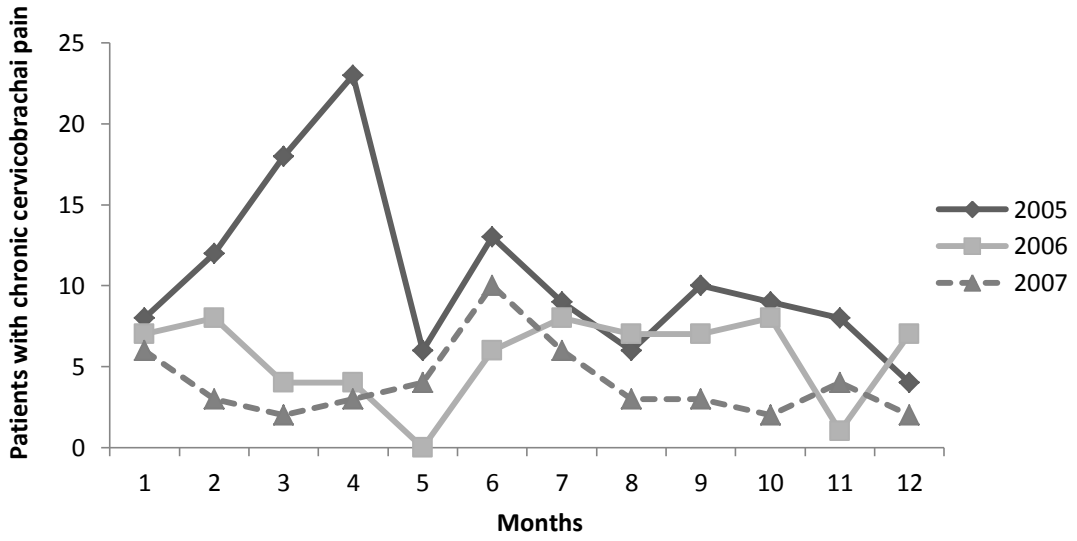


Figure 5-6: Audit of patients referred to physiotherapy with chronic cervicobrachial pain between 2005 to 2007

5.17.3 Randomisation in preliminary study

The randomisation procedure (Section 5.13) produced comparable groups at baseline with respect to age (a key demographic variable) and pain, mental health and chronicity (key clinical variables) (Table 5-3). Some differences were apparent on gender (more females in the Comparator group). However, it was anticipated that this difference would balance out with the much larger sample size required for the main trial.

Table 5-3: Key demographic and clinical variables in the preliminary study, by intervention group

	Intervention					
	Comparator (n=10)			**Mobilisation (n=8)**		
Key demographic variables	Mean (SD)	Min^n, Max^m	Missing	Mean (SD)	Min^n, Max^m	Missing
Age(years)	49 (17)	28, 65	0	49 (12)	29, 60	0
	n(%)			n(%)		
Gender Females	8 (44)		0	2 (12)		0
Key clinical variables	**Comparator (n=10)**			**Mobilisation (n=8)**		
	Mean (SD)	Min^n, Max^m	Missing	Mean (SD)	Min^n, Max^m	Missing
VAS (worst pain)	60 (19)	31, 97	0	65 (18)	28, 81	0
VAS (average pain)	48 (21)	29,97	0	42 (16)	22,65	0
SF-36	63 (16)	17, 85	0	59 (17)	21, 93	0
	n (%)			n (%)		
Chronicity (months)						
>3 - 6	2 (20)		1	2 (25)		0
>6 - 12	3 (28)			2 (25)		
>12	5 (42)			4 (50)		

Key: max^m =maximum value; min^m =minimum value; n= number of participants; SD=standard deviation

5.17.4 Evaluation of outcome measures used in preliminary study

Primary outcome measure - Pain

Although there was an indication of some reduction in median VAS(worst pain) for both groups, the changes were not clinically meaningful (being less than 20mm) (Figure 5-7). There was a wider range of VAS(worst pain) scores for participants in the Mobilisation group following intervention. However, the sample size was very small and findings from such preliminary studies should not be over-interpreted (Thabane et al., 2010).

The change scores from baseline to post intervention on VAS(worst pain) were compared with the Global Rating of Change Score (GROC) for patient-perceived change in pain, to consider their comparative responsiveness (Figure 5-8). There was an apparent linear association between change on VAS(worst pain) and GROC scores (Figure 5-8), providing some evidence that VAS(worst pain) was a responsive measure in the study population. None of the participants in the preliminary study were clinically worse at its endpoint and three were clinically better, two of whom were in the Mobilisation group. In contrast, a comparison of change on VAS(average pain) with GROC scores indicated only a low correlation between them, providing some evidence that VAS(average pain) was a less sensitive measure than VAS(worst pain). For this reason, VAS(worst pain) was identified as the primary outcome measure in the main trial (Section 5.18.3).

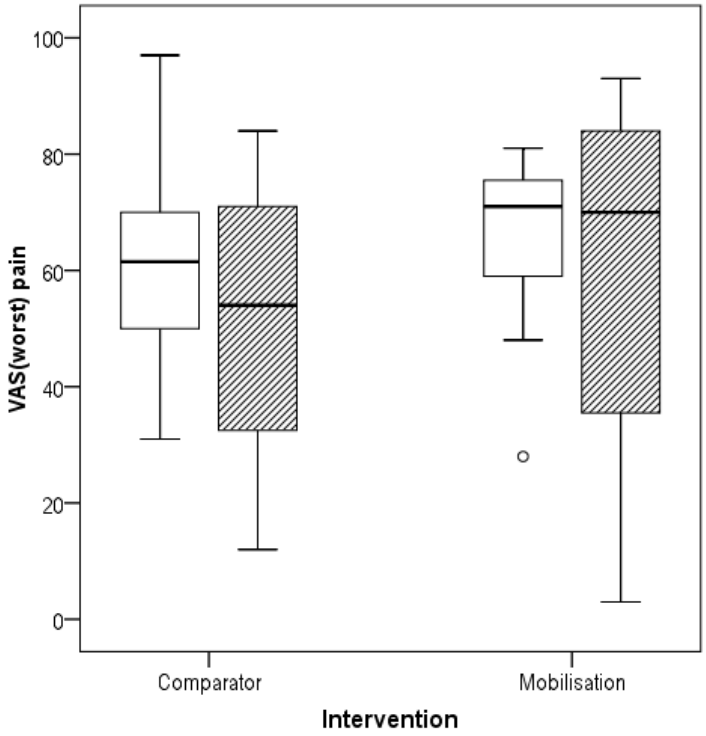


Figure 5-7 Boxplots for VAS(worst pain) at baseline and six week follow-up (n=15)

Key ☐Baseline
▨6 week follow-up

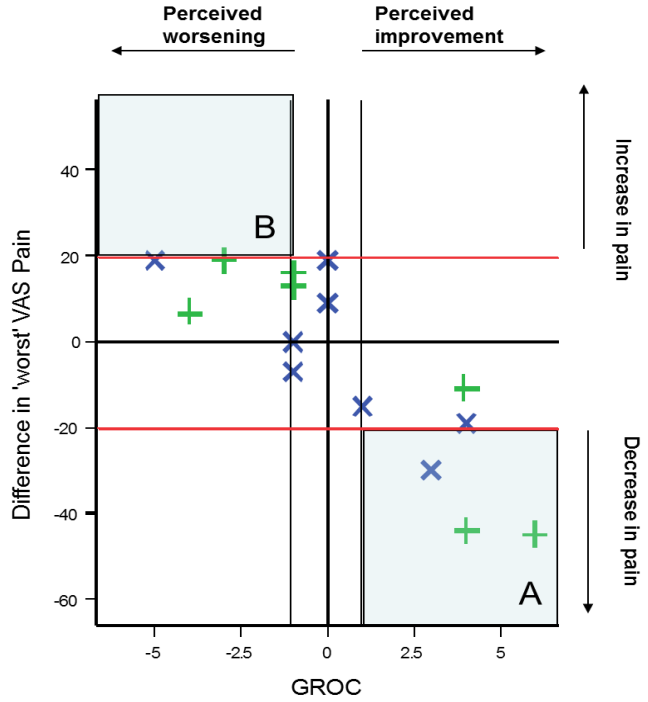


Figure 5-8 Change in VAS(worst pain) compared with GROC (n=15)

× Comparator
+ Intervention

GROC=Global Rating of Change score; VAS=Visual Analogue Scale

Footnote: On Figure 5-7 ° represents an outlier value for worst pain.

On Figure 5-8 The horizontal red line represents minimal clinically meaningful change on VAS pain
The vertical black line represents minimal clinically meaningful change on GROC
Responses in Box A indicate participants with a clinically meaningful improvement on both GROC and VAS
Responses in Box B indicate participants with a clinically meaningful worsening on both GROC and VAS

Secondary outcome measures - Function and disability

All 15 participants who returned the questionnaire completed the NULI and the SF36. There were some irregularities in the completion of both outcome measures. In five cases for the NULI and for eight cases on SF36, participants had circled two adjacent numbers and in one case (on NULI) had indicated a response between two numerical options. A method for data entry was put in place for the main trial: the data inputter was given written and verbal instructions that if this occurred in the main trial, the middle value was to be inputted. For example, if a participant chose both 6 and 7 as a response, or marked in-between these two options, the data was inputted as 6.5. This avoided any data entry bias in the main trial (Delgado-Rodriguez, 2004).

Secondary outcome measure - Harm

None of the participants withdrew from the preliminary study and no harms or undesirable effects were reported.

Secondary outcome measure - Cost

No problems were encountered with capturing data regarding the numbers of days off work or mean number of interventions during the intervention period.

5.17.5 Acceptability of proposed trial methods

A postal survey (Appendix I) was used to obtain participants' feedback on their experience and any perceived problems with the study (Moffatt et al., 2006). This feedback was used to identify if any change was required to the planned methods for the main trial. To aid compliance, the survey was kept short (7 questions were utilised), a personalised covering letter was sent to each participant explaining the

reason for the survey, and stamped addressed envelopes were issued (Edwards et al., 2002b; Edwards et al., 2009). Despite this, only five questionnaires were returned, out of 18 posted to participants. It was recognised that the limited response rate could have led to responder bias (with patients having a positive experience, more likely to respond) (Fitzpatrick, 1991). Responder bias can lead to some inappropriate methods from a preliminary study being taken forward into the main trial (Edwards et al., 2009). Incentives to encourage response were considered at the design stage, including the use of a monetary incentive, recorded delivery and telephoning non-responders (Edwards et al., 2009). The first two strategies have been reported to approximately double response rate (Edwards et al., 2002b). However, due to the lack of funding at the start, none of these options could be built into the study's design.

Feedback from the limited survey response was positive. Four of the five respondents reported that they were given sufficient information about the study and none had felt obliged to participate. All participants stated that, based on their experience, they would be happy to be involved in a future health research study. There was positive feedback regarding both the Self-management Booklet and the Mobilisation intervention, for example, feedback on the Booklet included "very useful, I was able to refer back to it" and "very good, the instructions and diagrams were easy to follow", and the feedback for the Mobilisation included "excellent - very professional and best of all - was successful" and "I found this was very good". No further changes to the Information booklet were identified for use in the main trial.

5.17.6 Issues with sample size based on preliminary data

Thirty has been recommended as the minimum number of participants required in a preliminary study to establish the sample size for an adequately powered trial (Lancaster et al., 2004). The number of participants in the preliminary study was less than that expected and did not reach the target of 30. It was not feasible to continue recruitment due to time constraints, therefore, it was accepted that additional strategies for power calculations were required to determine the required sample size for the main trial (Section 5.19).

5.18 Changes to the methods for the main trial

The preliminary study provided information that informed some changes to the following key features for the main trial: attrition, recruitment and outcome measures.

5.18.1 Addressing attrition for the main trial

Postal questionnaires were used for data collection in the preliminary study. At 6 weeks post-baseline, there was a 20% loss to follow-up in the Comparator group. It was anticipated that this figure would increase for the longer-term follow-up (at 26 weeks) and that the primary end point (52 week follow-up) would have a higher than acceptable level of attrition (Sackett et al., 2000; Schulz & Grimes, 2002c). Hence, further measures were required to reduce attrition in the main trial.

The primary method of data collection in the main trial was changed from postal questionnaires to follow-up appointments; this was to address attrition as well as to enable the incorporation of physical outcome measures at follow-ups (Appendix J). In addition:

a) Reminder letters were to be sent to participants one month prior to their 26 and 52 week follow-up appointments, to encourage their attendance.

b) Participants who did not attend their follow-up appointments would be contacted by telephone, within a fortnight of missing their appointment, to enquire whether an appointment could be made at a more convenient time for them.

Strategies (a) and (b) have been reported to be effective at reducing levels of attrition (Nakash et al. 2006).

c) Participants who did not attend the final appointment (despite the measures stated above) would be mailed a condensed version of the questionnaire (Appendix K), along with return paid postage to encourage return of completed postal questionnaires.

Incorporating multiple methods of data collection in this way has been advocated as effective to reduce attrition (Edwards et al., 2009; Lall et al., 2012). In addition, participants from differing demographic groups have been found to respond to different methods of data collection in clinical studies (Edwards et al., 2009; Lall et al., 2012). Hence, the incorporation of more than one method of data collection was expected to result in a wider response rate and an improved representation of treatment effect (Lall et al., 2012). Funding for £2000 from the Musculoskeletal Association of Chartered Physiotherapists (MACP) for the main trial was secured to reimburse participants for their travel expenses and for postage costs.

5.18.2 Addressing recruitment for the main trial

Two strategies were instigated to enhance recruitment rate to the main trial: - a) further centres were included in the trial; and, b) participants were recruited by

Assessment Physiotherapists from orthopaedic and musculoskeletal triage services, as well as, physiotherapy departments.

The main trial involved the preliminary study site and a further three National Health Service locations across the United Kingdom: two community health centres in Birmingham and one orthopaedic centre in Bristol. It was expected that enhanced generalisability would result by the recruitment of participants from a wide geographical spread and from primary, secondary and specialist locations (Appel, 2006).

5.18.3 Refinement of outcome measures for the RCT

Identification of a singular primary outcome measure

The primary outcome measure had been identified as VAS pain. VAS(worst pain) and VAS(average pain) were considered at the preliminary stage. The preliminary study found that differences on 'worst' pain scores were more responsive to change than 'average' pain scores when compared to the Global Rating of Change score (GROC) (Section 5.17.4). VAS(worst pain) had been used this way in another cervicobrachial pain study (Persson et al. (1997; 2001). Since commencing the trial, VAS(worst pain) has been validated as an accurate measure for establishing pain over the previous week (Bolton et al.. 2010). VAS(worst pain) was used as the primary outcome measure in the main trial.

VAS(average pain) was considered as a second primary outcome measure, however, identification of more than one primary outcome measure would have increased the required sample size and necessitated an alteration to the selected significance level (set at 0.05 in the preliminary study) to maintain a 5% chance of

incorrectly rejecting the hypothesis that mobilisation together with the Self-Management Booklet was equally as effective as the Self-Management Booklet on its own (i.e. to maintain the probability of a false positive result at 0.05) (Sim & Wright, 2000; Hulley et al., 2001; Freemantle et al., 2003; Zlowodzki & Bhandari, 2009).

Additional functional outcome measures

During the initial planning of the trial, all the selected outcome measures related to patient reported outcome measures (PROMs), which had been advocated for use in clinical studies (Fitzpatrick et al., 1998). The selected PROMs represented the participant's perspective of their outcome, which is justifiably important (Dawson et al., 2010). In contrast, performance based outcomes (PBOs) have been criticised as not being directly meaningful for the patient (Peat, 2002). However, PBOs are less open to self-reporting bias (Dodorico McDonald 2008; Jackson, 2008). Independent reviews of the preliminary study criticised the work for not including PBOs because participants in the study could not be blinded to the intervention they received, which could have biased answers when completing the PROMs at follow-up. If, at the time of completing their follow-up questionnaire, participants were able to recall their responses at baseline, there was potential to bias findings from the study.

In the main trial, PBOs were included to ensure that some outcome measures were completed by an independent assessor to improve the methodological quality of the trial (Dodorico McDonald 2008; Jackson, 2008). The Assessment Physiotherapists were the outcome assessors in the main trial and were blinded to treatment allocation throughout the duration of the trial. There was moderate evidence from multiple randomised studies (Noseworthy et al., 1994; Burkhoff et al., 1999; Oesterle

et al., 2000) that failure to blind the outcome assessor could exaggerate the effect-estimate for an intervention by up to 69% (SD 29-87%) (Hróbjartsson & Boutron, 2011), strengthening the rationale for having included PBOs in the main trial.

The requirement to add PBO measures and the strategy to address attrition rate resulted in a decision to collect data at clinic appointments.

Cervical active range of motion

Cervical spine movement is a PBO (Jull et al., 2008). The measurement of cervical active range of motion has been used as an outcome measure in previous studies addressing cervicobrachial pain (Howe et al., 1983; Klaber Moffett et al., 1990; Ragonese, 2009). There was low evidence to support cervical range as a valid tool to measure immediate post-intervention change in neck pain patients (Dvir & Prushansky, 2000; Prushansky & Dvir, 2008). However, it was unclear whether the studies by Dvir & Prushansky (2000, 2008) included patients with cervicobrachial pain, which limited interpretability of their findings for this patient population.

Klaber Moffett et al. (1990) used cervical range as an outcome measure for chronic cervicobrachial pain subjects, at three month follow-up. Whilst this was not a validation study, the results were consistent with PROMs used in the same study, indicating that cervical range of motion might be a responsive measure over a more extended duration.

The main trial used a simple inclinometer to measure cervical range of movement (Figure 5-9), as used in other cervicobrachial clinical studies (e.g. Klaber Moffett et al., 1990) and more recent studies (e.g. Ragonese, 2009). There was low evidence from three studies with consistent results, that inclinometers are reliable when used

in this context (Hole et al., 2000; Wainner et al., 2003; Gelalis et al., 2009). Intra-observer reliability was reported as being moderate to high in one study on patients with cervicobrachial pain (n=50): Intra-class correlation coefficient values range from 0.63 (95% CI 0.40 to 0.78) for left side bend, to 0.84 (95% CI 0.70 to 0.95) for extension (Wainner et al., 2003). An improvement of 10 degrees (or more) of change from baseline has been reported as being clinically meaningful and can be considered to represent an increase in range which leads to a functional improvement (Klaber Moffett et al., 1989; Sterling et al., 2002; Fletcher & Bandy, 2008).

Figure 5-9: Simple inclinometer used to measure cervical AROM
(positioned to measure flexion and extension)

Use of the inclinometer was taught to Assessment Physiotherapists in a training session led by the Principal Investigator, to ensure consistency of approach. Practice was continued until the Principal Investigator was satisfied that standardisation had been achieved.

The movements of flexion, extension and side-bend were measured with participants seated upright. Rotation was measured with participants in a supine position (Klaber Moffett et al., 1989; Sterling et al., 2002; Fletcher & Bandy, 2008). The inclinometer was placed on the participant's head and the dial set to zero in a resting position (as reported in Cleland, 2007). The Assessment Physiotherapists were instructed to keep the inclinometer in contact with the same point on the head, whilst the participant moved into the plane of movement, for example, flexion. When the participant had reached as far as they could in thier range of movement, the Assessment Physiotherapist took the recording from the dial on the inclinometer. Only one measure per movement was recorded to ensure uniformity.

A summary of the outcome measures is given in Table 5-4

Table 5-4: Summary of outcome measures used in main trial

Outcome measures	Scale	Representation	Comments
Primary outcome measure for pain			
VAS(worst pain)	0 to 100	Higher scores represent a higher level of perceived pain	Clinically meaningful difference is 20mm (Hayes & Wooley, 2000; Dworkin et al., 2008; Vernan & Humphreys, 2008)
Secondary outcome measures for pain			
VAS(average pain)	0 to 100	Higher scores represent a higher level of perceived pain	Clinically meaningful difference is 20mm (Hayes & Wooley, 2000; Dworkin et al., 2008; Vernan & Humphreys, 2008)
GROC	-6 to +6	Negative scores indicate a worsening; positive scores indicate an improvement. 0 represents no change	Clinically meaningful difference is 2 points on scale (Jaseschke et al., 1989; Michener et al. 2013)
Change in pain medication	4 point scale	A higher number indicates an increased need for pain medication	(Doleys & Doherty, 2000)
Secondary outcome measures for function and disability			
NULI	0 to 100	Higher scores represent reduced level of function 0=no functional limitations 100= severe functional limitations	[((sum of all applicable scores)-(number of applicable items)) /6x (number of items)]. (Stock et al., 2003; Stock, 2006)
MCS SF36v2 (RAND)	0 to 100	Higher scores represent good health 0=poor mental health 100= good mental health	Scores are coded depending on which of two categories they are in. Sum (coded scores)/number of answered items. Scores can be calculated with up to 50% of data missing. (Litwin, 1994;Ware, 2002)
Cervical AROM	0 to120 degrees	Higher scores represent a greater degree of movement	Clinically meaningful difference is 10 degrees (Klaber Moffett et al., 1989; Sterling et al., 2002; Fletcher & Bandy, 2008).
Secondary outcome measures for cost			
Physiotherapy utilisation	1 to 12	Higher number of appointments relate to higher costs	
Time off work	4 point scale	Higher number represents a greater amount of time off work	Represents time off work for cervicobrachial pain for the preceding month only
Secondary outcome measures for Harm			
Reported number of harmful effects	Three point scale	Mild harm, moderate harm, severe harm	Based on the Common Terminology Criteria for Adverse Events v3.0,(2006)

Key: AROM= Active Range of Motion; GROC= Global Rating of Change scale; MCS SF36=Mental Component Scale Short-Form 36; NULI=Neck and Upper Limb Index; TAMPA= Tampa scale of kinesiophobia; VAS=Visual Analogue Scale.

Fear of Movement (kinesiophobia)

The use of cervical movement as the physical outcome measure led to consideration of factors that could influence the validity of this tool. Cervicobrachial pain has not been related to kinesiophobia specifically, but moderate evidence has associated reduced levels of function with increased levels of kinesiophobia in cervical spine and upper limb disorders (Kori et al., 1990; Roelofs et al., 2007; Bränström & Fahlström, 2008; Hudes., 2011; Vernon et al., 2011; Verson et al., 2011; Howell et al., 2012).

The Tampa Scale of Kinesiophobia (TSK) is a 17-item psychological scale designed to measure fear of movement (Kori et al., 1990; Roelofs et al., 2007; Bränström & Fahlström, 2008; Hudes, 2011). Scores range from 17 to 68 with higher scores relating to a higher level of kinesiophobia (Kori et al., 1990; Roelofs et al., 2007; Bränström & Fahlström, 2008; Hudes, 2011). Other measures to evaluate kinesiophobia were considered, including the Fear of Pain Questionnaire (Roelofs et al., 2007), the Pain Anxiety Symptoms Scale (Rodlofs et al., 2007) and the Fear Avoidance Beliefs Questionnaire (Swinkels-Meewisse et al., 2003). Appropriateness of this choice was strengthened in a later systematic review (n of studies= 37) evaluating the psychometric properties of pain-related fear measures in chronic musculoskeletal pain (Lundberg et al., 2011) where it was concluded that the TSK was the best available tool to measure kinesiophobia.

5.19 Calculation of the sample size for the main trial

The sample size for the main trial was determined through statistical methods using the identified primary end point, VAS(worst pain) at 52 weeks, together with evidenced values for:

(i) the minimal clinically meaningful difference in a comparable patient population (Hulley et al., 2001); (ii) an estimate of standard deviation (SD) in the population of interest (Wittes, 2002; Zhong, 2009); (iii) the effect size calculated from (i) and (ii); and, (iv) adjustment for participant withdrawal (Cohen, 1992a; Kelly et al., 2003; Zhong, 2009; Machin & Fayers, 2010).

5.19.1 Primary outcome measure and estimation of effect size

The primary outcome measure (VAS(worst pain)) was a measure for the worst pain in the neck and arm over the previous week, measured on a 0 -100mm VAS scale (Section 5.11.1). The minimal clinically meaningful difference (MCMD) on VAS (worst pain) for patients with cervicobrachial pain was established as 20mm (Section 5.11.112) and the SD for VAS(worst pain) for patients in the trial population was estimated using data from the preliminary study (Lancaster et al., 2004; Thabane et al., 2010). This was justified since no changes were made to eligibility criteria for the main trial. The upper 99% confidence limit (CI) for the variance was used to estimate the value for SD because use of the standard deviation from the preliminary study could have led to an under-estimated value due to its small sample size (n=18) (Lancaster et al., 2004).

Using baseline data (Table 5-3), the estimated variance for VAS(worst pain) = 322.02, n=18

Following the method in Daly et al. (1995, pages 289 & 674)

$$\text{99\% CI variance (worst pain)} = \frac{(n-1) * \text{est}^d \text{ var}}{\chi^2_{.005,\, n-1}} \text{ to } \frac{(n-1) * \text{est}^d \text{ var}}{\chi^2_{.995,\, n-1}}$$

$$= \frac{17 \times 322.02}{35.72} \text{ to } \frac{17 \times 322.02}{5.70}$$

$$= 153.26 \text{ to } 960.41$$

The χ^2 values were obtained from statistical tables (Murdoch & Barnes, 1974)

So, estimated SD (worst pain) = sqrt (960.41) = 30.99 using the upper limit

Leading to an effect size = MCMD / estimated SD for VAS(worst pain)

= 20 / 30.99

= 0.65

A size of 0.65 represented a moderate to large effect (Cohen, 1992a) on VAS(worst pain).

5.19.2 Statistical Hypotheses

Statistical hypotheses were based on the primary objective (Section 5.2). The primary hypotheses, regarding worst pain experienced by patients with cervicobrachial pain, were stated as:

H0: There is no difference in effectiveness of self-management and the lateral glide mobilisation when compared with self-management alone

H1: There is a difference in effectiveness of self-management and the lateral glide

mobilisation when compared with self-management alone

Two sided statistical hypotheses and tests were selected since existing evidence was inconclusive on the effectiveness or otherwise of the lateral glide mobilisation (Hulley et al, 2001; Sim & Wright, 2000; Portney & Watkins, 2000). A statistical significance level of 0.05 (the probability of incorrectly rejecting H_0 in favour of H_1) and a power of 0.80 (the probability of correctly rejecting H_0 in favour of H_1) were selected to estimate the sample size (Cohen, 1992a; Hulley et al., 2001; Wittes, 2002; Kelly et al., 2003; Machin & Fayers, 2010; Sim & Wright, 2000; Zhong, 2009).

A significance level (also referred to as Type I error) of 0.05 has been reported as being a 'typical' value in health care research (Portney & Watkins, 2000; Cohen, 1992a & b) or within the conventional range of values (Hulley et al, 2001; Zhong, 2009), and was considered to be the highest acceptable value (Portney & Watkins, 2000; Biau et al., 2010). It equated to a 5% chance of incorrectly concluding that the lateral glide technique had an additional effect when delivered in conjunction with self-management.

A power of 0.8 was reported as conventional (Cohen, 1992b; Zhong, 2009) and has frequently been used in health care research (Machin & Fayers, 2010). It equated to an 80% chance of correctly rejecting the assumption of no additional effect of the lateral glide technique when used in conjunction with self-management.

Based on an effect size = 0.65, significance level =0.05, power = 0.80, the required sample size was 34 per group (Hulley et al., 2001, p85; Jones et al., 2003b p456), or total=68. See Figure 5-10

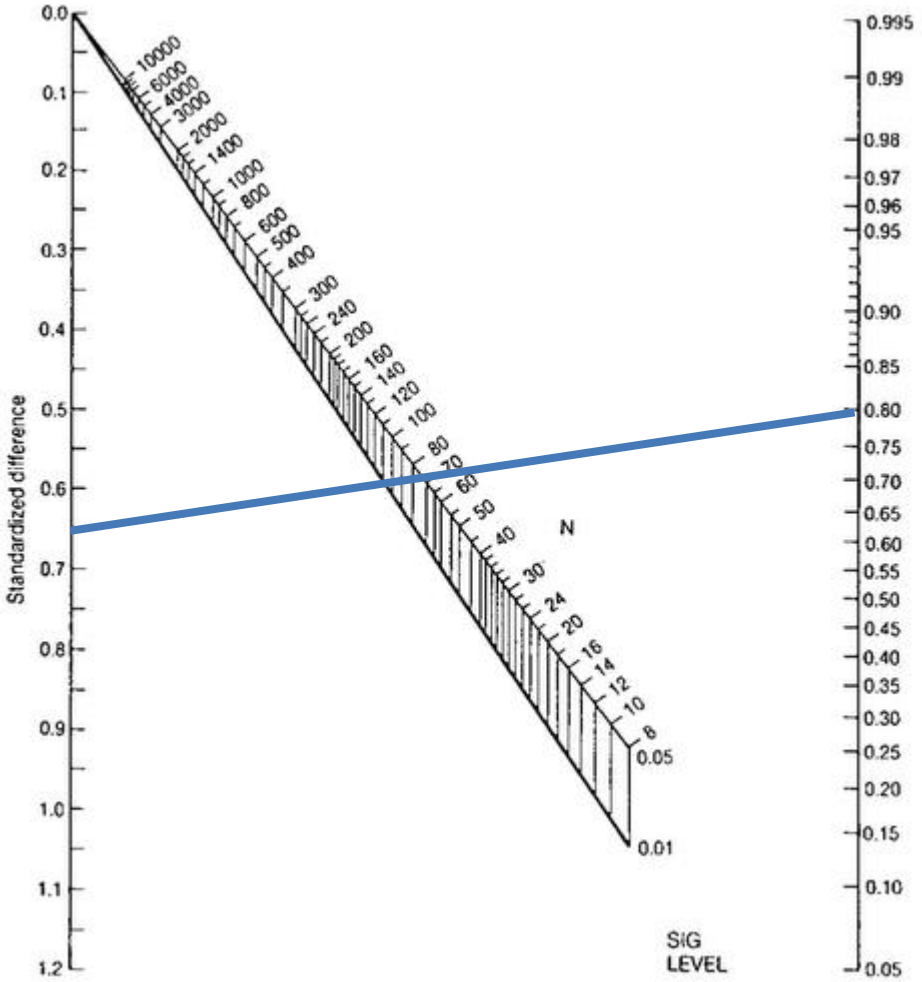


Figure 5-10 Nomogram for the calculation of sample size in main trial
[Adapted from Jones et al. 2003b p456]

5.19.3 Adjustment for participant withdrawal in main trial

An 11% attrition rate was allowed for at each of the three measurement periods, adjusting the sample size to account for participant withdrawals (Sim & Wright, 2000). Using the formula in Machin and Fayers (2010) (previously discussed in Fayers & Machin (2000):

$$\text{Adjusted n (allowing for attrition)} = \frac{\text{unadjusted n}}{(1-\text{anticipated attrition rate})^3} = \frac{68}{(1-0.11)^3}$$

$$= 96$$

Hence, it was estimated that 96 participants would be required for the trial, with 48 participants randomised to each of the two trial groups.

This adjustment equated to 42% adjustment at the 3rd follow-up time point (52 weeks).

The choice of 11% attrition was largely pragmatic (Fayers & Machin, 2000; Machin & Fayers, 2010). Loss to follow-up at six-weeks in the preliminary study was 17%, and consideration of reported losses to follow-up in other cervicobrachial pain studies indicated losses to follow-up of 2.5% to 32% at 52 weeks follow-up (Table 5-5).

Table 5-5: Attrition rates in cervicobrachial pain studies

Author	n	Intervention	Pain outcome measure	Attrition rates
Bernaards et al., (2007)	466	Behavioural therapy	NRPS	26 wks= 16% 52 wks= 32%
Kuijper et al., (2009)	205	Manual therapy and exercise	VAS	26 wks= 6%
Persson et al., (1997; 2001)	81	General physiotherapy	VAS	52 wks= 2.5%
Walker et al., (2008)	58	Manual therapy and exercise	VAS	52 wks= 6%

Key: n= number of participants; NPRS = Numerical Rating of Pain Score; VAS = Visual Analogue Scale; wks = weeks

5.20 Data analysis plan for the main trial

The Principal Investigator, who conducted the analyses, was blind to group allocation until all analyses had been completed. Summary statistics (for example: n, mean, standard deviation; or, median, interquartile ranges, minimum and maximum; or, percentage and 95% CI) were computed on full data sets for each intervention group. In addition, boxplots, line, bar or scatter graphs, as appropriate, were used to present the data diagrammatically. The primary research objective was addressed using

Analysis of Covariance (ANCOVA) to evaluate between-group differences on VAS(worst pain), the primary outcome measure, at the primary end point (52 weeks), with adjustment for important confounding variables. Several authors have recommended this approach in preference to an analysis of change scores (Laird et al., 1992; Everitt, 1994; Portney & Watkins, 2000; Vickers & Altman, 2001). Multi-level Modelling (MLM) was the main method used for longitudinal analyses of other continuous outcomes. Other statistical methods (for example, Mann-Whitney for evaluating ordinal data, and, Spearman's rho when testing for correlation) were used to evaluate some of the secondary and exploratory outcome measures. Checks were conducted on the assumptions underlying the use of statistical tests (Walker & Almond, 2010).

5.20.1 Baseline characteristics

Baseline comparisons across groups included demographic data (e.g. age, gender) and clinical data (e.g. pain level and chronicity). Data were summarised using parametric or non-parametric statistics, as appropriate. The summary data were tabulated by intervention group to provide information on between-group differences (Sim & Wright, 2000). Visual comparison of initial baseline VAS(worst pain) scores identified how effective stratification had been at achieving balance between the groups.

There has been debate about the meaning of findings from statistical tests on inter-group differences at baseline (Altman, 1985; Senn, 1994; Roberts & Torgerson, 1999; Dumville et al., 2006; Turk et al., 2008; Berger, 2009; Fayers & King, 2009; Berger, 2010). Statistical between-group differences at baseline have been criticised as an approach to identify variables that could influence results (Altman, 1985; Senn,

1994; Roberts & Torgerson, 1999; Dumville et al., 2006; Turk et al., 2008). CONSORT stated that: '*Tests of baseline differences are not necessarily wrong, just illogical. Such hypothesis testing is superfluous and can mislead investigators and their readers'* (Moher et al., 2010, p.17).

Historically, testing for baseline differences has been used to consider whether a) randomisation was achieved effectively and b) any between-group differences at baseline were likely to influence results at follow-up (Berger, 2010). However, statistically significant between-group differences might occur through chance alone. It is well documented that multiple statistical testing on baseline data can lead to multiplicity i.e. one or more statistically significant between group differences identified as a result of chance rather than representing a real effect (Fayers and King, 2009). In general, inter-group differences have been tested using baseline values for each primary and secondary outcome measure in an RCT. However, statistically significant tests at baseline do not necessarily constitute evidence of poor randomisation or of a true difference between the groups at the start of a study (Fayers and King, 2009). This reasoning has led to the use of statistical approaches such as ANCOVA and MLM (Multi-level Modelling) that incorporate potential baseline confounders in the statistical analysis and, thereby, account for any important baseline between group variability (Field, 2009) . Increasingly, papers published in high quality journals (with high impact factors) such as The Journal of American Medical Association (Impact factor 29.978) and The British Medical Journal (Impact factor 17.215) are publishing randomised controlled trials that do not report statistical tests conducted on baseline data (Reignier et al., 2013; Pinock et al., 2013). Whilst

this is not yet commonplace, it is likely to become the more conventional approach in the future.

Based on the reported evidence, it was decided not test for statistically significant inter-group differences at baseline.

5.20.2 Attrition

Attrition could be due to loss to follow-up (e.g. patient not attending a follow-up appointment) or to incompletion of outcome measures (e.g. a participant attending the follow-up appointment, but not completing an outcome measure on a questionnaire) (Howard et al., 1986). Both causes of attrition were recorded at all time points as:

- Number of participants lost to follow-up, by intervention group
- Number of participants who did not complete the primary outcome measure, by intervention group

Attrition was recorded for each intervention group to support consideration of between-group differences. This was important because imbalances in attrition across groups might bias trial results (Fewtrell et al., 2008). In partiular, if a large number of participants receiving mobilisation were to drop-out due to dissatisfaction with the intervention, and no-one dropped-out of the Comparator group, values of outcomes for responders in the mobilisation group could be positively biased, potentially leading to a large difference between the groups (Machin & Fayers, 2010) and a Type 1 error. The potential for response bias was considered through independent t-tests (when appropriate) on baseline values for important trial confounders (age, baseline VAS(worst pain), SF36), with participants assigned to

one of two groups according to whether they responded or not to the primary outcome at baseline.

5.20.3 Data Monitoring

All data were captured on paper forms and entered manually into an Excel database. Other methods of data collection and data entry were considered, including direct electronic data capture and double entry, however such systems were not available for this trial. An audit to evaluate a random 10% of the data was used to identify issues with accuracy of data entry (Appendix L). There was no standard approach to ensure accuracy of data entry, but checking a 10% random sample has been reported as providing an adequate check (Dixon & Pearce, 2010). In addition, SPSS syntax files were programmed to identify whether any inputted values were outside the expected range (Appendix M).

5.20.4 Analysis of change – Primary outcome measure - VAS(worst pain)

Primary and secondary analyses

The main analysis was to test between-group differences on the primary outcome measure, VAS(worst pain). The primary analysis was at 52 weeks (long-term effects) and the secondary analysis at 6 weeks (short-term effects). Inter-group differences on VAS(worst) pain at 52 weeks and at 6 weeks were assessed using analysis of covariance (ANCOVA). ANCOVA has been reported to have higher statistical power than tests on mean change scores (Vickers, 2001). Several authors have recommended ANCOVA in preference to an analysis of change scores because important, baseline covariates can be accounted for, providing a more powerful test on inter-group differences (Laird et al., 1992; Everitt, 1994; Portney & Watkins, 2000;

Vickers & Altman, 2001). Covariates used in this trial comprised gender, age, mental health, chronicity and 'worst' pain at baseline (justified in Section 2.4).

An 'intention to treat' approach (ITT) was followed for the analysis of data. This method analysed all participants according to the group to which they were randomised. Although this approach could have under-estimated the effect of the lateral glide mobilisation, it retained the balance in participant characteristics provided by the randomisation process and, hence, avoided a potential source of bias in the results (Hulley et al., 2001). This approach has been considered to be the gold standard for the analysis of data collected in clinical studies (Moher et al., 2010). Two aspects were considered for the analysis a) missing data, and b) non-adherence to protocol (Moher et al., 2010). If inadequately addressed, these factors could have led to misinterpretation of the results (Heritier et al., 2003; Moher et al., 2010).

Missing data: The choice was to impute the missing values or exclude participants without an outcome (Moher et al., 2010). Imputation requires strong assumptions, potentially leading to underestimation or overestimation of the treatment effect (Moher et al., 2010). No one method of imputation was preferred in the literature (Wood et al. 2004). Omitting missing data has been considered reasonable when the level of missing data is low and there is a balance of missing data across groups (Moher et al., 2010). Unfortunately, it was unclear from the literature what constituted a 'reasonable' level of missing data. It has recently been reported that up to 20% of missing data is acceptable (OCBEM, 2011; SIGN, 2012). Based on the different opinions, if missing values exceeded 20% and/or there was an imbalance of missing data between groups, the plan for analysis was to impute data using methods for both the worst case imputation and the best case imputation. No clear

guidance was found in the literature on what constituted an imbalance of missing data. It was decided to consider between-group differences 20% or less as an acceptable level of imbalance.

Protocol violations: Some participants might not have received the randomised intervention or received additional intervention to that outlined in the protocol. Exclusion of data for participants who violated the protocol could bias results (Moher et al., 2010). The CONSORT group advocated analysing groups as per randomisation – as long as missing data, deviations from protocol and co-interventions were reported in a clear and transparent way (Moher et al., 2010).

Tertiary analysis

Tertiary analysis on the primary outcome measure used multi-level modelling (MLM). There were two key reasons for this choice:

1. It provided a longitudinal evaluation (across time) of the data
2. Missing data were accommodated in this approach.

A longitudinal analysis evaluated treatment effect over time and graphs displayed the pattern of change over time for each group (Pocock et al, 2007). Unlike repeated measures analysis of variance, MLM could accommodate missing data and any general trend in the outcome over time (Gueorguieva & Krstal, 2004; Quene & van den Bergh, 2004; Misangyi et al., 2006; Field, 2009; West, 2009; Peugh, 2010; Kahn, 2011). A forward approach was used to include variables into the model, one at a time. The selected order was: time from baseline (input as 0, 6, 26, or 52 to model the weeks from baseline at which data were collected, to account for any overall underlying trend in the outcome), potential covariates (SF36, chronicity, gender and

age) and intervention group (coded as 0 or 1). Covariates were added one at a time, in the order of their relative importance as judged from published literature in related areas of research (Section 2.4). Non-significant covariates were omitted from further analysis (Bursac et al., 2008). Intervention group was the last variable added to the model (Appendix N), so that any effect on outcome due to an underlying trend or covariates was taken into account before testing for effect of the intervention (Greenland, 2000; Maas & Snjders, 2009; Quene & Bergh, 2004; Dedrick et al., 2009; Peugh, 2010). The use of stepwise methods, such as this, has been controversial. Some authors have criticised them for introducing bias by excluding previously identified, important covariates (Steyerberg et al., 2000; Thompson, 2001). However, others have reported that these criticisms constitute only a minor problem (Wahlby et al., 2002; Dartois et al., 2007) and, providing that the methods are used logically (for example, retaining a predictor variable with a very strong level of evidence to support its inclusion even when found to be statistically non-significant during the analysis), that they may prevent spurious error due to the inclusion of too many covariates, particularly, when evaluating data longitudinally (Armitage et al., 2002; Field, 2009).

Time was labelled as a random effect to account for deviations from the expected follow-up times (Field, 2009). It was anticipated that the combined findings from analyses using ANCOVA and MLM would provide stronger evidence on the primary outcome measure (Table 5-6).

Table 5-6: Planned approaches to data analysis for the Primary outcome measure VAS(worst pain)

Analysis	Statistical Test	Evaluation of intervention
Primary analysis	ANCOVA at 52 weeks	Long-term effects
Secondary analysis	ANCOVA at 6 weeks	Short-term effects
Tertiary analysis	MLM across all time points	Longitudinal effects

Key: ANCOVA=Analysis of Covariance; MLM=Multi-Level Models

5.20.5 Secondary outcome measures

Methods for the statistical analyses of data on secondary outcome measures are reported in Table 5-7. Longitudinal analysis from baseline to 52 week follow-up used MLM's and analysis of short-term effects (ie. at six week follow-up) used parametric or non-parametric tests as appropriate. All tests were conducted using a significance level of 5% and results used with caution since no adjustment was make for multiple testing (Section 5.20.8).

A correlation was computed for the association between six week scores on the Global Rating of Change score (GROC) with VAS(worst pain) to test for any association between patient perceived improvement in pain and the primary outcome measure (VAS(worst pain)). Spearman's rho (r_s) was used because data from GROC were at an ordinal level of measurement. Spearman was selected in preference to the Kendall's tau because it has been reported as being the more powerful non-parametric test of correlation (Siegal & Castellan, 1988; Walker & Almond, 2010). Scatter diagrams were drawn to visually show any association (Sim & Wright, 2000). A correlation coefficient of 0 represented no association and plus 1

or minus 1 indicated perfect association between the variables tested (Walker & Almond, 2010).

MLMs were also conducted to analyse the longitudinal effects of intervention on secondary outcome measures for pain (VAS(average pain)), function and disability (NULI, SF36 & cervical AROM). The methods were the same as those used for the tertiary analysis on the primary outcome measure (Section 5.20.4), whereby a forward approach was used adding time (0, 6, 26 and 52 weeks), co-variates (SF36, chronicity, gender and age). Tampa score for kinesiophobia was added as a covariate to potentially be taken forward into the model (if found statistically significant) when analysing cervical AROM as this had been identified as a possible confounder specific to this outcome measure (Section 5.18.3). Side of symptoms was added as a covariate to potentially be taken forward for cervical rotation and side bend measures as it was unknown if the unilateral nature of the condition could affect these unilateral measures. Interventional group was added as the last step in the model.

Use of medication and cost (relating to time off work) were ranked with higher points indicating the need for more medication or increased time off work, with ‘no pain medications’ ranked at 0, ranging up to ‘stronger/needing to start taking medications’ ranked at 3. The non-parametric Mann-Whitney test was used for between-group comparisons for all ordinal data (Field. 2009; Sim & Wright, 2001; Walker & Almond, 2010).

Reported costs relating to physiotherapy utilisation were analysed as non-parametric data because of the small data range (between 2 to 12 appointments, based on

patients being able to return up to twice a week for six weeks). There were no published, standardised NHS cost utility index measures that were appropriate for use in this research, therefore, mean numbers of attendances per group were converted to monetary values using a local departmental costs for staff time from the hospital Trust where the preliminary and main studies were conducted.

Harm was expressed as the number (and percentage) of participants who had reported harms associated with an intervention (Table 5-2) and a descriptive analysis was conducted to consider the incidence rates of harm (Ioannidis et al., 2004).

For secondary outcomes where MLM was not possible, only the six week follow-up period was analysed. It was recognised that the secondary outcomes had no statistical power and it was possible that a greater level of variation could occur over a longer period of time.

Table 5-7 Planned method of analysis for secondary outcome measures

Outcome measures	Statistical Test
Pain:	
VAS(average pain)	MLM
GROC* with VAS(worst pain)	Spearman's rho correlation at 6 weeks
Use of medication	Mann-Whitney test at 6 weeks
Function & Disability:	
NULI, MCS SF36 (PROs)	MLM
Cervical AROM (PBO)	MLM
Cost:	
Time off work	Mann-Whitney test at 6 weeks
Physiotherapy utilisation	Mann-Whitney test at 6 weeks
Harm:	
Reported number of harmful effects	Expressed as a % at 6 weeks

Key: ANCOVA=Analysis of co-variance; AROM= Active Range of Motion; GROC=Global Rating of Change; MCS SF36=Mental Component Scale Short-Form 36; MLM=multi-level models; NULI=Neck and Upper Limb Index; PBO = Performance Based Outcome measure; PRO = Patient Reported Outcome measure; VAS=Visual Analogue Scale; * measure of patient-perceived change.

5.20.6 Exploratory analyses plan

Exploratory analysis focused on evaluating whether the presence of a neuropathic component or a preference to receiving the lateral glide had influenced values of the primary outcome measure VAS(worst pain) (Table 5-8).

Analysis of neuropathic cervicobrachial pain

Spearman's rho correlation (Walker & Almond, 2010) was computed between baseline values for S-LANNS and the primary outcome measure VAS(worst pain) to evaluate if a higher neuropathic component (scores of 12 or more) correlated with a change in pain outcome in the short-term. A Spearman's rank correlation was computed since there was no evidence to support a linear association (Sim & Wright, 2005; Field, 2009; Walker & Almond, 2010). It had been theorised that patients with a neuropathic component of the condition would be less likely to respond well to manual therapy (Hall, 2009) and a study was being conducted to evaluate this association for lumbar radiating pain (later reported to identify an association (Schäfer et al. 2011)). A correlation was analysed at six week follow-up to explore any short-term association with this theory.

Analysis of mechanically sensitised cervicobrachial pain

ANCOVA was used to analyse whether patients who were mechanically neutrally sensitised (i.e. had a positive upper limb nerve extensibility (ULNE) test) had between-intervention group differences on mean scores for VAS(worst pain) at six weeks. ANCOVA was used to analyse the data in the same way as had been used for the main cohort of participants. It was recognised that the trial had not been powered for this, however, it would enable comparisons to be made to post-

intervention pain outcomes of other cervicobrachial studies that had stipulated the presence of a positive upper limb nerve extensibility (ULNE) test as a prerequisite for inclusion (Allison et al., 2002; Cowell & Phillips., 2002; Coppieters et al., 2003; Ragonese, 2009).

Analysis of intervention preference

ANCOVA was used to test whether participants' preferences influenced outcome on VAS(worst pain). 'Intervention' and 'preference' were used as fixed factors, with baseline VAS(worst pain) as the covariate. Preference was analysed in the short-term (six weeks) because any additional treatment that participants had after the intervention period could have included manual therapy intervention, potentially leading to a type II error in the results.

Table 5-8 Planned method for exploratory analysis

Outcome measure	**Statistical Test**
S-LANSS correlating with VAS(worst pain)	Spearman's rho correlation at 6 weeks
ULNE (+ve) with VAS(worst pain)	ANCOVA at 6 weeks
Participant preference with VAS(worst pain)	ANCOVA at 6 weeks

Key: ANCOVA=Analysis of covariance; S-LANSS= Self-report Leeds Assessment of Neuropathic Signs and Symptoms; ULNE= Upper Limb Nerve Extensibility test; VAS=Visual Analogue Scale.

5.20.7 Satisfying assumptions for use of the selected statistical tests

Incorrect conclusions might be drawn when the assumptions underlying statistical analyses are violated (Petrie & Sabin, 2005; Field, 2009). Assumptions were checked for all statistical tests conducted for this trial (Table 5-9). It was possible that assumptions relating to normally distributed data were achieved through the random allocation across groups (Walker & Almond, 2010). Statistical tests such as Pearson's skewness coefficient and *z*-score for skewness were considered, however as larger samples (30 or more) tend to normalise sampling distribution of erroneous variables, significance tests were not considered necessary (Field, 2009; Walker & Almond, 2010).

Findings from tests on other assumptions e.g. homogeneity of variance, were reported alongside the results.

Table 5-9: Assumptions underlying use of statistical tests

Statistical Test	Assumptions
ANCOVA	Data measured on an interval or ratio level of measurement Groups are independent Homogeneity of inter-group variances (Levene's test) Distribution of the data approximates to a normal distribution(sample greater than 30) (Field, 2009; Almond & Walker; 2010)
MLM	Repeated measures taken over time Groups are independent Homogeneity of variance (Goodness of fit- chi-square) Distribution of data approximates to a normal distribution (sample greater than 30) (Field, 2009)
Spearman's rho correlation	Both variables are measured on the same participants Minimum of 4 data points per scale (Almond & Walker; 2010)
Mann-Whitney test	Groups are independent Can be used for ordinal data Minimum of 4 data points per scale (Field, 2009; Almond & Walker; 2010)

5.20.8 Considerations for Multiplicity

The Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT) recommended testing multiple outcomes in a clinical study to enable a more holistic understanding of the effectiveness of an intervention in a specific population (Turk et al., 2006). However, conducting statistical tests on multiple outcome measures increases the size of the overall Type I error (retaining the statistical null hypothesis when it is not true), potentially leading to the incorrect reporting of one or more statistically significant effects (Senn & Bretz, 2007; Turk et al., 2008; Wittes, 2012). This is known as multiplicity. Statistical strategies to address multiplicity include the use of Bonferroni-corrected alpha or significance level (Hung et al., 2007; Turk et al., 2008; Wittes, 2012) to reduce the overall chance of a Type I error (Walker & Almond, 2010). However, in some circumstances, adjusting the value of alpha may lead to an increase in the Type II error (rejecting the statistical null hypothesis when it is true) (Turk et al., 2008; Wittes, 2012). The IMPACT group recommended that, for additional outcome measures, providing supportive or exploratory information are given, adjustment for multiplicity was unnecessary (Turk et al., 2008). Therefore, adjustment for multiplicity was not included in this trial.

5.21 Summary of design and methods used in the clinical trial

The methods selected for the main trial were based on a critical consideration of the methods used in previous studies, information from audits (to inform recruitment) and the preliminary study (to establish feasibility of trial design and methods). Choice of methods for the data analyses was based on relevant articles in the research literature and information in research texts. The aim was to further the understanding of whether manual therapy (in the form of the lateral glide) could benefit patients with cervicobrachial pain.

6 RESULTS FROM THE RANDOMISED CONTROLLED TRIAL

6.1 Introduction to results

A randomised controlled trial was conducted according to the design and methods described in Chapter 5. The aim of the trial was to investigate whether the lateral glide mobilisation was effective in the management of cervicobrachial pain. This chapter will present the results, in line with relevant sections of the Consolidated Standards of Reporting Trials (CONSORT) statement (Schulz et al, 2010).

6.2 Participant flow

All data were obtained from one of the trial sites (Section 6.3 discusses why data from only one site were included). Assessment Physiotherapists identified a total of 286 patients with cervicobrachial pain who were suitable for physiotherapy. Of these, 174 were ineligible to participate due to co-existing upper limb pathology (n=57), being older than 65 years of age (n=22) and other reasons (n=66) such as involvement in litigation, the presence of bilateral symptoms or presence of red flags (Figure 6-1). Some participants had multiple reasons for ineligibility (n=29).

Eligible participants (n=112) were invited to attend the first appointment with a Trial Physiotherapist (Section 5.4.2). Thirteen patients decided not to participate in the trial; 99 gave informed consent and were randomised to receive lateral glide mobilisation and self-management (n=49; Mobilisation group) or self-management alone (n=50; Comparator group). The randomisation procedure resulted in a balance of numbers across groups (Figure 6-1). One participant in the Mobilisation group

withdrew after starting treatment due to dissatisfaction with the intervention because he did not believe that he was actually receiving treatment.

Ninety two percent (n=46) of participants in the Comparator group and 86% (n=42) in the Mobilisation group completed assessments at the primary end point (52 weeks) (Figure 6-1). Completion numbers exceeded the minimum number required for the primary analysis i.e. 34 per group (Section 5.19). Loss to follow-up was below the reported acceptable level of 20% at each time point (Sackett et al., 2000; Schulz & Grimes, 2002c) (Figure 6-1).

Six participants who attended the 6 week follow-up (n=2 Comparator group; n=4 Mobilisation group), and 2 participants who attended at the 52 week follow-up (n=2 Mobilisation group) did not complete VAS pain scores, which could have been due to positioning of the VAS scales in the questionnaire (on the reverse side of the front page). Overall, there was a balanced level of attrition across groups for the primary outcome measure at 6 (n=8 Comparator group; n= 6 Mobilisation group) and 52 week follow-up (n=4 Comparator group; n=7 Mobilisation group), thus, imputation tests for missing data were not conducted later in the analysis (Section 5.20.4).

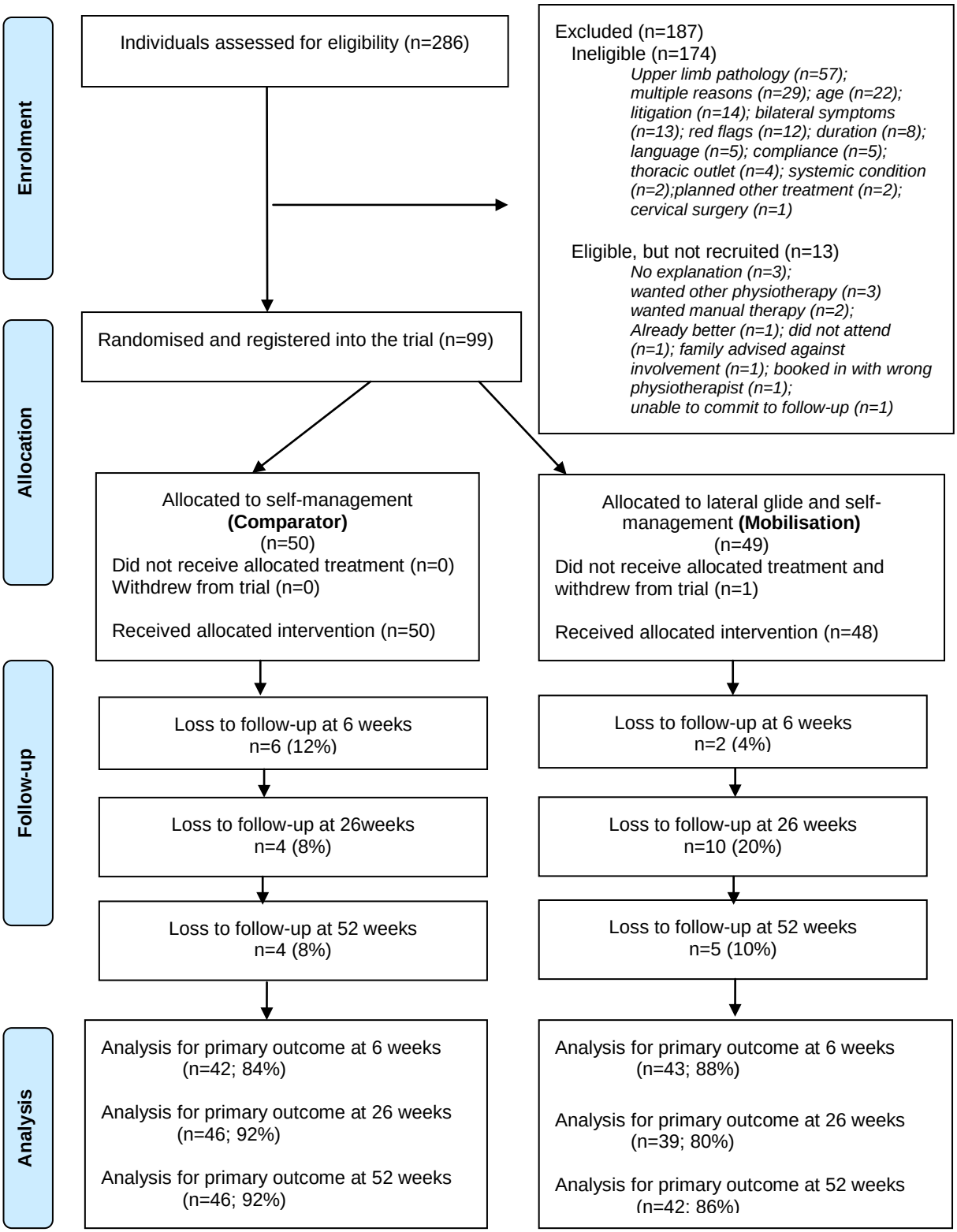


Figure 6-1: Participant flowchart of the trial (Adapted from Moher et al., 2010)

Footnote: For each Group, at each endpoint, the number of participants who were eligible for inclusion in analysis of the primary outcome measure= the number of participants in that Group less the number who were lost to follow-up and/or did not complete VAS(worst pain) at that endpoint.

6.3 Recruitment

Participants were recruited from 7th July 2009 to 30th August 2011. Initially, four centres were included as part of the trial: two community primary care centres in Birmingham, one acute general hospital in the West Midlands and one orthopaedic centre in Bristol. However, neither community centre recruited any participants during the first year of the trial. Whilst a combination of events contributed to this, the major reason was changes to the musculoskeletal service at each centre that resulted in a noticeable negative effect on staff morale and resignation of several staff, including those who had been trained to participate in the research trial. Additional staffing and service pressures prohibited commitment from the local collaborator at one of the centres and the research co-ordinator at the other went on maternity leave. Consequently, it became unfeasible to run the trial at these sites and participation of the two community centres was discontinued one year into the trial.

There were also difficulties at the orthopaedic centre, with only three participants being recruited over one year. The local collaborator attributed the low recruitment (two participants in the first four months) to a period of annual leave affecting many of the staff involved with the trial. When recruitment did not improve (over the next two months), the Principal Investigator arranged a meeting with the local collaborator and research co-ordinator. The key issue was that potential participants were not being seen by Assessment Physiotherapists, so, were not being identified for the trial. Although a number of strategies were put in place to address this, further issues prevailed, including maternity leave of clinical staff, sickness absence and role change of clinical staff involved in the trial. Given these difficulties, the local collaborator felt unable to continue overseeing the project and, therefore,

participation of the orthopaedic centre was discontinued. Data from the three participants recruited from this site were excluded from the data analysis, since it has been reported that recruitment imbalance across sites may lead to loss of study power (Senn, 1998; Lin, 1999). Although statistical models have been developed to address imbalance in multi-centre studies (Ruvuna, 1994; Vierron & Giraudeau, 2009), when extreme imbalance exists (as in this trial) excluding participants has been advocated as a more practical option (Pickering & Weatherall, 2007).

Ninety nine participants were recruited over a period of 25 months from the acute general hospital in the West Midlands. Average rate of recruitment increased over the duration of the trial (Figure 6-2)

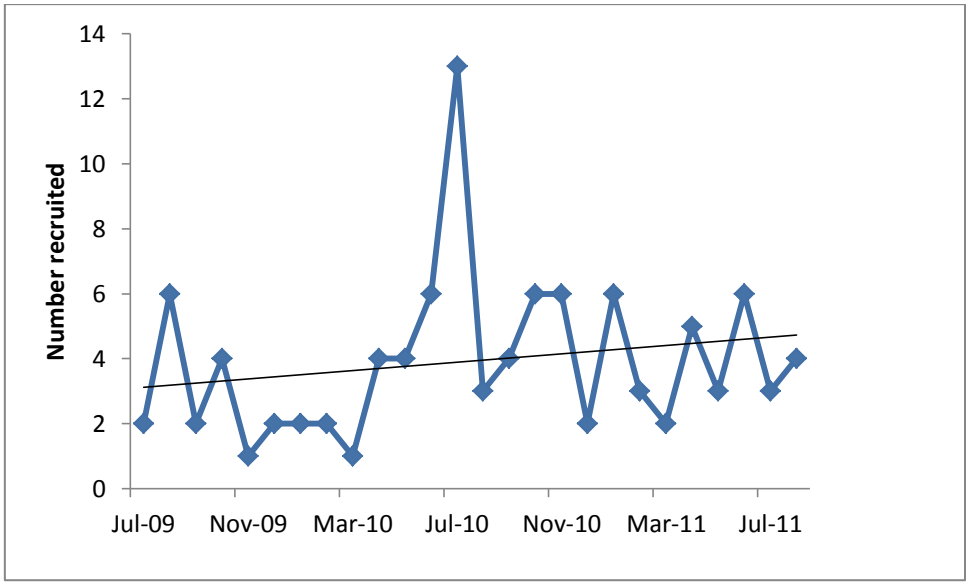


Figure 6-2: Recruitment from the West Midlands site over the course of the trial

The increase was achieved through the following actions by the Principal Investigator: a) advertising the trial to local general practitioners in March 2010, resulting in an increased number of GP referrals for patients with cervicobrachial pain

to the physiotherapy department; b) informing orthopaedic consultants at the Trust, in July 2010, about the trial during a verbal presentation on physiotherapy developments within the Trust, resulting in a substantial rise to the number of participants referred by the orthopaedic team in July 2010.

6.4 Characteristics of Trial Physiotherapists

Five physiotherapists delivered the intervention. They had been qualified at least 2 years, with between 1 and 4 years' experience in musculoskeletal physiotherapy; one had never used the lateral glide and 4 had sometimes used it (Table 6-1). The majority of Trial Physiotherapists did not have a preference at the start of the trial, but developed a preference in favour of the lateral glide by the end (Table 6-1).

Table 6-1: Characteristics of Trial Physiotherapists (n=5)

	Trial Physiotherapists	
Time	**Characteristic**	**n(%)**
Start of trial	Number of years qualified:	
	2 - 3	3 (60)
	4 - 5	1 (20)
	>5	1 (20)
	Number of years in MSk PT:	
	1 -2	3 (60)
	3 -4	1 (20)
	>4	1 (20)
	Familiarity of lateral glide:	
	Never used	1 (20)
	Sometimes used	4 (80)
	Frequently used	0 (0)
	Preference to mgt:	
	Self-mgt with mobilisation	1 (20)
	Self-mgt	0 (0)
	No preference	4 (80)
End of trial	Preference to mgt	
	Self-mgt with mobilisation	4 (80)
	Self-mgt	0 (0)
	No preference	1 (20)

Key: mgt= management; MSk PT=musculoskeletal physiotherapy; n= number of Trial Physiotherapists

6.5 Variability in participant follow-up

6.5.1 Follow-up time point

Deviations from the planned follow-up time points of 6, 26 and 52 weeks post the commencement of intervention (Table 6-2) were due to reasons such as holidays, sickness and work commitments. Such reasons were expected in a pragmatic clinical trial (Gueorguieva & Krystal, 2004; Kwok et al., 2008). It was recognised that this could have had a confounding effect for analyses using ANCOVA, but were addressed by using the MLM analyses.

Table 6-2: Participant follow-up times (in weeks)

Planned follow-up points	Intervention					
	Comparator (n=50)			Mobilisation(n=49)		
	Mean (SD)	Min^n, Max^m	Missing	Mean (SD)	Min^n, Max^m	Missing
6 weeks	7 (2)	4,16	8	6 (2)	4, 12	6
26 weeks	27 (3)	22,37	4	27 (4)	23,40	10
52 weeks	55 (5)	47,70	4	53 (9)	48,107	7

Key Max^m =maximum data point; Min^m =minimum data point; n= number of participants; SD= standard deviation

6.5.2 Variability in method of follow-up

Different methods for data collection were used for some of the outcome measures at 52 weeks (final outcome time point). Most participants (n= 78; 88%) completed the standard questionnaire at final outcome time point. Eleven participants (12%), who did not attend the 52 week review appointment, completed a shortened version of the

questionnaire via the postal system. The postal questionnaire was used by 9(10%) and 2(2%) of the Comparator and Mobilisation groups, respectively.

6.6 Baseline data of participants

No statistical tests were conducted on baseline differences as identifying whether a variable was statistically different or not, was not the method for selecting confounders for the main analyses (Section 5.20.1). However, an appreciation of between-group characteristics was included to provide information to support arguments when interpreting the results.

Baseline demographic data (Table 6-3) indicated that participants in the two groups had similar characteristics. The mean age of participants was 47 years, in each group. There were slightly fewer female participants in the Comparator group (n=24; 47%), compared with the Mobilisation group (n=27; 53%).

The range of occupations was similar across groups. More participants in the Mobilisation group (n=10) had an extended time off work (>16 days) compared to the Comparator group (n=3). Thirty-five participants in the trial smoked. The majority of smokers were male (n=20). Thirty per cent (n=15) in the Mobilisation group smoked compared with 40% (n=20) in the Comparator group.

Table 6-3: Demographic characteristics for randomised participants, at baseline (n=99)

Variables	Intervention					
	Comparator (n=50)			Mobilisation(n=49)		
	Mean (SD)	Min^n, Max^m	Missing	Mean (SD)	Min^n, Max^m	Missing
Age(years)	47 (11)	18,64	0	47 (11)	21,65	0
	n(%)			n(%)		
Gender						
Females	24(47)		0	27(53)		0
Occupation						
Retired	3(6)		1	4(8)		0
Unemployed	3(6)			3(6)		
Desk worker	14(28)			10(20)		
Manual work	20(40)			22(45)		
Other	9(18)			10(20)		
Sickness (days)			0			0
None	35			35		
1 - 5	1			0		
6 -10	2			1		
11 -15	2			0		
>16	3			10		
Not applicable	7			3		
Smoker Yes	20(40)		0	15(30)		2

Key: Max^m =maximum data point; Min^m =minimum data point; n= number of participants; SD= standard deviation

Baseline clinical characteristics were similar across groups, with no clinically meaningful differences (Table 6-4). The majority of participants (78% Comparator group; 73% Mobilisation group) were mechanically neutrally sensitised (positive ULNE), had symptoms in a C5/6 distribution (44% Comparator group; 59% Mobilisation group), had pain with sensory dysfunction (55% Comparator group; 56% Mobilisation group) and had symptoms for greater than one year (42% Comparator group; 40% Mobilisation group). The majority of participants were right arm dominant; however, there was no apparent relationship between arm dominance and side affected by cervicobrachial pain.

More participants in the Mobilisation group had received physiotherapy for their cervicobrachial pain in the past. Benefit from previous physiotherapy was less in the Mobilisation group (47%) compared to the Comparator group (92%); however past physiotherapy experience did not affect preference for intervention-type.

Table 6-4: Clinical characteristics for randomised participants, at baseline (n=99)

Variables		Intervention					
		Comparator (n=50)			Mobilisation (n=49)		
		Mean (SD)	Min[n], Max[m]	Missing	Mean (SD)	Min[n], Max[m]	Missing
VAS(worst pain)		65(20)	3, 96	0	63 (22)	0, 97	0
SF-36		65(17)	18, 87	0	60 (18)	22, 91	0
VAS(average pain)		48(19)	2, 89	0	47 (20)	0, 89	0
NULI		30(17)	7,78	0	36 (19)	0,88	0
TAMPA		37(6)	24, 49	0	37(7)	23, 60	1
S-LANSS		11(5)	0, 24	3	11(5)	3, 24	4
		n (%)			**n (%)**		
Chronicity (months)	2 - 3	5(10)		0	6(12)	0	
	>3 - 6	10(20)			11(22)		
	>6 - 12	14(28)			13(25)		
	>12	21(42)			19(40)		
ULNE test	Positive	39 (78)		0	36(73)	0	
WAD	Yes	6 (12)		0	5 (10)	1	
Dominant arm	Right	45 (92)		1	47 (96)	0	
Side involved	Right	27 (54)		0	28 (57)	0	
Distribution	C4/5	22(18)		0	11(22)	0	
	C5/6	9(44)			29(59)		
	C6/7	14(28)			5(10)		
	C7T1	5(10)			4(8)		
Dysfunction	Pain only	9(18)		1	11(23)	1	
Pain & sensory change		27(55)			27(56)		
Pain, sensory & motor change		13(27)			10(8)		
Preference	None	36 (72)		0	36 (74)	0	
	To control	2 (4)			2 (4)		
	To lateral glide	12 (24)			11 (22)		
Previous physiotherapy	Yes	14 (29)		1	19 (39)	0	
Benefit from previous physiotherapy	Yes	12 (92)		1	9 (47)	0	

Key: NULI= Neck and Upper Limb Index; n= number of participants; SF-36= Short-from 36; S-LANSS= Self Leeds Assessment of Neuropathic Signs and Symptoms; SD= standard deviation; TAMPA= Tampa scale of kinesiophobia; ULNE= Upper Limb Nerve Extensibility; VAS= Visual Analogue Scale; WAD= Whiplash associated disorder

6.6.1 Baseline characteristics of responders versus non-responders

Important trial variables at baseline were analysed for participants who completed the VAS(worst pain) outome (i.e. responders) and those who did not complete the VAS(worst pain) outcome (i.e. non-responders) at the primary end point (52 week follow-up). Table 6-5 shows that no statistically significant differences were found on age, VAS(worst pain) and SF36. More male participants responded in the Comparator group compared to the Mobilisation group, but, the same trend was not seen for females. Increased levels of chronicity led to an increase in response rate in the Comparator group, however this did not seem to affect response rate in the Mobilisation group.

Table 6-5: Potential baseline confounding variables for responders and non-responders, by intervention group, on key variables at 52 week follow-up

	Non-responders		**Responders**		
Variable	**Comparator**	**Mobilisation**	**Comparator**	**Mobilisation**	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean(SD)	P value
Age	52(10)	41(7)	47(11)	49(11)	0.33
VAS(worst pain)	71(6)	68(33)	65(20)	63(22)	0.41
SF36	68(4)	53(22)	65(17)	59(18)	0.37
	n(%)	n(%)	n(%)	n(%)	
Gender					NA
Female	2(4)	3(6)	22(43)	24(47)	
Male	1(2)	4(8)	25(52)	18(38)	
Chronicity (months)					NA
2 - 3	2(18)	1(9)	3(27)	5(46)	
>3 - 6	0(0)	2(10)	10(47)	9(43)	
>6 - 12	1(4)	1(4)	13(50)	12(42)	
>12	0(0)	3(8)	21(53)	16(40)	

Key: n = number of participants; SD= standard deviation; NA= not applicable

Footnote: p= probability from Independent sample t-test between responders to non-responders; Responder= participants who responded to 52 week follow-up on VAS(worst pain);
Non-responder= participants who did not respond to 52 week follow-up on VAS(worst pain).

6.7 Protocol violations at each follow-up

6.7.1 Protocol violations at six-week follow-up

In this trial, all participants received their randomised intervention. There was one protocol violation during the intervention period (defined as the period up to the six week follow-up). A participant in the Mobilisation group received additional treatment (acupuncture). This participant later withdrew and did not attend any follow-up period.

6.7.2 Protocol violations beyond six week follow-up

Forty-seven participants (47%) received additional treatment following the intervention period (Table 6 6). Although this was a seemingly high level of additional treatment, there was no statistically significant inter-group difference (for responders at one year) on the use of additional treatment between the end of the intervention period and one year follow-up (p= 0.93).

Table 6-6: Treatment received beyond the intervention period (6 weeks to one year)

	Intervention			
	Comparator	**Mobilisation**	Total	p value
Additional Treatment	n (%)	n (%)		
None	15 (30)	13 (27)	28	
Some	23 (46)	24 (49)	47	
Unknown	12 (24)	12 (24)	24	
Total	50	49	99	p=0.93

Key: n = number of participants; p= probability from Chi-Square test

Most additional treatment included other forms of physiotherapy intervention, including acupuncture. None of the participants went on to receive any injection therapy. Two participants went on to receive surgery to the cervical spine; both were in the Mobilisation group.

6.8 Primary outcome measure - VAS(worst pain)

Scores on VAS(worst pain) varied from 0 to 97mm in the Comparator group and 0 to 100mm in the Mobilisation group (Table 6-7, Figure 6-3). Mean scores ranged from 65 (baseline) to 37 (52 week follow-up) in the Comparator group and 63 (baseline) to 40 (26 weeks) in the Mobilisation group.

Table 6-7: Summary statistics for VAS(worst pain) at each time point

	Intervention							
	Comparator				**Mobilisation**			
Time point:	n (%)	Mean (SD)	Median (Q1,Q3)	min^m, max^m	n (%)	Mean (SD)	Median (Q1,Q3)	min^m, max^m
Baseline	50(100)	65(20)	70(50,78)	3,96	49(100)	63(22)	71(46,78)	0,97
6 week follow-up	42(84)	46(28)	44(22,72)	1,94	43(88)	49(29)	54(27,73)	0,100
26 week follow-up	46(92)	40(31)	38(10,71)	0,93	39(80)	40(28)	40(12,66)	0,84
52 week follow-up	46(92)	37(32)	29(6,6)	0,97	42(86)	42(30)	44(8,97)	0,94

Key: max^m =maximum value; min^m =minimum value; n= number of participants; SD=standard deviation; Q1=lower quartile; Q3=upper quartile

6.8.1 Primary analysis (long-term effects)

There was a mean decrease of 28mm for the Comparator group and 21mm for the Mobilisation group for VAS(worst pain) at 52 week follow-up compared to baseline (Table 6-7). This indicated that there was a clinically meaningful improvement, on average, for participants in both groups.

There was no statistically significant difference in mean scores on VAS(worst pain) between groups at follow-up 52 weeks, using a covariate analysis (p=0.37; 95% CI -17.76 to 6.61) (Table 6-8).

Table 6-8: VAS(worst pain) at 52 weeks (n=88) using ANCOVA

		95% CI		
	Mean difference between baseline and 52 weeks	**Lower bound**	**Upper bound**	**p-value**
Between intervention difference	-5.57	-17.76	6.61	0.365
Covariates				
Age (years)	-0.30	-0.86	0.25	0.281
Gender	8.95	-2.99	20.90	0.139
VAS(worst pain) at baseline	-0.51	-0.82	-0.20	0.002*
SF36 at baseline	-0.39	-0.75	-0.28	0.035*
Chronicity a baseline	4.28	-1.90	10.46	0.172

Key: CI= confidence interval; n= number of participants; SF-36= Short-from 36

Footnote: Differences in mean VAS(worst pain) computed as follow-up minus baseline
* indicates a statistically significant finding at 0.05
Levene's test for homogeneity p=0.78, therefore heterogeneity did not violate the test

6.8.2 Secondary analysis (short-term effects, 6 week follow-up)

There was a mean decrease of 19mm for the Comparator group and 14mm for the Mobilisation group for VAS(worst pain) at 6 week follow-up compared to baseline (Table 6-7). This indicated that there was no clinically meaningful improvement, for participants in either group.

There was no statistically significant difference in mean scores on VAS(worst pain) between groups at follow-up 6 weeks, using a covariate analysis (p=0.52; 95% CI -14.72 to 7.44) (Table 6-9).

Table 6-9: ANCOVA analysis for VAS(worst pain) at 6 weeks (n=85)

	Mean difference between baseline and 6 weeks	95% CI		p-value
		Lower bound	Upper bound	
Between intervention Difference (at baseline)	-3.64	-14.72	7.44	0.515
Covariates				
Age (years)	0.13	-0.42	0.67	0.640
Gender	2.35	-8.68	13.38	0.673
VAS(worst pain)	0.66	0.37	0.95	0.000*
SF36	-0.07	-0.41	0.26	0.663
Chronicity	6.53	0.97	12.09	0.022*

Key: CI= confidence interval; n= number of participants; SF-36= Short-from 36

Footnote: Differences in mean VAS(worst pain) computed as follow-up minus baseline
* indicates a statistically significant finding
Levene's test for homogeneity p=0.79, therefore heterogeneity did not violate the test

6.8.3 Tertiary analysis (longitudinal effects)

Using MLM (Section 5.20.4), there was a statistically significant decrease in VAS(worst pain) over time (p=0.001) (Figure 6-7). After accounting for time and statistically significant baseline covariates (SF36 p=0.0005; age p= 0.049) there was no statistically significant difference in mean VAS(worst pain) scores (p=0.808; 95% CI -6.81 to 8.73) between the Comparator and Mobilisation groups over time (Figure 6-7). Details of this analysis are given in Appendix O.

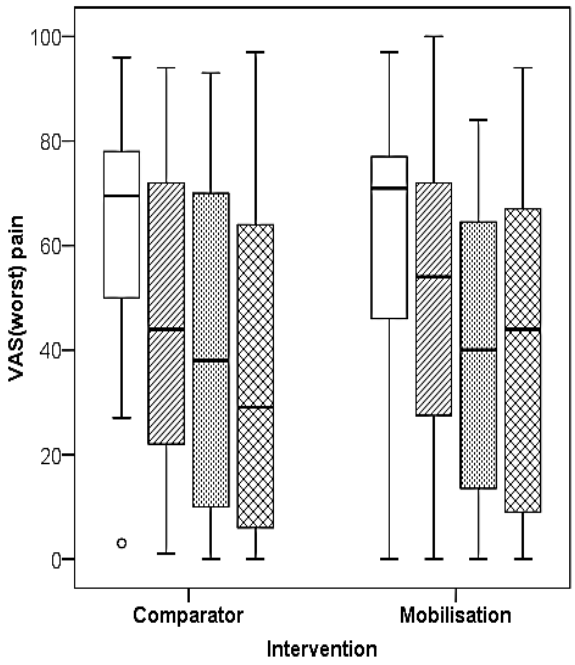


Figure 6-3 Boxplots for VAS(worst pain) over time

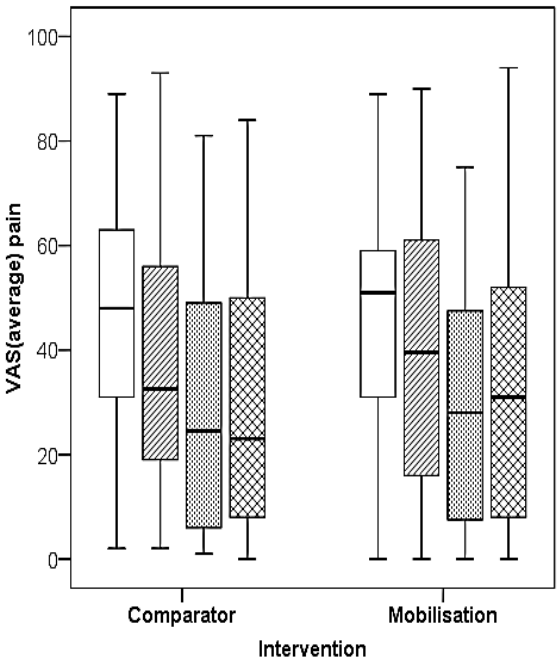


Figure 6-4 Boxplots for VAS(average pain) over time

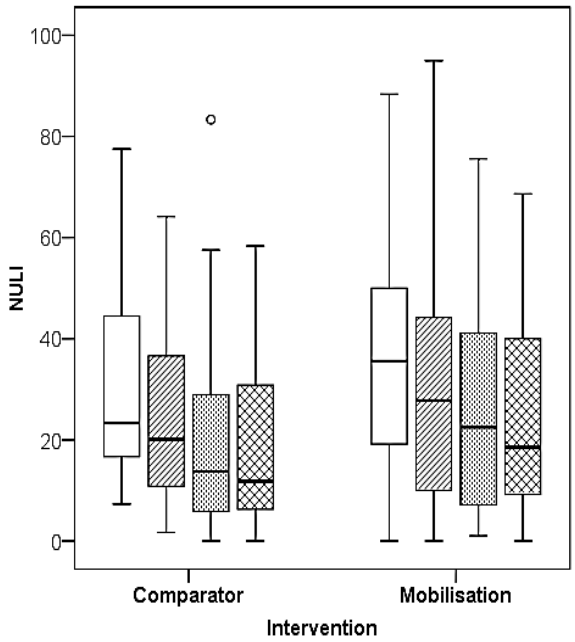


Figure 6-5 Boxplots for NULI over time

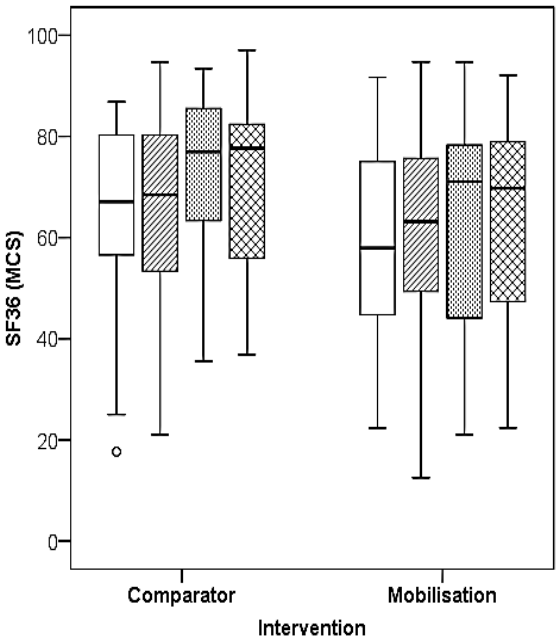
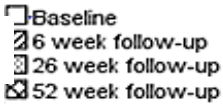


Figure 6-6 Boxplots for SF36 over time

Key for figures 6-3 to 6-6:



° represents an outlier value.

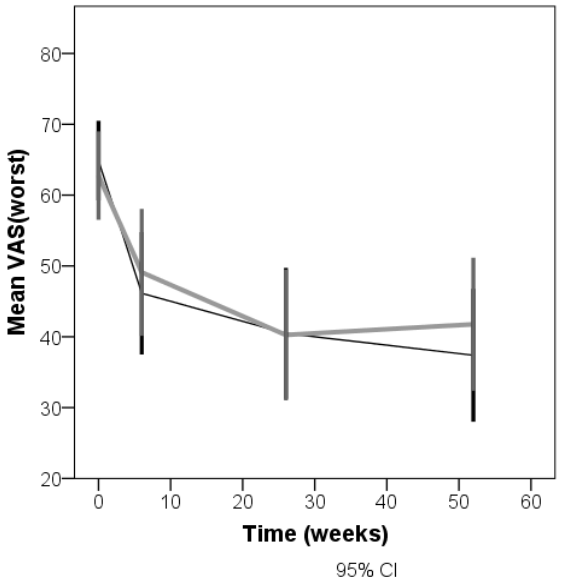


Figure 6-7 Longitudinal VAS(worst pain) (MLM)

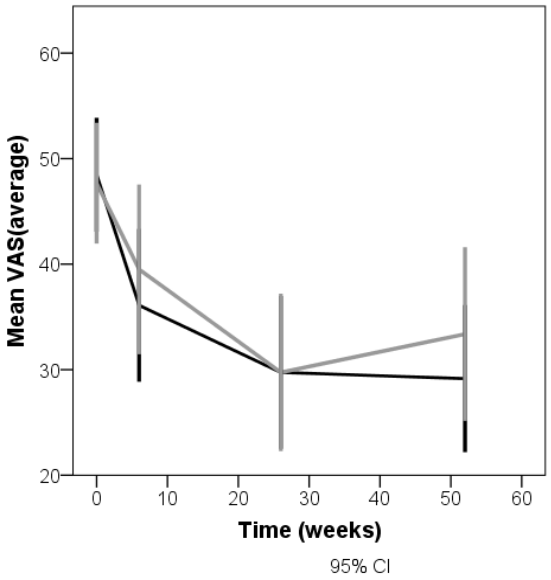


Figure 6-8 Longitudinal VAS(average pain) (MLM)

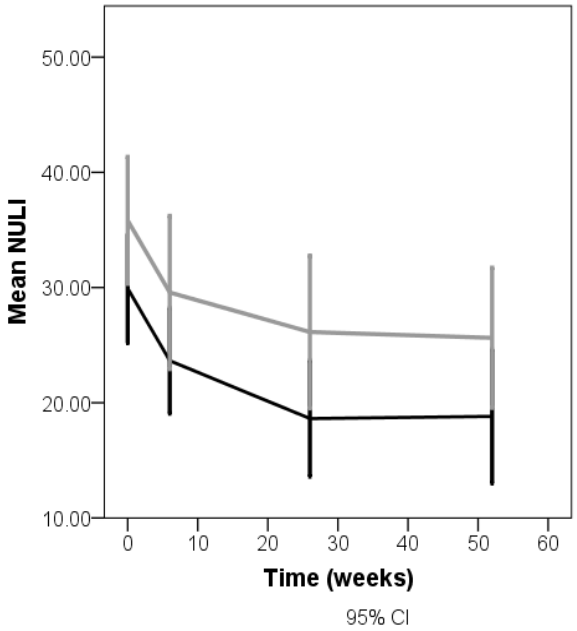


Figure 6-9 Longitudinal NULI (MLM)

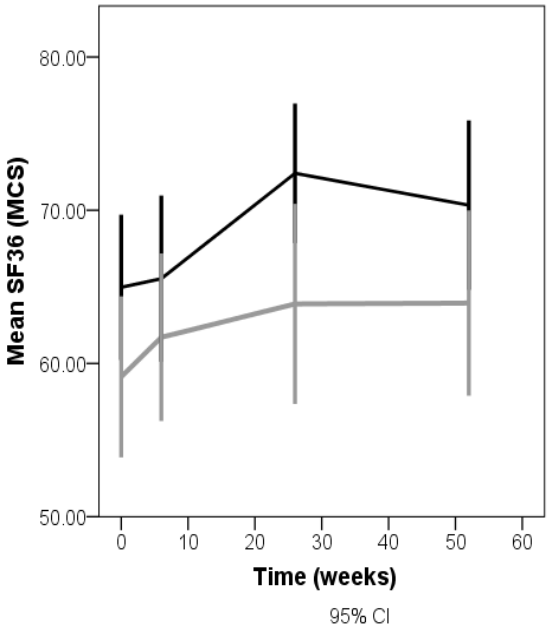


Figure 6-10 Longitudinal SF36 (MCS) (MLM)

Key for Figures 6-7 to 6-10: ▌ Comparator group
▌ Mobilisation group
CI= Confidence Interval

Footnote: A reduction in scores on VAS and NULI represent an improvement.
Increases in scores on SF36 (MCS) represent an improvement.
The 95% CI's are for individual interventions and not the difference between interventions

6.9 Secondary outcome measures for pain

The secondary outcome measures on pain were ‘average pain over the past week’ (VAS(average pain)), Global rating of change (GROC) and use of medication (meds)

6.9.1 VAS(average pain)

VAS(average pain) varied from 0 to 93 in the Comparator group and 0 to 94 in the Mobilisation group (Table 6-10, Figure 6-4). Mean scores ranged from 48 (baseline) to 28 (52 week follow-up) in the Comparator group and 48 (baseline) to 30 (26 weeks) in the Mobilisation group. There was a mean decrease of 20mm for the Comparator group and 15 for the Mobilisation group at 52 week follow-up compared to baseline (Table 6-10). This indicated that there was a clinically meaningful improvement for the Comparator group only. The mean between-group difference from baseline to 52 week follow-up was 5mm, which was not a clinically meaningful difference.

Using MLM, there was a statistically significant decrease in VAS(average pain) over time across both groups at six weeks (p=0.001) and 26 weeks (p=0.03), but not at one year (p=0.08) (Figure 6-8). After accounting for time and statistically significant baseline covariates (SF36 p<=0.005; age p=0.04), there was no statistically significant difference in mean VAS(average pain) scores (p=0.867; 95% CI -5.91 to 7.00) between the Comparator and Mobilisation groups (Figure 6-8).

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Table 6-10: Summary statistics for secondary outcome measures for pain at each time point

	Intervention							
	Comparator				Mobilisation			
Time point:	n (%)	Mean (SD)	Median (Q1,Q3)	min^m, max^m	n (%)	Mean (SD)	Median (Q1,Q3)	min^m, max^m
VAS(average pain)								
Baseline	50(100)	48(20)	48(31,63)	2,89	49(100)	48(21)	51(30,60)	0,89
6 week follow-up	42(84)	36(23)	32(19,57)	2,93	44(90)	40(26)	39(16,61)	0,90
26 week follow-up	46(92)	29(24)	24(6,50)	1,81	39(80)	30(23)	28(6,48)	0,75
52 week follow-up	35(70)	28(24)	22(8,50)	0,84	52(86)	33(27)	32(8,55)	0,94
GROC								
6 week follow-up	43(86)	2(2)	3(1,4)	-5,6	44(90)	2(3)	2(0,4)	-4,6
		n (%)				n (%)		
Use of medication (at 6 week follow-up)	41(82)				44(90)			
No meds		14(28)				12(25)		
Weaker meds		2(4)				6(12)		
Same meds		23(46)				21(43)		
Stronger meds or started to take meds		2(4)				5(10)		

Key: max^m =maximum value; meds= medication; min^m =minimum value; n= number of participants; SD=standard deviation; Q1=lower quartile; Q3=upper quartile

6.9.2 Global rating of change score

GROC scores varied from -5 to 6 in the Comparator group and -4 to 6 in the Mobilisation group at 6 week follow-up, meaning that the range for a perceived worsening was greater in the Comparator group by one point (Table 6-10, Figure 6-11). Mean scores were 2 across groups indicating that, on average, both groups had achieved a clinically meaningful improvement (Table 6-10).

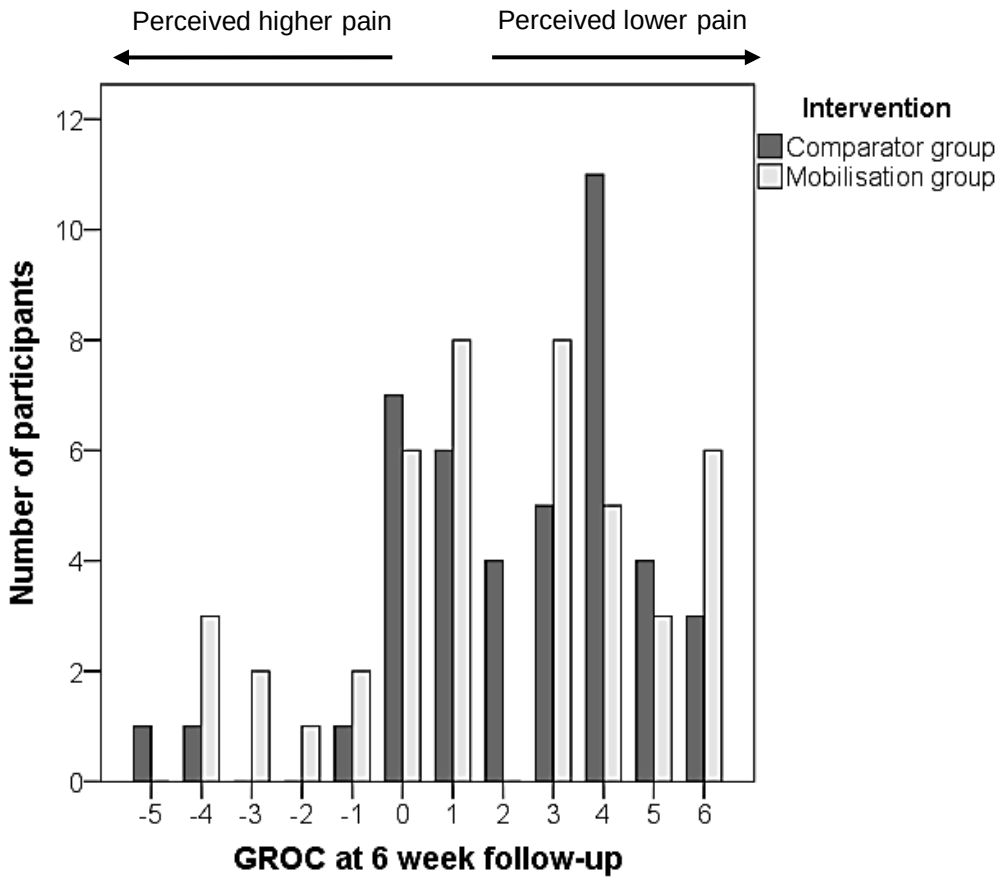
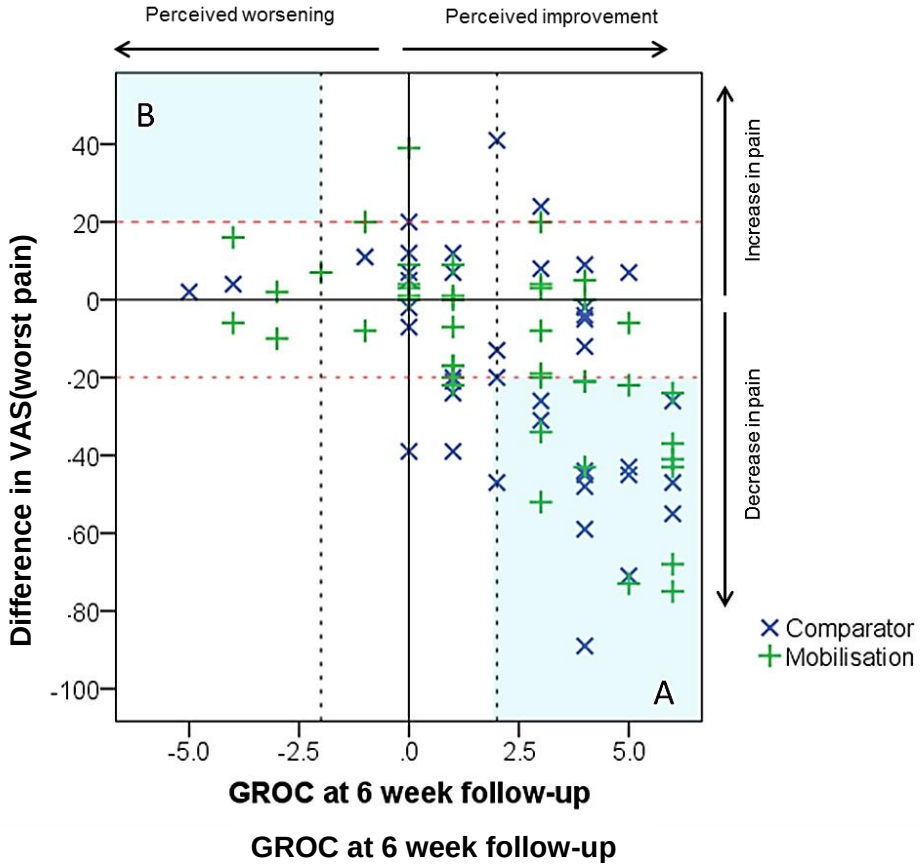


Figure 6-11: GROC scores at 6 week follow-up (perceived changes in pain from baseline)

Footnote: interpretation for GROC scores. –ve signs indicates worsening of pain, +ve signs indicates lessening of pain

0 no change
2 minimal clinically meaningful difference
3 moderate clinically meaningful difference
4 large clinically meaningful difference
5 very large clinically meaningful difference

There was a moderate association (Spearmans rho = 0.69; p<0.001) between GROC and VAS(worst pain) at six weeks (Figure 6-12). No participant was clinically worse on both outcome measures (VAS(worst pain) score > or equal to 20 and GROC score < or equal to 2; Figure 6-12, box B). Twenty-seven of the participants were clinically improved on both outcome measures (box A), 13 of which were in the Mobilisation group.



GROC at 6 week follow-up

Figure 6-12: VAS(worst) difference in pain score (from 6-week follow-up to baseline) compared with GROC at six weeks follow-up

Key: GROC=Global Rating of Change score; VAS=Visual Analogue Scale

Footnote: Red dotted line represents clinically meaningful difference on VAS
Black dotted line represents clinically meaningful difference on GROC
Box A indicates a clinically meaningful improvement on both GROC and VAS
Box B indicates a clinically meaningful worsening on both GROC and VAS

6.9.3 Use of medication

Approximately half the participants (n=44; 52%) were using the same medications at six week follow up as at baseline (Table 6-10). There was no statistically significant between-group difference on medication use at 6 week follow-up (Mann-Whitney Z score = -0.49; p=0.63).

6.10 Secondary outcome measures - function & disability

The Neck and Upper Limb Index (NULI) scores varied from 0 to 83 in the Comparator group and 0 to 95 in the Mobilisation group (Table 6-11, Figure 6-5). Mean scores ranged from 30 (baseline) to 19 (26 and 52 week follow-ups) in the Comparator group and 36 (baseline) to 26 (26 and 52 weeks) in the Mobilisation group. There was a mean decrease of 11 points for the Comparator group and 10 points for the mobilisation group on NULI at 26 week follow-up compared to baseline. This improvement was maintained in both groups at 52 weeks (Table 6-11).

Table 6-11: Summary statistics for secondary outcome measures for function and disability at each time point

Time point:	Intervention							
	Comparator				Mobilisation			
	n (%)	Mean (SD)	Median (Q1,Q3)	min^m, max^m	n (%)	Mean (SD)	Median (Q1,Q3)	min^m, max^m
NULI								
Baseline	50(100)	30(17)	23(17,45)	7,78	49(100)	36(19)	36(19,51)	0,88
6 week follow-up	44(88)	24(15)	20(11,37)	2,64	45(92)	30(22)	28(10,44)	0,95
26 week follow-up	46(92)	19(17)	14(6,30)	0,83	39(80)	26(20)	23(7,42)	1,76
52 week follow-up	36(72)	19(17)	12(6,32)	0,53	42(86)	26(20)	19(9,40)	0,69
SF36								
Baseline	50(100)	65(17)	67(56,80)	18,87	49(100)	59(18)	58(45,76)	22,92
6 week follow-up	44(88)	66(18)	68(53,80)	21,95	44(90)	62(18)	63(49,77)	13,95
26 week follow-up	46(92)	72(15)	77(63,86)	36,93	39(80)	64(20)	71(43,80)	21,95
52 week follow-up	36(72)	70(16)	78(55,83)	37,97	42(86)	64(19)	70(47,79)	22,92

Key: max^m =maximum value; min^m =minimum value; NULI= Neck and Upper Limb Index; n= number of participants; Q1=lower quartile; Q3=upper quartile, SD=standard deviation; SF36 (MCS) = Short-form 36 (Mental Component Summary); Tampa= Tampa scale of kinesiophobia.

Using MLM, there was a statistically significant decrease in NULI over time at six weeks (p=0.001) and 26 weeks (p=0.01), but not at one year (p=0.19) (Figure 6-9). After accounting for time and statistically significant baseline covariates (gender p=0.04; chronicity p=0.04), there was a statistically significant difference in mean NULI scores (p=0.03; 95% CI -13.53 to -0.92) between the Comparator and Mobilisation groups, favouring the effectiveness of the Comparative intervention (Table 6-12, Figure 6-9).

The SF36 (MCS) scores varied from 18 to 97 points in the Comparator group and 13 to 95 in the Mobilisation group (Table 6-11, Figure 6-6). Mean scores ranged from 65 (baseline) to 72 (26 week follow-up) in the Comparator group and 59 (baseline) to 64 (26 and 52 weeks) in the Mobilisation group (Table 6-11, Figure 6-6). There was a mean increase of 5 points in both groups at 52 week follow-up.

Using MLM, there was no statistically significant decrease in SF36 (MCS) over time at any of the follow-up periods (p>0.05). After accounting for time and statistically significant baseline covariates (gender p=0.01; chronicity p=0.00), there was no statistically significant difference in mean SF36(MCS) scores (p=0.07;95% CI -0.37 to 12.07) between the Comparator and Mobilisation groups (Table 6-12, Figure 6-10).

Table 6-12: Participant based outcome measures: MLM between-group analysis

Outcome measure	Estimate of effect	95% CI		p-value
		Lower bound	Upper bound	
NULI	6.91	-13.53	-0.92	0.03*
SF36 (MCS)	5.85	-0.37	12.07	0.07

Key: NULI=Neck and Upper Limb Index; SF36(MCS)=Short-form 36 (Mental Component Summary)
Footnote: * indicates a statistically significant finding

6.10.1 Cervical Active Range of Movement (AROM)

Cervical active range of motion varied from 10° to 100° in the Comparator group and 5° to 95° in the Mobilisation group (Table 6-13). Mean scores varied from 35° (baseline right side bend) to 72° (left rotation at 52 weeks) in the Comparator group and 34° (baseline right side bend) to 69° (left rotation at 26 weeks) in the Mobilisation group (Table 6-13). None of the movements had clinically meaningful difference from baseline (a change of 10°) at any of the follow-up time points.

Table 6-13: Summary statistics for cervical active range of motion at each time point

Movement		Intervention							
		Comparator				Mobilisation			
		n(%)	Mean (SD)	Median (Q1,Q3)	min^m, max^m	n(%)	Mean (SD)	Median (Q1,Q3)	min^m, max^m
Flexion	Baseline	50(100)	49(15)	50 (39,60)	20,80	49(100)	47(13)	45 (40,60)	15,70
	6 wk follow-up	44(88)	53(16)	55 (45,64)	10,100	45(92)	49(15)	50 (40,55)	15,70
	26 wk follow-up	46(92)	57(15)	60 (45,70)	25,90	39(80)	49(15)	50 (40,60)	20,85
	52 wk follow-up	36(72)	56(14)	58 (45,65)	25,80	42(86)	51(16)	50 (44,61)	15,80
Extension	Baseline		48(14)	45 (35,56)	20,85		46(15)	45 (40,55)	15,75
	6 wk follow-up		52(14)	50 (45,60)	20,100		49(16)	50 (35,58)	20,90
	26 wk follow-up		51(14)	50 (45,60)	10,90		49(15)	50 (40,60)	15,80
	52 wk follow-up		50(14)	50 (40,60)	20,80		46(14)	45 (36,55)	15,70
Right side bend	Baseline		35(12)	35 (25,45)	10,55		34(10)	35 (28,41)	15,60
	6 wk follow-up		41(13)	40 (35,45)	20,85		39(12)	35 (30,45)	15,80
	26 wk follow-up		44(14)	40 (35,50)	15,85		38(14)	35 (30,45)	20,90

	52 wk follow-up	42(11)	40 (35,50)	20,65	36(12)	35 (30,45)	5,65
Left side bend	Baseline	38(11)	35 (30,46)	15,60	35(11)	35 (25,42)	15,65
	6 wk follow-up	40(13)	40 (31,45)	10,85	37(12)	35 (30,45)	15,70
	26 wk follow-up	45(15)	40 (34,51)	20,90	36(14)	35 (30,45)	15,85
	52 wk follow-up	42(13)	40 (30,50)	20,70	36(11)	35 (29,45)	15,65
Right rotation	Baseline	65(20)	70 (55,85)	20,100	58(17)	60 (45,70)	15,95
	6 wk follow-up	67(18)	70 (60,82)	30,95	63(20)	65 (51,75)	15,95
	26 wk follow-up	67(18)	70 (55,80)	20,95	61(18)	65 (50,75)	25,90
	52 wk follow-up	71(16)	70 (60,85)	40,100	64(18)	65 (50,80)	30,90
Left rotation	Baseline	64(18)	69 (50,80)	25,95	62(17)	60 (53,73)	15,90
	6 wk follow-up	69(19)	75 (55,85)	30,95	64(19)	65 (50,75)	20,95
	26 wk follow-up	70(16)	70 (60,81)	40,95	69(14)	75 (57,80)	35,90
	52 wk follow-up	72(16)	75 (61,85)	35,95	67(18)	65 (55,85)	5,90

Key: max^{m} =maximum value; min^{m} =minimum value; n= number of participants; Q1=lower quartile; Q3=upper quartile, SD=standard deviation; wk= week.

Footnote: number and percentages are shown for flexion, but were the same for all movement outcome measures.

Using MLM, a statistically significant increase in range over time was found at 6 week follow-up for flexion, extension and left rotation. After accounting for time and statistically significant baseline covariates for right rotation (age p= 0.02; gender p=0.00; side involved p=0.00), left rotation (gender p=0.00), right side bend (duration p=0.00), left side bend (age p=0.00) and flexion (gender p= 0.04), there were mixed results. Output from statistical tests indicated no statistically significant findings for most movements measured ($p<0.05$). Statistically significant results were found for left rotation (p=0.04; 95% CI -11.55 to -0.23) and left side bend (p=0.03; 95% CI 0.58 to 8.49) (Table 6-14, Figures 6-13 and 6-14)

Table 6-14 Performance based outcome measures: MLM Between-group analyses

Movement	Estimate of effect	p-value	95% CI	
			Lower bound	Upper bound
Flexion	4	0.11	-0.92	8.93
Extension	3	0.28	-2.09	7.12
Right rotation	5	0.12	-1.19	10.62
Left rotation	6	0.04*	-11.55	-0.23
Right side bend	3	0.06	-1.15	6.92
Left side bend	5	0.03*	0.58	8.49

Footnote: * indicates a statistically significant finding
Covariates included age, gender and side affected by pain

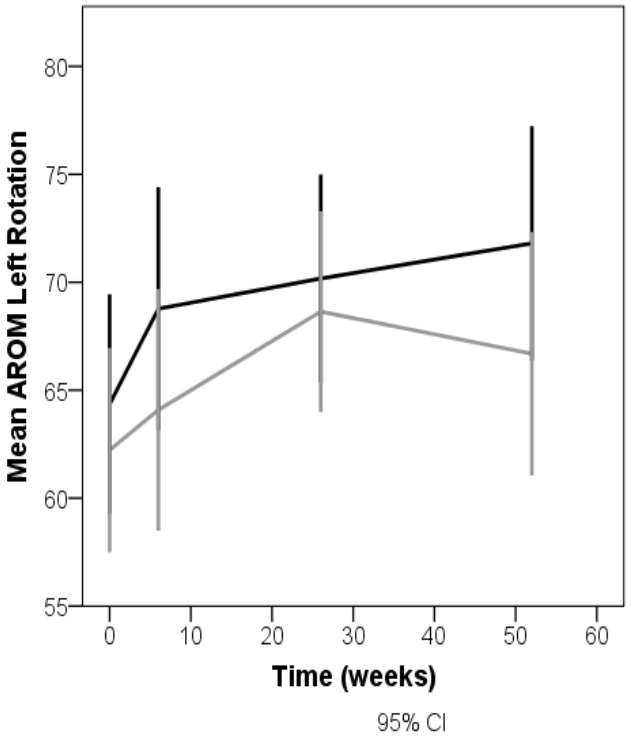


Figure 6-13 Longitudinal AROM into left rotation (MLM)

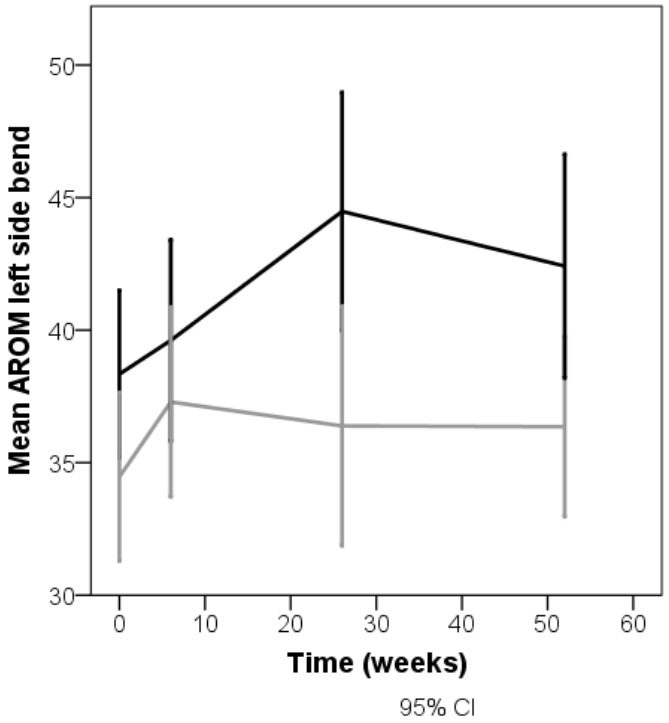


Figure 6-14 Longitudinal AROM into left side bend (MLM)

Key for Figures 6-13 to 6-14: Comparator
Mobilisation
AROM= Active range of motion; CI= Confidence Interval

Footnote: Increases in scores in AROM represent an improvement.
The 95% CI's are for each individual intervention and not the difference between interventions

6.11 Secondary outcome measures on cost

6.11.1 Sickness absence

There was a reduction in the amount of time required off work immediately following the intervention period (6 week follow-up) for both groups. Summary statistics are shown in Table 6-15.

Table 6-15: Time requirements from work due to cervicobrachial pain

	Intervention			
Time off work (within last month)	n	**Comparator** n (%)	n	**Mobilisation** n (%)
Baseline	50		49	
No time off		35(70%)		35(71%)
Time off		8(16%)		11(23%)
Not applicable		7(14%)		3(6%)
Missing		0(0%)		0(0%)
6 week follow-up	50		49	
No time off		34(68%)		28(57%)
Time off		4(8%)		9(18%)
Not applicable		6(12%)		8(16%)
Missing		6(12%)		4(9%)

Key: n= number of participants

Data relating to sickness absence were analysed from 75 participants at six week follow-up: fewer participants were taking time off from work in the Comparator group compared to the Mobilisation group, but this did not reach a statistically significant level using a Mann-Whitney test (p=0.079).

6.11.2 Physiotherapy utilisation

The amount of physiotherapy intervention required by each participant was recorded during the intervention period. The intervention period was defined as the period from baseline to the six week follow-up. During this period the mean number of

attended sessions was more than twice as much for the mobilisation group than in the comparator (Table 6-16). This finding was statistically significant using the Mann-Whitney test (p=0.000).

Table 6-16: Attended sessions during the intervention period (first 6 weeks)

	Control (n=50)	**Mobilisation (n=49)**
Quantity of PT sessions		
Mean (SD)	2 (1)	5 (1)
Range	1 - 4	1 - 8
Missing	2	0

Key: n= number of participants; SD= standard deviation; PT= Physiotherapy

The average 30 minute 'unit cost' for a physiotherapist working at the site was £11.75. Based on this figure, the average cost in the intervention period was £23.50 for a participant in the Comparator group, and £58.75 for a participant in the Mobilisation group.

6.12 Secondary Outcome Measures on Harm

Neither intervention led directly to any severe or moderate harm during the course of the intervention period (as defined in Table 5-2). Minor harm was reported during the intervention period in the trial (Table 6-17).

Table 6-17: Table listing minor harms per intervention type

Self-management (n=99)	**Lateral glide mobilisation (n=49)**
Initially painful to do exercises (n=4) Ear pain when initially started exercises(n=1)	Temporary pain following the glide, resolved next day (n=4) Temporary worsening of paraesthesia following glide for few hours (n=1) Temporary headache following glide, resolved next day (n=1) Pressure from mobilisations uncomfortable (n=1) Slightly dizzy on sitting up following mobilisation (n=1)

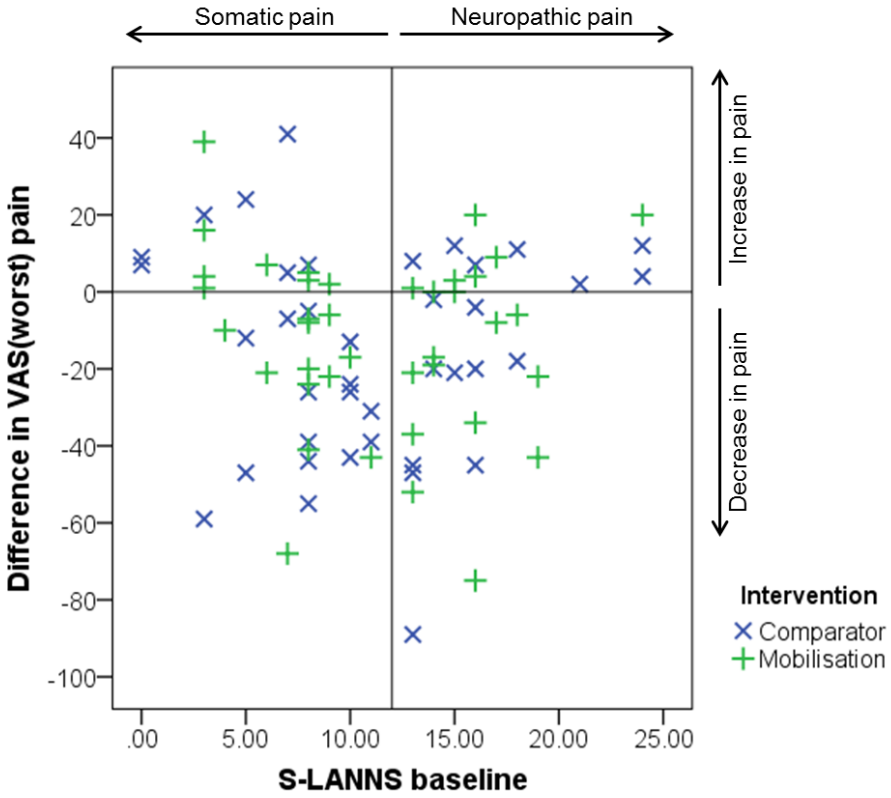
Key: n= number of participants

Minor harm was associated with 5% of self-management intervention compared to 16% of the mobilisation intervention.

6.13 Exploratory analyses

6.13.1 Pain mechanism correlated with VAS(worst pain)

Baseline S-LANNS scores were correlated with differences in VAS(worst pain) to evaluate if a higher neuropathic component (scores of 12 or more) correlated with a change in pain outcome in the short-term. No linear association was seen between the two measures (Figure 6-15). A two tailed analysis using Spearmans Rho found no statistically significant correlation (p=0.74).



Key: S-LANSS= Self Leeds Assessment of Neuropathic Signs and Symptoms; VAS= Visual Analogue Scale

Figure 6-15: VAS(worst pain) (6 weeks minus baseline) compared with SLANSS

6.13.2 VAS(worst pain) outcome for patients with positive ULNE test

The majority of participants in the trial had a positive ULNE test at baseline (n=75; 77%). There was a balanced number of participants with a positive ULNE in each intervention group (Comparator n=39; Mobilisation n=36). Sixty-two participants with a positive ULNE test (90%) were analysed at 6 week follow-up, with an equal split between the groups (Comparator n=32; Mobilisation n=30). Analysis of covariance for mean between-group difference having accounted for baseline values at 6 weeks and covariates used in the main analysis, found no statistically significant change in VAS(worst pain) for this sub-group (p=0.30; 95%.CI -19.02 to 5.94).

6.13.3 Participant preference

Table 6-18 summarises preferences participants had prior to randomisation who were assessed for VAS(worst pain) at six week follow-up. Most participants had not expressed a preference. Of those who did, the lateral glide intervention with self-management was selected more than self-management alone. There was an equal level of preference to receive the lateral glide between the two groups.

Table 6-18: Participant preference at the start of the trial

	Control (n=50)	Mobilisation (n=49)
Preference for intervention		
No preference	30 (60%)	32 (65%)
Self- management	2 (4%)	1 (2%)
Lateral glide	10 (20%)	10 (20%)
Missing	8 (16%)	6 (12%)

An ANCOVA for VAS(worst pain) at six weeks, that used patient preference and intervention as fixed factors, found no statistically significant between group difference (p=0.81). There was no evidence of an effect of patient preference on short-term outcomes for pain response to intervention.

6.14 Summary of results

To retain the trial hypothesis, a statistically significant between-group difference was needed to favour the lateral glide mobilisation in reducing pain at one year. As statistical between-group differences were not found between the lateral glide mobilisation and comparator groups, the null hypothesis (no additional effect of mobilisation) was retained. Consistent findings for other pain outcomes and across time points supported the likelihood that the lateral glide mobilisation, in this instance, did not provide additional affect on pain reduction.

Scores from self-report measures, NULI and SF36 (MCS), were inconclusive. The NULI had a between-group statistically significant result, favouring the Comparator group. SF36 (MCS) between-group scores also found a trend to support the Comparator group, but this did not reach a statistically significant level. However, it was recognised that these outcome measures were not powered for this trial and therefore needed to be interpreted with caution. There were inconsistent findings for functional measures relating to performance based outcome measures (AROM), however, most movements found no statistical between-group differences.

There was no significant between-group difference on sickness absence from work due to cervicobrachial pain. However, a between-group difference was found on Physiotherapy utilisation, with the Mobilisation group requiring approximately double the amount of intervention than that of the Comparator group. Harm associated with the mobilisation was also approximately double that of the comparative intervention. These findings do not support the addition of the lateral glide to a self-management intervention.

Further analyses were used to explore the correlation between pain states on outcome, or whether a selected sub-group of participants (those who were mechanically neutrally sensitive) had different responses to the intervention on the primary outcome. In both instances, there was no evidence of any differences in the findings, indicating that neither participants with a neuropathic dominant pain state, nor participants who were neutrally mechanically sensitive were more or less responsive to different interventions, than in the main study cohort.

There was some evidence that patient preference for use of the glide had no bearing on improved outcome. An unexpected finding was that therapist preference favouring the lateral glide developed during the course of the trial. Although the sample for this was small, and interpretation therefore limited, it is interesting that the directional preference for the therapists was converse to some of the trial outcomes.

The next chapter will discuss and evaluate the merits and limitations of this trial compared to others, to enable a clear understanding for the value of the lateral glide in cervicobrachial pain.

7 DISCUSSION

7.1 Introduction to discussion

This chapter focuses on the findings of the systematic literature review and main trial to critically analyse how manual therapy, and specifically the lateral glide, contributes to the management of cervicobrachial pain. The key outcome measure of pain is evaluated in detail. Secondary outcome measures are related to function and disability. Other factors that are considered include: risk of harm, patient values, patient preferences and cost (Balshem et al., 2011) to enable recommendations and conclusions to be drawn from this body of research.

7.2 Summary of thesis findings

7.2.1 Systematic literature review

The systematic literature review evaluated the effectiveness of non-invasive management for cervicobrachial pain. It identified that, in general, the provision of manual therapy with exercise had a low level of evidence to support its use in reducing pain. There was variability in the manual therapy techniques used in the included studies, with the most frequently reported manual technique being the lateral glide mobilisation. Studies that reported the use of the lateral glide mobilisation consistently reported a positive effect on pain (Allison et al., 2002; Coppieters et al., 2003; Ragonese et al., 2009). However, in the majority of these studies (Allison et al., 2002; Ragonese et al., 2009), the lateral glide was used as part of a manual therapy package, therefore, it was not clear how much improvement in pain was due to the lateral glide mobilisation, or, due to co-interventions used. Only one study evaluated the effectiveness of the lateral glide as a singular treatment

modality (Coppieters et al., 2003) and reported that the mobilisation provided a statistically significant decrease in pain. There were limitations with this study: it was not powered, between-group differences were not reported and only immediate pain response was evaluated. However, the results of the study by Coppieters et al. (2003) were consistent with findings from other studies in which the lateral glide (used in isolation) was effective in reducing pain in neck and upper limb disorders (Vincenzino et al., 1996, 1998; McClatchie et al., 2009; Sterling et al., 2010). However, as with Coppieters et al. (2003), these studies only evaluated the immediate effects of the technique. A need was identified for a statistically powered clinical trial to evaluate whether the lateral glide was effective in reducing pain in either the short or long-term for patients with cervicobrachial pain. Short-term assessment was to establish post-interventional effects and long-term assessment was to justify the efficacy of treatment. It had been reported that both of these time-frames were important to establish the clinical value of interventions, particularly in chronic forms of musculoskeletal disorders (Hurwitz et al., 2008; Derry et al., 2012).

7.2.2 Randomised clinical trial

A randomised clinical trial was selected as the most suitable method for detecting a clinical effect of the lateral glide mobilisation on pain. The trial was successful in recruiting 99 participants, with a balanced number randomised to each intervention group: the Mobilisation group (the lateral glide with self-management) and the Comparator group (self-management alone). Sufficient participants were retained in each group at the primary, long-term follow-up (52 weeks), and at the short-term follow-up (6 weeks), to provide statistical power for analyses on the effectivenss of the lateral glide.

Baseline participant characteristics

Demographic characteristics

Key demographic characteristics included age and gender. Participants were equally balanced on age, but there were slightly more females in the Mobilisation group. As baseline age and gender had been established as potential covariate parameters in the main analysis (Finocchietti & Trindade 1973; Kostova & Koleva 2001; Kaki, 2006), any aspects of confounding were addressed.

The prevalence of smoking in this trial cohort was higher than the national average at 35 participants (35%). In 2009/10, the national figures for people who smoked in the UK generally, and West Midlands specifically, was 21% (Cancer Research, UK, 2012). There were no gender differences in the regional statistics, however in this trial 44% of the males smoked compared to 29% of the female participants. This trend was consistent with previous reports that male smokers might have a higher prevalence for developing cervicobrachial pain (Kostova & Koleva, 2001). Participants in the Comparator group had a higher number of male smokers, but there were no published data to suggest that this would adversely affect prognosis and, therefore, outcome.

Participants in the Mobilisation group had taken more time off work prior to starting the trial compared to those in the Comparator group, but there was no evidence to indicate that an increased time off work resulted in a poor prognosis for this condition.

Clinical characteristics

There was no evidence from key baseline clinical data (Table 6.4) that the mean VAS(worst pain) scores were different across groups, indicating effective stratification (Sim & Wright, 2000; Schulz & Grimes, 2002a). It had been reported that higher scores on VAS pain at baseline needed to be reduced by a greater amount to detect a clinically meaningful difference (Bird and Dickson, 2001; Tubach et al., 2004; Emshoff et al., 2011). Achieving similar mean baseline scores (with similar variation) within each group for the primary outcome measure enabled a higher level of confidence when interpreting mean change scores for VAS(worst pain) (Emshoff et al., 2011).

Other clinical factors (including pain type (S-LANSS), fear avoidance (TAMPA), whiplash associated disorder, chronicity, treatment preference and positive neural tests (ULNE)) had similar values across groups. There was no evidence of a difference in baseline mean values on function and disability scores (NULI and SF-36). As baseline disability levels had been established as covariate parameters in the main analysis, any aspects of confounding have been addressed in the analyses. Mean scores for the SF36 MCS in this trial (mean= 63) were better than had been reported elsewhere. Scores in this trial were higher than UK norm-based scores (mean=50) (Jenkinson et al., 1999), and higher than those previously reported for patients with cervicobrachial pain (mean= 45) (Daffner et al., 2003). It is not known whether geographic differences accounted for this disparity; as the work by Daffner et al. (2003) was based in the United States.

One of the largest between-group differences at baseline was the response to previous physiotherapy. Less than half the responders who had received physiotherapy in the Mobilisation group reported a previous benefit to physiotherapy (n= 9; 47%), whereas nearly all participants in the Comparator group reported a positive response (n= 12; 92%). There is very low evidence from one longitudinal cohort study (n=2793 over a 5 year period) that past experience of physiotherapy might predict future response to intervention (Joling et al., 2002). However limitations of the methods used to establish outcome effect from intervention in Joling et al.'s study (2002), means that no strong conclusions could be made. It is possible that the disparity between previous intervention responses could have had a confounding effect on the outcomes of the current trial, negatively biasing results in the Mobilisation group.

Protocol violations

A high percentage of participants (n=47; 47%) received additional treatment following the intervention period (beyond six-week follow-up). Although the groups were well balanced on numbers receiving additional intervention, they were not balanced on intervention type. Two participants in the Mobilisation group received surgery compared to none in the Comparator group. This could indicate that receiving mobilisation, might lead to a greater dependence on receiving future treatment, possibility due to moving the locus of control away from the patient, leading to interventions that involve higher risk and greater cost (Joling et al., 2002). However, other factors could have accounted for this finding. For example, the two participants who had surgery could have been the most debilitated and were most likely to have

required surgery at outset, yet, by chance they were randomised to the Mobilisation group.

Variability around follow-up

There was some variation around planned and actual follow-up times due to availability of participants. Twenty-three participants returned for their 6 weeks follow-up prior to the planned six week time slot. The majority of these (19 participants) returned one week earlier, and four participants returned two weeks earlier, than planned. The mean follow-up for the 52 week follow-up (primary end point) was similar across the groups with the majority of participants (n= 81; 82%) who attended the follow-up, doing so within one month of the planned follow-up time. There was one outlier in the Mobilisation group who completed final follow-up at 107 weeks following baseline, (over double the planned follow-up time). This participant had not attended the planned follow-up appointment, but had returned to the department for persisting problems with cervicobrachial pain on a separate occasion, one year later, at which point the participant agreed to complete the follow-up questionnaire and have physical outcome measures recorded. It had been expected that there would be some variability in return time-points; therefore the MLM included 'time' as a random factor as part of the model to account for this variation.

Most participants (n= 78; 88%) completed the standard questionnaire at the final (52 week) time point. The postal questionnaire was used by 9(10%) and 2(2%) of the control and intervention groups, respectively. Some authors have indicated that different administration methods may lead to bias (Erhart et al., 2009). However, criticisms related to using a combination of patient-complete and administrator complete methods. For example, a patient might feel compelled to respond more

positively if verbally answering questions rather than completing a questionnaire independently (Erhart et al., 2009). This could introduce administration bias if both methods were adopted in the same study. In this trial, both methods captured data using a patient-complete method, thereby making any administration bias unlikely (Hawthorne, 2003).

There were no statistical between-group differences on baseline key variables age, pain (VAS(worst pain)) and mental health (SF36, MCS) for participants who responded compared with those who did not respond at 52 weeks follow-up. There were some gender and chronicity differences, with male participants, and participants with more chronic symptoms, being more likely to respond in the Comparator group compared to the Mobilisation group. The MLM had the ability to account for this variation by nesting data variables per individual, thereby overcoming differences between differing levels of variability in response rate between groups (Field, 2009).

Between-group differences at follow-up

Pain

This trial was powered to evaluate a 20mm between-group difference for the worst pain (in the previous week), at long-term follow-up (52 weeks post baseline) on a visual analogue scale for pain. The results found no evidence of between-group differences (p=0.37; CI -17.76 to 6.61), indicating that for this cohort of patients, there was no additional, long-term benefit from receiving the lateral glide.

The analysis at 52 weeks was based on an intention to treat principle, with all participants analysed according to their intended intervention. However, a large

proportion of participants received additional treatment prior to 52 weeks (n=47; 47%), which introduced additional sources of variation in the intervention actually received by participants in each group. This additional variation could have confounded the results for the long-term measures. It was therefore not possible to ascertain whether the between-group differences at 52 weeks represented a 'true' level of effectiveness of the lateral glide.

Within the intervention period (first six weeks), all bar one of the participants received the protocol intervention as the only treatment received. The one participant who received additional treatment during this period withdrew from the trial. This meant that analysis at six weeks effectively became a per-protocol analysis and was more likely to reveal the 'true' level of effectiveness for the lateral glide. Analysis at this follow-up time found no between-group difference on VAS(worst pain) (p=0.52; 95% 95% CI -14.72 to 7.44). Interestingly, a trend in pain reduction was greater in the Comparator group than the Mobilisation group (19mm compared to 14mm respectively). This finding contrasted to studies reporting positive immediate effects of pain relief in response to the lateral glide (Vincenzino et al., 1996, 1998; Coppieters et al., 2003; McClatchie et al., 2009; Sterling et al., 2010). This indicates that the pain relieving effects from the lateral glide might not extend beyond an immediate or very short-term effect.

The longitudinal analysis showed that there was an improvement over time in pain VAS(worst pain) (p=0.001) for both groups which resulted in a clinically meaningful improvement (exceeded 20mm of change) at primary end point (52 weeks). Without a no-intervention control, it was unknown if trends for improvement reflected a natural history of reduced pain over time, or, that both forms of intervention were effective. A

trend was observed between groups from 26 to 52 weeks: participants receiving mobilisation had an increase in pain whereas the trajectory for the Comparator group continue to improve (Figures 6-3 and 6-7). A similar trend was found for VAS(average pain) (Figures 6-4 and 6-8). It might be that dependence on more passive intervention (such as the lateral glide mobilisation) moved the locus of control away from the participants in the Mobilisation group, resulting in them being less able to manage their symptoms and/or have a greater risk of re-occurrence of symptoms (Biurrun et al. 2002; Swenson, 2003; Peres et al., 2010; Mitrovich, 2011).

Outcome measures evaluating self-perceived change in pain (GROC) and pain medication usage were evaluated in the short-term (6 week follow-up). Correlation analysis for changes in VAS(worst pain) to patient perceived change (Figure 6-12) found a moderate linear trend between the two measures (Spearman's rho=0.69) which supported validity for each, strengthening interpretation. A trend for a greater level of improvement in the Comparator group compared to the Mobilisation group was found, which was consistent with findings from the VAS outcome measures. These findings contrasted to the results of the preliminary study, highlighting that without a powered study, very different interpretations might be made. No significant between-group difference (p=0.63) for pain medication usage was identified. Outcome measures for pain including VAS(worst pain) , VAS(average pain), GROC and pain medication usage, consistently found that the lateral glide was no more effective in reducing pain than the comparative intervention in the short-term.

Function and disability

The results from functional patient reported outcome measures in this trial found a statistically significant difference in mean NULI score across time (p=0.03; 95% CI -13.53 to -0.92) between the Comparator and Mobilisation groups, favouring the effectiveness of the comparative intervention (Figure 6-9). A similar trend was seen in SF36 (MCS) (Figure 6-10), but this did not reach statistical significance (p=0.07; 95% CI -0.37 to 12.07).

The estimate of effect on participant reported functional measures was small. Both the NULI and the SF36 MCS are measured on a 0 to 100 scale. The NULI had a between-group effect of 7, which may be considered as the comparative intervention being 7% more effective than the lateral glide mobilisation. No clinically meaningful differences have been reported on this outcome measure from which to draw comparisons. The SF36 (MCS) had a between-group effect of 6, equating to the comparative intervention being 6% more effective than the lateral glide mobilisation. Within-group differences in the SF36 MSC (from baseline to 52 weeks) were +5.4 for the Comparator group, and +4.8 for the Mobilisation group. It has been reported that change scores need to reach +5.8 to represent a clinically meaningful difference (Ware, 2000 p 3134).

The results from performance based functional outcome measures (cervical active range of motion) produced mixed results in this trial. Statistically significant results were found for left rotation (p=0.04; 95% CI -11.55 to -0.23) and left side bend of the cervical spine (p=0.03; 95% CI 0.58 to 8.49), favouring the effectiveness of the comparator intervention (Figures 6-13 and 6-14). It was possible that multiplicity

(conducting statistical tests on multiple outcome measures) increased the rate of error accounting for the variability in findings for cervical range across time i.e. significant findings resulted by chance.

The estimate of effect on performance based outcome measures was small. AROM into left rotation showed the greatest between-group effect as 6 degrees. None of the movements had clinically meaningful difference from baseline (a within-group change of 10°) across time (Klaber Moffett et al., 1989; Sterling et al., 2002; Fletcher & Bandy, 2008).

Cost –effectiveness

Cost was considered in relation to sickness absence and treatment costs. The results of this trial found no statistically significant between-group difference in sickness absence at 6 week follow-up (p=0.08). There was a trend that participants in the Comparator group required less time off work at this time point.

The mean number of attended sessions during the intervention period for the Mobilisation group was greater (n=5; SD=1) than the Comparator group (n=2; SD=1). This was a statistically significant difference (p<=0.0005). The costs to provide intervention for the Mobilisation group were double that of the Comparator group.

If more expensive interventions show little or no therapeutic advantage compared to less expensive interventions, then, the interventions with less cost should be the preferred intervention (Tonelli, 2012). This trial was not powered to evaluate cost-effectiveness; therefore, the findings of this trial provided a low grade level of evidence, that the addition of the lateral glide was not cost-effective.

Harms

Only minor harm was associated with both interventions in this trial. An interventional difference of 11% was found, with more harm being reportedly associated with the mobilisation. In most cases, minor harm was described as a temporary increase in pain following intervention. This type of response to intervention has been defined as 'treatment soreness' and is considered not to cause any long-term harm (Adams & Sims, 1998). It has been reported to occur in response to non-invasive therapy for spinal pain (Furlan et al., 2010). It is not clear why it occurs in some but not all individuals. No evidence was found in the literature to substantiate whether treatment soreness is just a transient effect, or, whether it has the potential to cause long-term harm. Identifying long-term harm is obviously important to determine. Providing that long-term harm is not associated with treatment soreness, transient soreness is likely to be acceptable to a patient if benefit from the intervention extends beyond the initial soreness period.

Pain mechanism

In this trial, there was no evidence that a neuropathic pain state (S-LANSS score of 12 or greater) affected outcome on pain response (VAS(worst pain)) at six-week follow-up ($p= 0.74$). This would suggest that either the S-LANSS tool was not effective in evaluating pain mechanism for this population, or, the response to treatment was not pre-determined by pain mechanism. The lateral glide has not been established to be a mechanism dominant intervention i.e. it does not selectively affect nerve or somatic tissue structures; it has the potential to affect both (Section 4.2.2).

Therefore, a mechanism dominant sub-category might not necessarily result in a different intervention response.

Participants with a positive ULNE (nerve mechano-sensitivity) had no statistically significant between-group difference for VAS(worst pain) at six weeks (p=0.30; 95% 95% CI -19.02 to 5.94), as was the case for the analysis including all participants (with and without a positive ULNE) (p=0.52; 95% CI -14.72 to 7.44). As the majority of participants included in the trial had a positive ULNE test (n=75; 77%), it is possible that the presence of nerve mechano-sensitivity is a frequently associated feature of this condition. Despite the majority of patients having nerve mechano-sensitivity (positive ULNE), only the minority had a positive neurogenic pain mechanism (12 or more on S-LANSS) (n=44; 46%). This indicated that either it was possible to have mechanical neutrally sensitivity without having a dominant nerve pain mechanism, or, the S-LANSS and/or ULNE were not tests that could specifically identify a nerve dysfunction in this patient group.

Participant preference

In this trial, participant preference did not affect outcome on VAS(worst pain) at 6 week follow-up (p=0.81). Previous studies on the lateral glide have not evaluated patient preference, so there is no specific indication of the effect preference might have. However, findings from a recent systematic literature review (Pradya et al., 2013) reported that patients with strong preferences could turn down involvement in a study to enable them to receive a preferred treatment, thereby reducing the ability to detect an effect of preference on outcome (Pradya et al., 2013). This was unlikely to be the case in this trial, as only two patients were not recruited due to their

concern that they might not receive the mobilisation. Data from this trial was limited and not powered to detect preference, therefore provides only very low evidence that preference for the lateral glide does not affect outcome on pain.

Trial Physiotherapist characteristics

At the start of the trial, one of the five Trial Physiotherapists had a preference for the lateral glide mobilisation, whereas by the end of the trial this had changed to four of the five (Table 6.1). There is disparity between the results of the trial and the change of opinion of the therapists. This change could have been influenced by the clinician patient relationship. A patient might feel obliged to be more optimistic about their response to an intervention, particularly when it involves a level of physical contact i.e. 'hands on' intervention. Participants in the Mobilisation group might have felt compelled to report positive responses to the therapist delivering the intervention, or, it could be that, as participants in the Mobilisation group, they had more appointments with the therapist. The therapist could have been exposed to a greater level of positive feedback from participants in the Mobilisation group, thus biasing their own opinion about the apparent 'success' of the intervention. This finding reflects the current belief that that much of health care is based on the experience of a physiotherapist, which is concerning if experience in itself is subject to bias (Daykin & Richardson, 2004; Pincus et al., 2006). This leads to question why patients in the Mobilisation group returned for twice as much intervention than the Comparator group. The trial was designed to enable the Trial Physiotherapist together with the participant to determine how much intervention was required. If the Trial Physiotherapist believed the mobilisation was effective they might have influenced the decision to continue with treatment over more episodes resulting in higher costs.

The results from this trial provide no substantive evidence to support this belief. Alternatively, it was possible that there was a true benefit to the participants, but that the nature of the trial was not sensitive enough to detect this. It has been suggested that the rigour of study conditions used in RCTs do not reflect the complexity of the real world and are therefore not effective in revealing the 'truth' for the effectiveness of an intervention (Grapow et al. 2006; Cartwirght & Munro, 2010; Kerry et al., 2012). Alternative frameworks to RCTs have been suggested as ways to identify 'truths' in health care, such as the use of large cohort studies (Grapow et al., 2006). However, methods that adopt a more candid approach to research and may increase risk of bias and chance also lose some of the rigor associated with the randomised controlled design (Sim & Wright, 2000).

7.3 Comparison of findings to current literature

Comparisons may be made to previous studies on cervicobrachial pain relating to pain, function & disability, harm and pain mechanism. Comparisons to cost effectiveness or preference were not possible, as no other studies evaluating the lateral glide mobilisation have considered these factors.

7.3.1 Pain

The results of this trial did not find that manual therapy (in the form of the lateral glide) provided any preferential reduction in pain compared to a comparator in the short or long-term. This finding is in contrast to previous studies that have found beneficial effects from providing the lateral glide mobilisation for cervicobrachial pain in the short-term (Allison et al., 2002; Ragonese, 2009) (Table 3-3). Since completing the systematic literature review (Chapter 3) and commencing the main trial, a further study has reported that the lateral glide, added to exercise and advice, has a beneficial effect on short-term pain reduction (Nee et al., 2012). The disparity between the results of this trial with other randomised studies might be explained by the different methods used. These include statistical power, homogeneity, dose and delivery of intervention, the provision of additional intervention within protocols and duration of follow-up.

Trial power

This trial was the only study with statistical power to evaluate a clinically meaningful change in pain. It has been well documented that interpretations from small, underpowered studies, or studies that evaluate pain as secondary analyses but have not been powered for that purpose, could lead to erroneous conclusions (Moher et

al., 2010); therefore the results from this trial (with no statistically significant between-group findings for pain outcome measures) provides the best available current evidence for short and long-term effectiveness.

Homogeneity

None of the other studies conducted their research in the UK. It is possible that geographic location could be responsible for differing outcomes, however, all studies were conducted in developed countries with similar culture, meaning responses across populations are likely to be comparable. Some of the studies used a self-selection method of recruitment (Allison et al., 2002; Nee et al., 2012). There is moderate evidence that participants who choose to be involved in a clinical study (in response to advertising) do not represent the general population well, leading to self-selection (or volunteer) bias (Eysenbach & Wyatt, 2002; Hernan et al., 2004; Oswald et al., 2012).

The disparity between findings of this trial and other similar studies (Allison et al., 2002; Nee et al., 2012) could be attributed to methods in the selection process, including the presence of a positive ULNE. The presence of a positive ULNE as a pre-requisite for inclusion (Allison et al., 2002; Coppieters et al., 2003; Nee et al., 2012) was one of the key differences between this trial and other randomised studies evaluating the lateral glide. For this reason, an exploratory sub-group analysis was conducted on participants with a positive ULNE. The majority of participants in the trial had a positive ULNE test (n=75; 77%) with an equal balance between the two intervention groups (Comparator n=39; Mobilisation n=36). Results from the sub-group analysis found a non-significant difference on VAS(worst pain) at six weeks (p=0.30; 95% CI -19.02 to 5.94). Whist it was recognised that this analysis was not

powered, it does indicate that the inclusion of a positive ULNE was unlikely to account for the differences seen on pain outcomes.

Dose and delivery of intervention

Only one other study clearly specified both the dose and delivery of the lateral glide (Nee et al., 2012). Differences between this trial and that of Nee et al. (2012) included the following: Nee et al. (2012) used a 'pulling' technique (as opposed to 'pushing' technique) to provide the translatory oscillation. Mobilisations were administered to multiple levels of the cervical spine (as opposed to the one level used in this trial) for two, 30 second doses (compared to three 60 second doses). Although low evidence supported that similar effects might be gained by using different mobilisation approaches in general (Cleland et al., 2005; Aquino et al., 2009) (Section 4.2.3), other studies that have reported the use of multi-level lateral glide mobilisations in their cervicobrachial pain studies (Coppieters et al., 2003; McClatechie et al., 2009; Ragonese, 2009) have had consistently positive effects on pain as an outcome. It is therefore possible that the difference in approaches to the lateral glide could have accounted for differences in outcome for pain in this trial compared to the study by Nee et al. (2012).

Provision of additional manual therapy treatment

Two randomised studies used the lateral glide with other mobilisation techniques as part of a manual therapy package of care (Allison et al., 2002; Ragonese, 2009). Coppieters et al. (2003) and Nee et al., (2012) used the lateral glide as a singular mobilisation technique, as was the situation in this trial. Unlike this trial, both Coppieters et al. (2003) and Nee et al. (2012) found evidence to support the use of

the lateral glide technique to reduce cervicobrachial pain to a greater degree than a comparator in the immediate and short-term. For Nee et al. (2012), both intervention groups (comparator and mobilisation) were advised to stay active, however only the mobilisation group received the education and exercises as well as the mobilisation, thus, the improvement found in their study might be attributed to the exercise and education component of the physiotherapy intervention rather than the lateral glide component. Coppieters et al. (2003) used an ultrasound comparator and gave the lateral glide as the sole intervention (no advice or exercises added). Limitations with their study included methodological flaws (lack of power, no between-group difference reporting) which could have biased results. However, this finding along with others supports the immediate effect of the lateral glide in other neck and upper limb disorders (Vincenzino et al., 1996, 1998; McClatchie et al., 2009; Sterling et al., 2010).

Duration of follow-up

This trial was the only randomised study that followed-up participants over an extended period of time. Other cervicobrachial pain studies evaluating pain ranged from the immediate effects (Coppieters et al., 2002) to 8 weeks following baseline (Allison et al., 2002) (Table 7.1). This suggests that the lateral glide mobilisation might be effective for a short duration following its administration but does not provide information on long-term outcomes. This limits support for the clinical usefulness of the lateral glide mobilisation for the treatment of cervicobrachial pain as longer term benefit would be desirable to make treatment cost effective, however, long-term outcomes might be problematic in isolating the effects for specific interventions.

Table 7-1: The lateral glide mobilisation effect on pain outcomes for chronic cervicobrachial pain

Study	Study design	Participants	Recruitment	Participant classification and chronicity	Interventions & assessment points	Outcome measures	Results
Allison et al. (2002) Australia	RCT with crossover design 3 groups: A: Neural PT with exercise; n=10 B: Articular PT with exercise; n=10 C: No treatment; n=10	n=30 Mean age 54 F=20 (67%)	Self-selected from advertisement	**Neurogenic cervicobrachial pain** Positive ULNE. Mean duration of symptoms: 26 months (chronic)	A: Cervical lateral glide, shoulder girdle oscillation, muscle re-education and home exercise. B: Glenohumeral and thoracic mobilisation, and home exercise. Treatment is given over an 8/52 period. Quantity of treatment not specified. Assessment at baseline, 4/52 and 8/52.	VAS pain, SF McGill.	Significant between-group differences in improvement of mean VAS pain for A compared to B at 8/52 (p=0.03). No statistically significant between-group differences on SF McGill (p=0.15).
Coppieters et al. (2003) Australia	RcT 2 groups: A: Cervical mobilisation (lateral glide used a contralateral 'pulling technique'); n=10 B: Therapeutic ultrasound; n=10	n=20 Age range 35- 63 Mean age 48. F=16 (80%)	Physiotherapy	**Neurogenic cervicobrachial pain** Positive ULNE. Mean duration of symptoms: 2.7 months (sub-acute/chronic)	A: Single session of lateral glide mobilisation to the cervical spine to one or more of C5,6,7,T1. B: Single session of therapeutic ultrasound to most painful area. Assessment at baseline and immediately following treatment in response to the ULNE.	NPRS in response to ULNE	No between-group differences were reported. Significant immediate improvement in mean pain reduction pre compared to post treatment for A (p<0.005), but not for B (p=0.28).
Nee et al. (2012) Australia	RcT 2 groups: A: Cervical mobilisation with exercise (lateral glide used a contralateral 'pulling technique'); n=40 B: Advice to continue usual	n=60 Age range 18-60 Mean age 47 F=38 (63%)	Self-selected from advertisement	**Neurogenic cervicobrachial pain** Positive ULNE Mean duration of symptoms: 26 weeks (Chronic)	A: Lateral glide cervical mobilisations: Two sets of 30 second mobilisations to C4,5,6,7, education and nerve gliding exercises for 4 treatments over two weeks. Advised to stay active B: Advised to stay active Assessment at baseline and 3-4 weeks following commencement of physiotherapy	NPRS	Significant between-group differences in improvement of mean VAS pain for A compared to B at 3-4/52 (p<0.05) Neck pain - 0.9 (95% CI -0.5 to -1.3) Arm pain -0.7 (95% CI -0.3 to -1.1)

	activities; n=20						
Ragonese (2009) USA	RcT 3 groups: A: Manual PT; n=10 B: Exercise PT; n=10 C: Combined manual and exercise PT; n=10	n=30 Age range or mean not stated. F=19 (63%)	Physiotherapy	**Cervical radiculopathy** Definition: neck and/or upper extremity symptoms. Presence of either a positive spurlings test or cervical distraction test or ipsilateral cervical rotation less than 60° or ULNE test. Chronicity not stated	A: Cervical lateral glide and thoracic mobilisations and neural dynamic techniques for the median nerve. B: Deep neck flexor, lower and middle trapezius and serratus anterior strengthening (supervised) C: combined approaches of A and B Treatment given three times a week for 3/52 for each intervention group. Assessment at baseline, 1/52, 2/52 and 3/52.	NPRS	Significant between-group differences for reduced mean pain for C compared to A and B ($p<0.01$) at 3 week follow-up.
Salt, (2013) *(This trial)* UK	RcT 2 groups: A Cervical mobilisation with self-management (lateral glide used a 'pushing technique'); n=49 B: Self-management; n=50	n=99 Age range 18-65 Mean age 47 F=52 (53%)	Physiotherapy	**Cervicobrachial pain** Mean duration of symptoms: One year (Chronic)	A: Lateral glide (pushing) cervical glide mobilisations: Three sets of 60 second mobilisations to C5/6 and self-management. Up to 6 weeks of treatment. B: Self-management. Assessment at baseline and at 6 weeks, 26 weeks and 52 weeks following baseline	VAS(worst pain)	Non-significant between group difference for A compared to B at 6 weeks (p=0.79) 52 weeks (p=0.37) Longitudinal (p=0.81)

Key: C= cervical vertebra; F= female; n= number of participants; NPRS= Numeric Pain Rating Scale; PT= Physiotherapy; RCT= Randomised controlled trial; RcT= Randomised clinical trial; SF McGill= Short-form McGill Questionnaire; VAS= Visual Analogue Scale.

To summarise, there was a very low grade of evidence that the lateral glide mobilisation was more effective in providing an immediate reduction in pain. There was very low evidence from conflicting results that the lateral glide (coupled with a self-management approach) was more beneficial than self-management approaches in the short-term. There was a moderate grade of evidence that the lateral glide (coupled with self-management) provided no additional benefit on pain compared to a bio-psychosocial approach of self-management used in isolation, in the long-term (Table 7-2).

Table 7-2: The lateral glide effects on reducing pain in cervicobrachial pain

Grade	Evidence
Moderate	The lateral glide with self-management is no more effective in reducing pain in the long-term compared to self-management alone *(this trial)*
Very Low	The lateral glide with advice and exercise is more effective at reducing pain in the short-term compared to advice to stay active (Nee et al., 2012)
	The lateral glide with self-management is no more effective in reducing pain in the short-term compared to self-management alone *(this trial)*
	The lateral glide is more effective in the immediate reduction of pain than ultrasound treatment (Coppieters et al., 2003)

Footnote: Refer to Table 2-3 for interpretation of grades

7.3.2 Function and disability

Evidence that the lateral glide improved function and reduced disability in cervicobrachial pain, in the short-term was conflicting. Both Ragonese (2009) and Nee et al. (2012) found between-group statistically significant improvements in the Neck Disability Index (a patient-report measure), favouring the intervention with the lateral glide up to one month following baseline ($p<0.05$). Nee et al. (2012) also found between-group statistically significant differences on the patient specific functional scale (a patient report measure) favouring the group who received the

lateral glide with advice and exercise (p.0.05). However, there have also been reports of no statistically significant between-group differences on the Northwick Park Questionnaire (a patient-report measure) and cervical active range of movement (performance based outcome measure) (Ragonese, 2009) up to one month post baseline indicating a lack of consistency in functional outcome measures.

The results of this trial found a trend that the addition of the lateral glide to self-management intervention had a negative effect on outcome relating to function and disability in contrast to other studies. None of the studies (including this trial) were adequately powered to detect between-group differences for the effects of the lateral glide on function. Consequently, there is no substantive evidence to support or refute whether the addition of the lateral glide as part of non-invasive management for cervicobrachial pain has an effect on function.

7.3.3 Harm

In this trial, 16% of participants in the Mobilisation group reported minor harm that they attributed to the lateral glide. This figure was less than reported elsewhere where minor harm constituted 42% for participants receiving the lateral glide mobilisation with nerve mobilisation exercises (Nee et al., 2012). It might be that the minor harm reported by Nee et al. (2012) was aggravation from the nerve-based exercises rather than the lateral glide specifically. Neither study found that the lateral glide resulted in severe or moderate harm.

There was a low grade of evidence that the lateral glide had a greater risk for minor harm compared to self-management interventions. There was low evidence from

non-powered studies that moderate and serious harms were not associated with the lateral glide in the short-term.

7.3.4 Pain mechanism

There was insufficient evidence to establish whether the presence of a dominant pain state could predict which patients would be more likely to respond to manual therapy and exercise. Findings from this trial, where no correlation was found, was in contrast to findings from Nee et al. (2013) who reported that cervicobrachial patients with S-LANSS scores of 12 or more (indicating a dominant neuropathic pain state) had a less favourable outcome to manual and exercise therapy interventions in the short-term. This contradictory evidence could be due to differences in study methods previously outlined (Nee et al., 2012). For example, in the study by Nee et al., (2012), S-LANSS scores were correlated with patients rating their perceived overall improvement to treatment on the global rating of change score. This method of analysis was subject to a large self-reporting bias which could have confounded the results. In this trial, whist correlations were also made to a patient reported measure (VAS(worst pain)), patients were blinded to their baseline responses, thereby reducing self-report bias.

Footnote: Nee et al., 2013 used the same participant group as for Nee et al., 2012

7.4 Limitations: Internal validity

Key issues around selection, performance and attrition were addressed within the framework of the randomised trial, to limit bias. There were, however, a number of aspects which could have affected internal validity.

7.4.1 A Priori specification

Reporting methods prior to commencing a study reduces the likelihood of reporting bias (Moher et al., 2010; Higgins & Green, 2011; Rushton et al., 2011). However, at the time of writing the protocol and planning the trial, the body of literature advocating publishing the full protocol was not available. This trial was registered; therefore, some details of the trial plan, including sample size requirement and key inclusion criteria were available. Also, although not published, a detailed protocol was written and then reviewed by the ethics and research and development committees.

7.4.2 Issues identified with selected follow-up time points

Follow –up time points were selected as 6, 26 and 52 weeks. The rationale for this choice was: 6 weeks provided a short-term analysis, 52 weeks the long-term analysis and 26 provided additional data for a longitudinal analysis and kept participants involved in the trial.

The short-term analysis was at 6 weeks post baseline. It was recognised that for some participants (e.g. those who had received intervention for six consecutive weeks), this was a more immediate representation than for those who had received one or two interventions during the first two weeks post baseline. This was accepted as a necessary compromise in a pragmatic design (Patsopoulos, 2011).

The final time-point was at 52 weeks post baseline. The rationale for selecting this as the primary time-point, over the other time-points was determined at the planning stage (Section 5.9). Between the 6 week and 52 week follow-up, just under half of participants received additional treatment (47%). As both groups were balanced, there was no indication that one group was advantaged over another, however, the trial at this point was not comparing intervention and comparator as intended, therefore caution was needed when interpreting the results at 52 weeks (Smyth et al., 2011; Sweetman & Doig, 2011).

7.4.3 Problems encountered with outcome measures used in the trial

VAS pain scale

The primary outcome measure was the visual analogue scale (VAS). This tool was selected overs others as it had been found to be a sensitive, specific and reliable measure (van Kleef 1996; Allison et al., 2002; Walker et al., 2008; Kuijuper et al., 2009) (Section 5.10.1). During the preliminary study there had been no reason to suspect it was not a sound method to evaluate pain. Across all time points, there were 49 occasions (14%) where VAS(average pain) scores exceeded VAS(worst pain) scores for the same participant at the same time point. In most cases (47 occasions) the difference between the scores was small (indicating the 'average pain' was much the same as the 'worst pain') with differences not exceeding more than 2mm, however on two occasions the difference was substantial (>20mm). Both occasions were from the same participant who consistently rated VAS(average pain) higher than VAS(worst pain) suggesting a potential lack of comprehension of the outcome measure.

On one occasion baseline pain was scored as 0 (indicating the participant had no pain) when pain was an inclusion criterion. Cross-analysis with other scales and consulting the participant's case notes indicated that the VAS scale, in this instance, might have been completed in reverse with 0 indicating extreme pain.

Generally, the VAS outcome measures correlated well with other measures, for example the Global Rating of Change (GROC) indicated that validity of the both tools for this population were good.

Function and disability

The Short-from 36 (SF36) was a global outcome measure which had been validated for use in patients with cervicobrachial pain (Daffner et al., 2003) and had established norm-based population scoring, enabling comparisons from this trial to a standardised reference point and established clinically meaningful differences to assist in the interpretation of results (Ware, 2000). The Neck and Upper Limb Index (NULI) was the selected condition-specific measure chosen because of its content validity for this patient population (Stock et al., 2003). However, the limitation of NULI was there was not any population norm-based data or established clinically meaningful differences to compare the data from this trial to. The ability to interpret change scores found in NULI was therefore limited.

Pain medication usage

The use of pain medication was recorded at follow-up to give an indication of change in medication use during the course of the trial. The outcome measure was worded to enable identification of participants who had needed to take pain medication since the start of the trial (which might indicate an increase in pain), but did not allow for

identification of participants who no longer needed pain medication at follow-up when they had been using them at baseline as there was no knowledge of baseline medication. In addition, the value of change in pain medication i.e. from a stronger to a weaker medication (or vice versa) was dependent on the knowledge the participant had about the medication they were taking. Interpretation of medication usage was, therefore, limited. This limitation had not been identified during the preliminary study.

Cost effectiveness

This trial was not designed to incorporate a full economic evaluation, but did aim to establish any differing trends between the groups.

The quantity of appointments was used to establish demands on Physiotherapy resources. Participants in the Mobilisation group, on average, used more than twice as many appointments as those in the Comparator group. As there was no statistically significant between-group difference on the primary outcome measure at six weeks, the comparator intervention could be considered the more cost-effective of the two. But, evaluation was only during the intervention period; therefore the long-term cost-effectiveness could not be established.

Sickness absence due to cervicobrachial pain was established at each time point as the number of days taken off from work in the preceding month because of cervicobrachial pain. This data provided an insight into how the condition might impact on employment. However, methods used relied on individuals recalling how much time they had off due to their cervicobrachial symptoms. Recall bias in this instance could, have led to inaccuracy. This was minimised by asking participants to recall the sickness they had taken for the preceding month which was considered

more accurate than for the period across the duration of their involvement in the trial (one year) (Phillips et al., 2008)..

Harms

Harm data was collected during the intervention period. It was not known whether any harm resulted from intervention beyond this period of time. Adverse effects following manual therapy to the cervical spine have been reported in the literature (Haldeman et al., 2002; Dziewas et al., 2003; Debettw & Les, 2009; Thomas et al., 2011). Cervical artery dissection has been recognised as a rare consequence of manual therapy, with most reported instances involving techniques using cervical rotation and high velocity manoeuvres (Miley et al., 2008), which are not characteristics of the lateral glide mobilisation. At the time of planning the trial, most adverse events were reported to have occurred within a few hours of receiving manual therapy treatment (Haldeman et al., 2002; Dziewas et al., 2007), however more recent figures suggest that effects could be delayed up to weeks or months post intervention (Debetw & Leys, 2009; Thomas et al., 2011). This trial evaluated harms in the short-term supported by literature available at the time of planning the trial. In light of more recent reports, establishing any development of harm during the course of the trial would have been an appropriate additional measure.

Participant satisfaction

Patient satisfaction was not evaluated in the trial. Patient satisfaction has, in recent years, been recognised to have increasing importance in the development and provision of service development and service planning (National Health Service Commissioning Board, 2012). Patient satisfaction has become a frequently used

outcome measure in research studies on spinal pain (George & Robinson, 2010; Lamb et al., 2010). In these studies, satisfaction was used to evaluate whether patients in one group had a better experience of therapeutic package of care compared to another. However, patient experience may be influenced by multiple factors such as how positive a relationship is with a therapist or the waiting times for appointments (Alrashdi, 2012). It has been cautioned that the use of satisfaction as an outcome might mislead interpretation for the effectiveness of specific interventions (Williams, 2004; Fenton et al., 2012).

7.4.4 Effect size

Effect size was a way of quantifying the size of difference between the interventions. The sample size for this trial was based on a power calculation, using a moderate to large effect size (20mm of change) for the primary outcome measure, VAS(worst pain). Moderate or large effect sizes have been criticised to lead to a type two error (rejecting a hypothesis when, it is in fact true) due to insufficient power to detect a small yet meaningful change in effect (Machin & Fayers, 2010). If the trial had been powered to detect a smaller effect size, it is possible that a statistically significant between-group difference might have been detected (Machin & Fayers, 2010). However, a smaller effect size is less clinically meaningful and, therefore, results from studies using small effect sizes might not be clinically meaningful.

If one intervention requires greater expenditure compared to another (as in the case of this trial), it may be justified as appropriate to have identified at least a moderate effect size for interventional effect. The rationale for using this method is thus validated.

7.5 Limitations: generalisability

One reason to study chronic cervicobrachial pain was that it was considered to be a prevalent condition (Section 2.4.1). Audit data from the preliminary study showed that chronic forms of cervicobrachial pain accounted for just 2% of the overall musculoskeletal referrals to physiotherapy at a department in the West Midlands. This data from the audit indicated a lower prevalence for chronic cervicobrachial pain than had been indicated from other studies on neck pain (Persson & Carlsson, 1999; Sterling et al., 2002b; Daffner et al., 2003; Antonaci et al., 2006, Vincent, 2010). It was possible that the majority of chronic cervicobrachial pain patients were being managed in primary care settings, as, at the time of conducting the trial, the UK government was trying to ensure that chronic musculoskeletal conditions were being managed in primary rather than secondary care settings (Department of Health- NHS Improvement Plan, 2004; Department of Health- Musculoskeletal Service Framework, 2006). The main trial was developed to include two primary care locations. Unfortunately the primary care locations failed to recruit anyone to the trial, but, it was not clear if this was due to a lack of patients being available or issues with staffing and organisational changes in the participating centres. The external validity of the trial had some limitations due to the use of a single rather than multi-centre site. In addition, use of multiple exclusion criteria impacted on generalizability of the trial's findings.

7.5.1 Single centre trial

This was a single-site trial. As participants were recruited over a long duration, results should be fairly representative for all patients at this location. Results of this trial are limited to patients who match the characteristics and demographics of those involved

in this trial and, therefore, represent a select sample of patients attending physiotherapy in secondary care, in the West Midlands. Data from participants from primary or tertiary centres and in different geographic locations would have led to a better generalisability, however, as the location used serves a population with mean figures for socio-economic UK demographics, it is possible that the results from this study may be considered a fair representation for a wider population.

Discontinuation of sites in this trial was due to a lack of recruitment secondary to staffing and changes in organisational structures for service delivery. Problems with recruitment such as these are not uncommon in multi-centre studies (Campbell et al., 2007; Menon et al., 2008). Strategies to aid cross-site recruitment might include web-based systems for study management and constant monitoring systems by dedicated management teams to address problems and seek solutions as soon as they arise; however this trial had limited funding and resources, so these strategies were not possible.

The secondary care location (where the trial was conducted) contrasted to the other centres by seeing a steady increase in recruitment over the duration of the trial. One factor that might have facilitated recruitment to this site was that all referrals for neck and upper limb disorders were seen by physiotherapists who specialised in this field of practice. All potential patients with cervicobrachial pain were seen by a member of this team and it became part of the culture to recruit in these clinics. An attempt was made to roll out this model to the other sites, however due to their generalist way of working (all physiotherapists seeing all musculoskeletal conditions); it was not feasible to implement this approach.

7.5.2 Multiple recruitment criteria

This trial included eleven criteria. It has been criticised that too many exclusion criteria reduce generalizability (Schulz & Grimes, 2002c). Exclusion criteria should be designed to prevent contraindications and identify patients who are more likely to impose a greater loss to follow-up (Schulz & Grimes, 2002c).

Co-existing upper limb pathology accounted for the largest number of participants excluded due to ineligibility (n=57; 33%). This figure was similar to findings by a previous study (Cannon, 2007) suggesting that cervicobrachial pain in the chronic form is frequently associated with other upper limb pathology. Co-existing upper limb pathology is not a contraindication nor would it have necessarily imposed a greater loss to follow-up, however, if co-existing upper limb pathology had been included a greater number of participants might have needed additional treatment, possibly including the intervention period. The presence of upper limb pathology remained a valid reason for exclusion in this trial.

Some exclusion criteria in this trial were based on the prevention of confounding effects e.g. age and litigation, however on reflection, as methods for analysis were selected to take confounders into account (ANCOVA and Multi-level models), the exclusion of these criteria might have been over zealous.

Sixty-one percent of patients with cervicobrachial pain were excluded based on not meeting selection criteria. This rate was much higher than figures reported in previous non-invasive cervicobrachial studies where exclusion rate was consistently 25% (Allison et al., 2002; Bernnards et al., 2007; Walker et al., 2008; Kuijper et al., 2009; Young et al., 2009). Other studies had not included exclusion factors such as

co-existing upper limb pathology. Whist reducing the exclusion criteria in this trial might have improved recruitment and enabled better generalisability of findings; it could have led to greater heterogeneity, thus masking results.

7.6 Future recommendations

Findings from the systemic review revealed the need for the trial. The results from this trial suggest that a minimal intervention approach of self-management might be a cost-effective, low risk intervention, however, without a control group, it was not clear if the gains made in the Comparator group exceeded that of natural progress over time (Maughan & Lewis, 2010). Better knowledge of how chronic cervicobrachial pain evolves over time would provide useful information to inform evaluation of interventions.

This trial evaluated one form of physiotherapy with another. Evaluation of the interventions against a no-intervention control would be able to determine the effectiveness of specific interventions. There are issues around a failure to provide any intervention when patients present for treatment. Historically, this has been overcome by methods such as using waiting list patients as control participants. However, with NHS targets focused on faster access to services, with a maximum wait time of 18 weeks for non-urgent appointments such as musculoskeletal physiotherapy (Department of Health, 2013), a waiting list control is not usually a viable option. Effective placebo treatments are often difficult to achieve in manual therapy trials. Comparative interventions in clinical physiotherapy research trials are therefore frequently used. It is important to highlight that this trial was not designed to identify the value of physiotherapy in the management of chronic cervicobrachial

pain; however, as the self-management booklet (which was unique in that it provided a component of behavioural modification) a future trial to evaluate the effectiveness using the booklet could be supported.

The lateral glide mobilisation had a beneficial effect for some, but not all participants. The ability to identify which specific sub-classification of patients will benefit from this approach of physiotherapy has yet to be determined. A cohort study could be conducted to identify which patients achieve improvements with the lateral glide mobilisation compared to those who do not.

Prevalence data on chronic cervicobrachial pain is needed to ascertain how much of an impact this condition has on society and health care services to justify the continued use of resources to support research in this field. Prevalence statistics for the UK population and for patients seeking treatment for the condition across primary, secondary and tertiary health care services would inform where best to conduct future UK studies in this condition and enable effective recruitment.

7.7 Conclusion

The systematic review and clinical trial have extended the knowledge base for the effectiveness of the lateral glide mobilisation on the management of cervicobrachial pain. Evidence from this thesis finds a very low grade of evidence to support the use of the lateral glide to reduce pain in the immediate-term, conflicting evidence that the lateral glide with self-management is more effective at reducing pain in the short-term and moderate evidence that the lateral glide with self-management is no more effective in reducing pain in the long-term compared to self-management alone. Evidence for effectiveness on function and disability, cost, risk and perceived improvement is mixed. The overall strength of evidence to support recommendation of the use of the lateral glide for cervicobrachial pain in clinical practice is low.

This study is the only one that evaluates the value of the lateral glide as a specific mobilisation technique over a prolonged period of time. In doing so, pragmatic problems were encountered including a large number of participants receiving additional treatment which had the potential to introduce a confounding effect at long–term analysis. This questions how viable RCT studies are to evaluate specific modalities for long-term management in cervicobrachial pain. Evaluation of intervention effects in the short, medium and long-term and a cost analysis is appropriate to inform health policy; however different methods to evaluate effectiveness might need to be considered for different time-frames to identify the true effects of an intervention. Randomised controlled trials are considered the gold standard in research design (Silverman, 2009). However, heterogeneity in a cohort of participants used in RCTs could lead to some confounding of results, which might have been the case in this trial. A well-designed longitudinal observational study

might identify clinically important differences among therapeutic options for specific sub-groups of patients with a condition. This method might be considered a more appropriate way of providing data on long-term intervention effectiveness and safety (Silverman, 2009), and thus more effectively lead to the development of clinical practice guidelines.

Appendices

Appendix 1A: GRADE as a tool for evaluating prognosis

From: Guyatt, Gordon [guyatt@mcmaster.ca]
Sent: 11 September 2012 23:36
To: Emma Salt
Cc: s.m.kelly@bham.ac.uk; c.c.wright@bham.ac.uk
Subject: Re: Query on the use of GRADE for risk and prognostic evaluations

Although not developed for prognosis, turns out GRADE concepts work nicely for prognosis

We will be writing more about this

If you were to share your experience using GRADE in this setting we might collaborate in future

Sent from my iPhone

On 2012-09-11, at 4:46 AM, "Emma Salt" <EJS495@bham.ac.uk> wrote:

Dear Professor Guyatt,

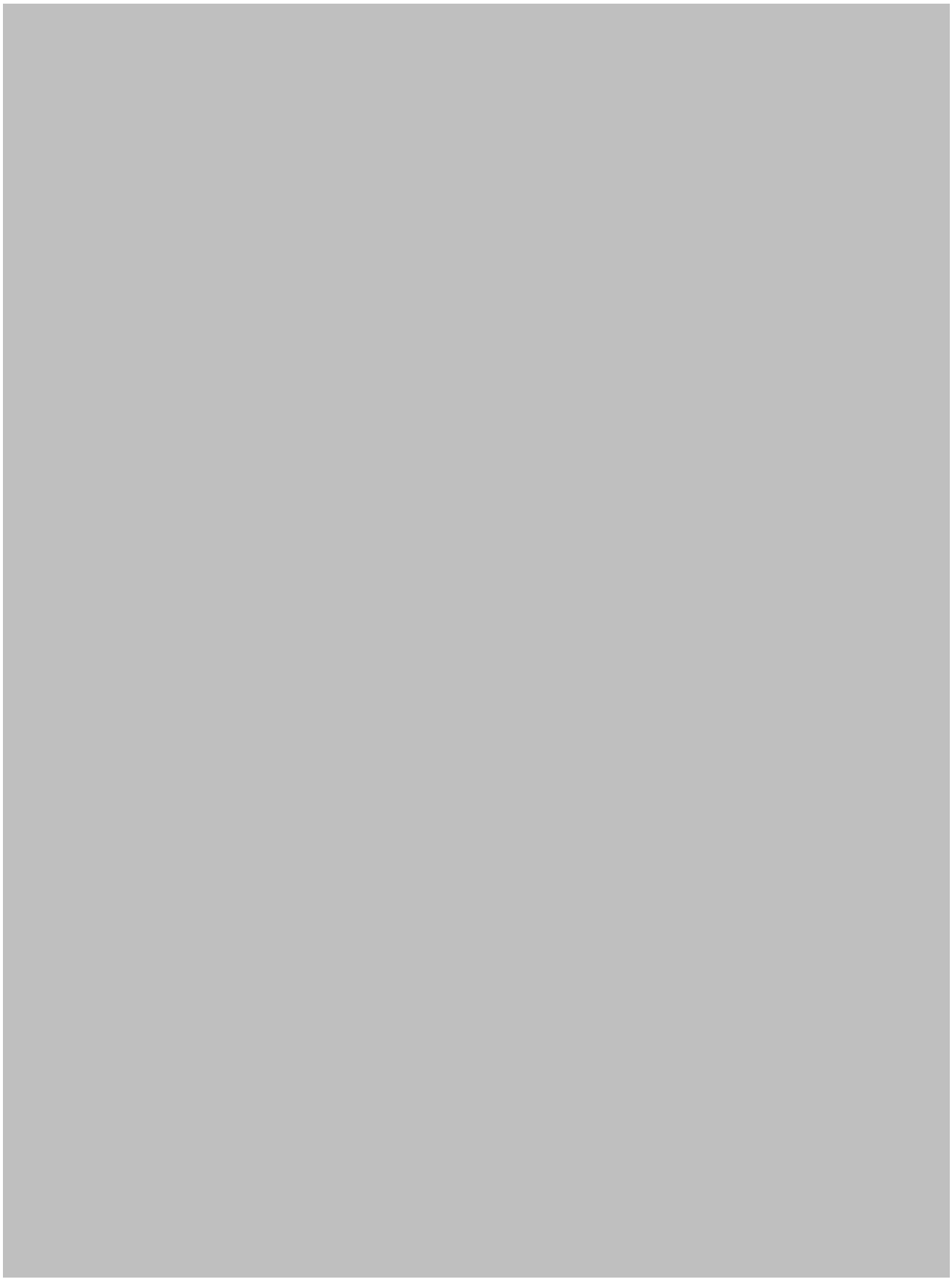
I am a PhD student and am currently writing my thesis. I have chosen the GRADE approach to evaluate the literature within my thesis. For one of the chapters, I cover risk and prognostic factors. I see from one of the series of articles you wrote that GRADE has not been developed to answer questions related to risk and prognosis:

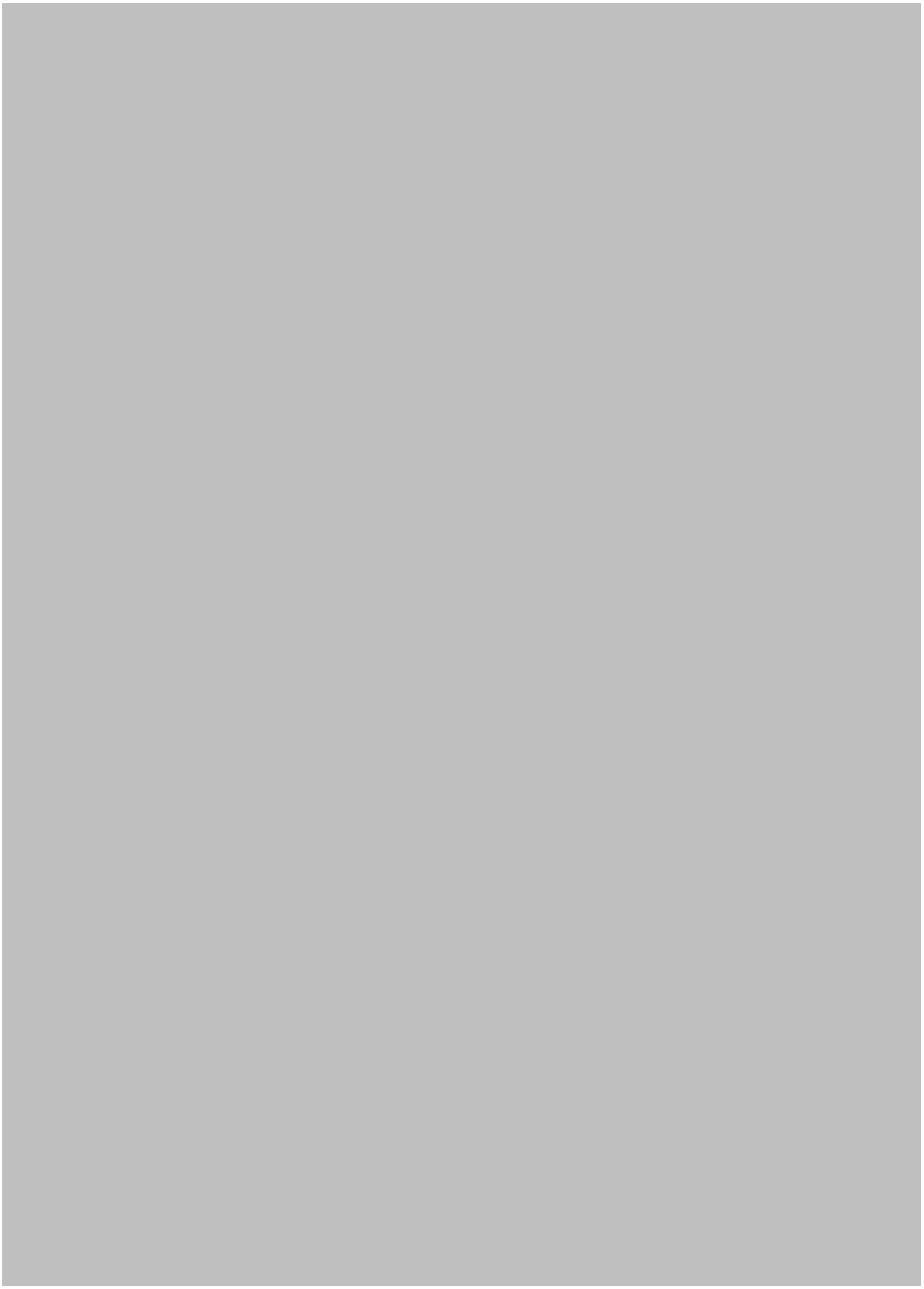
(Guyat et al., 2011 GRADE guidelines 1. Introduction- GRADE evidence profiles and summary of finding tables. Journal of Clinical Epidemiology, 64(4): 383-394).

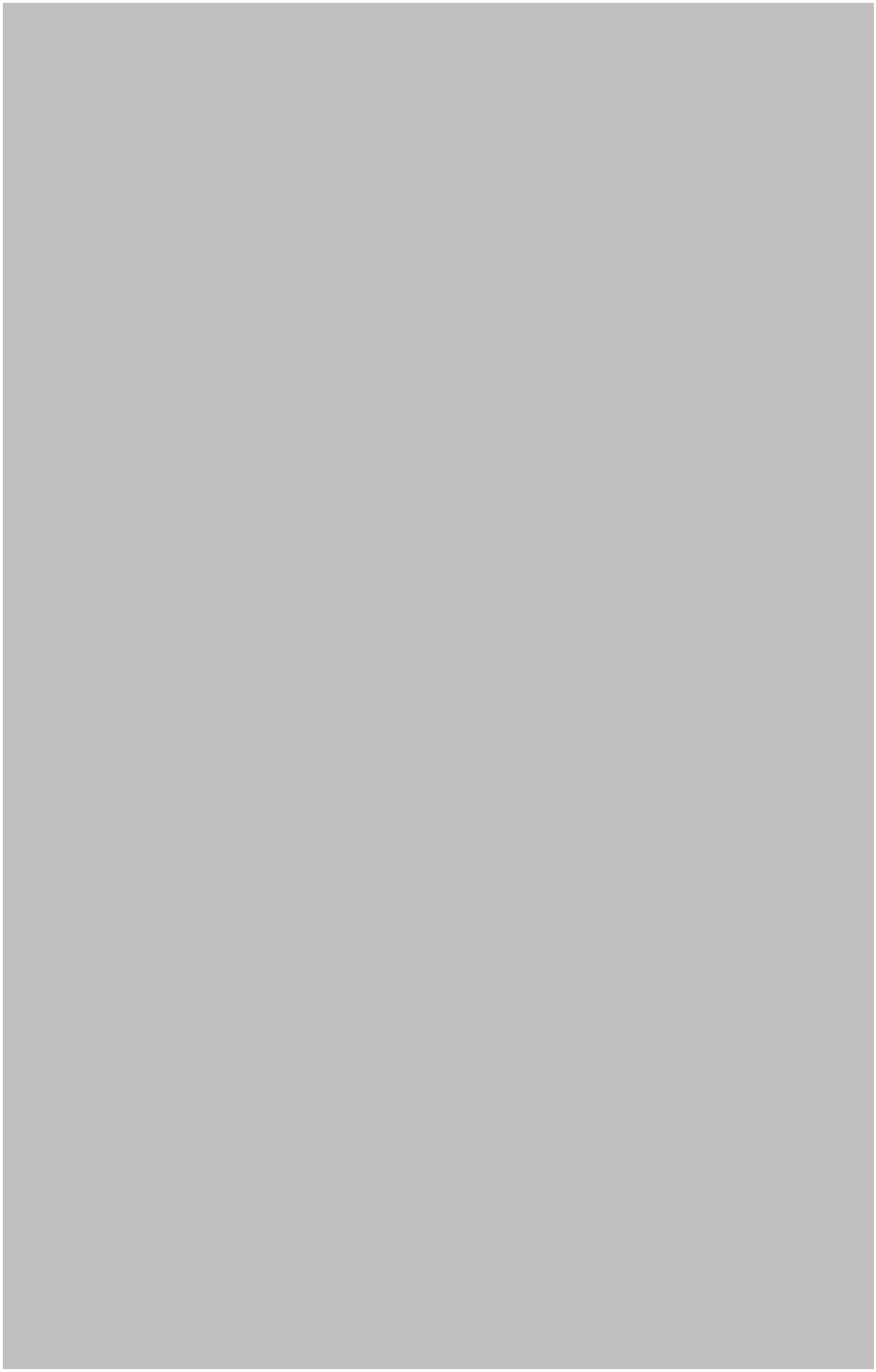
To keep my thesis consistent, I would like to use the GRADE approach for the purpose of evaluating risk and prognosis. Is this acceptable?

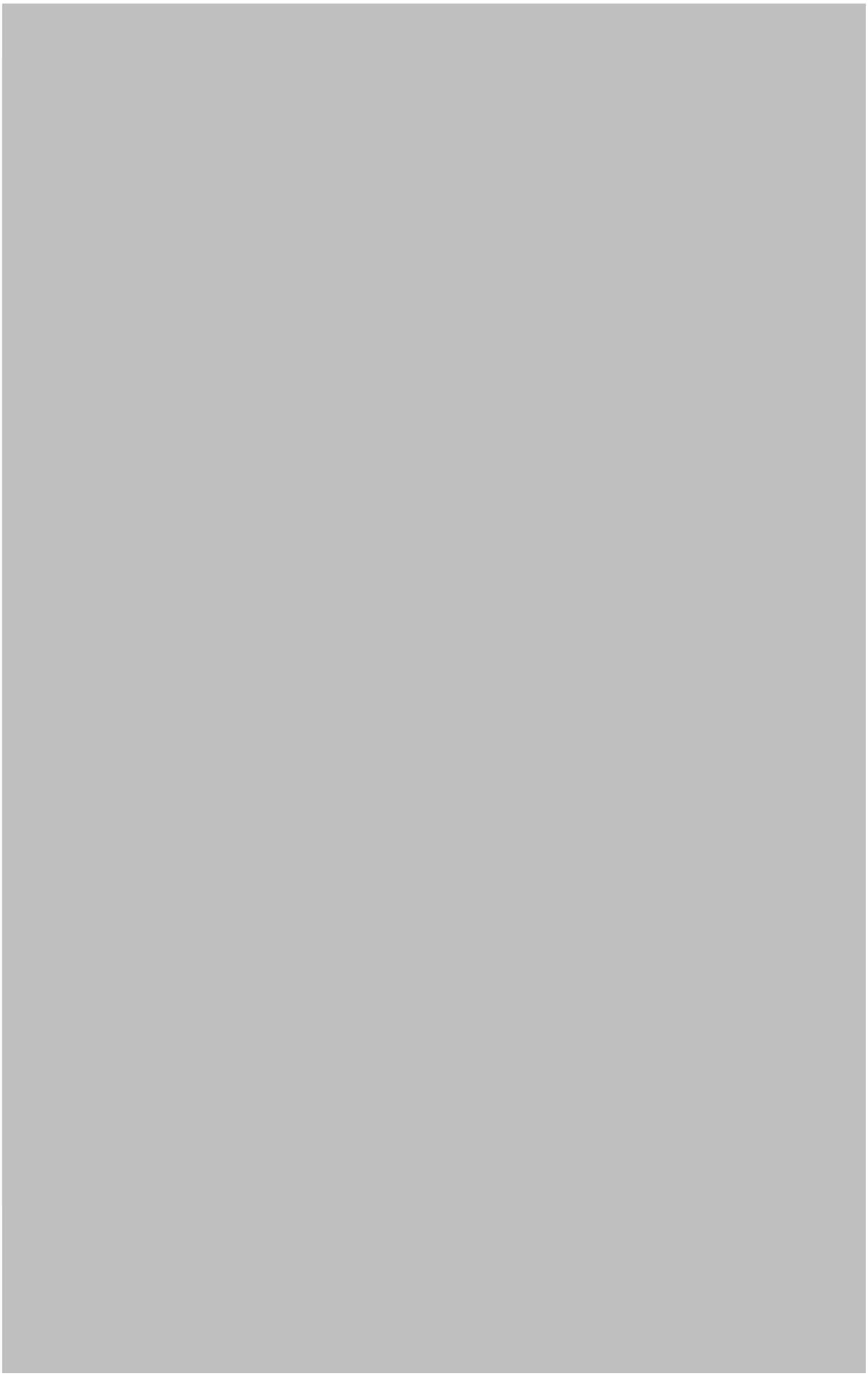
Emma

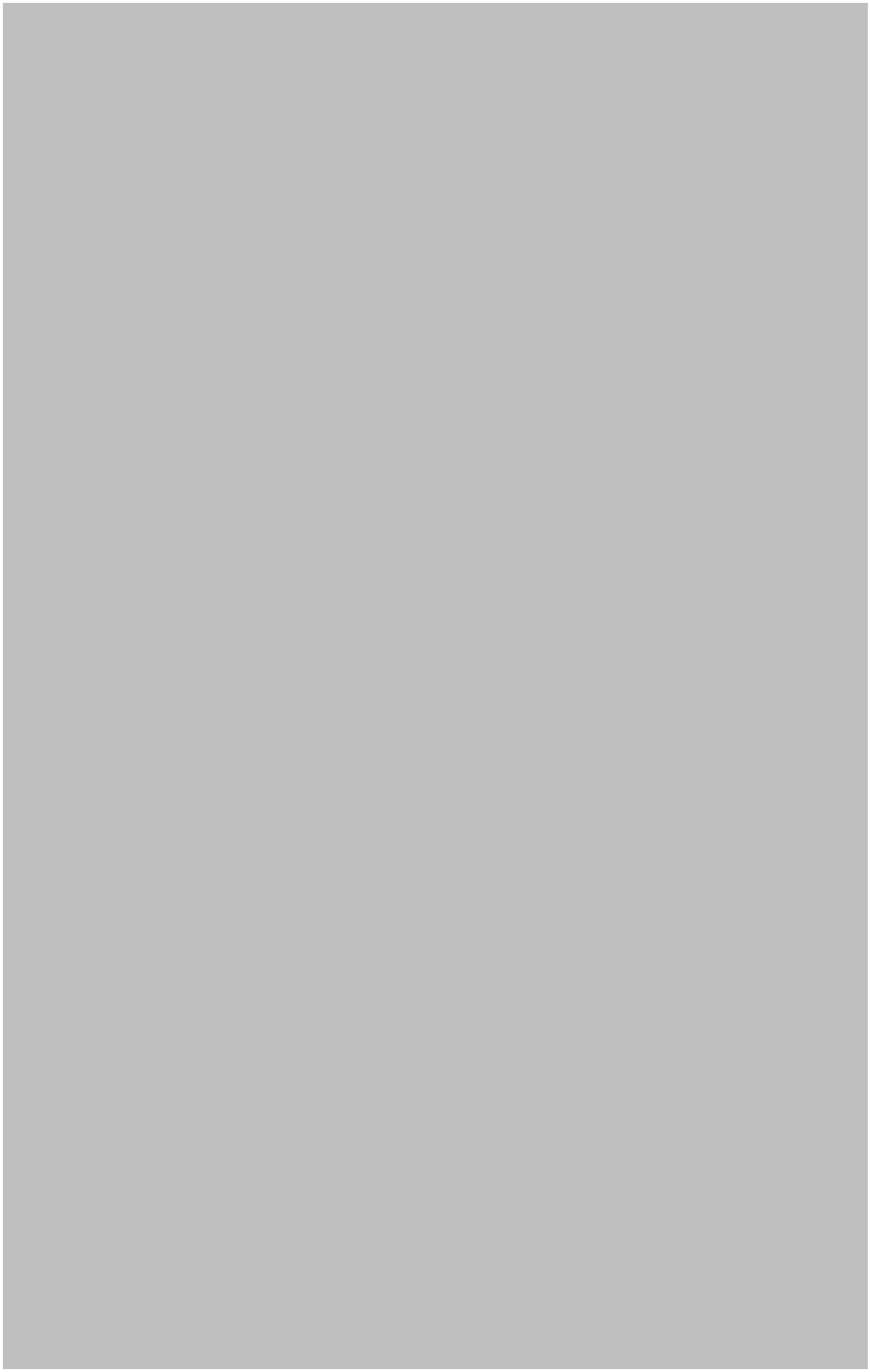
Appendix A: Published systematic literature review

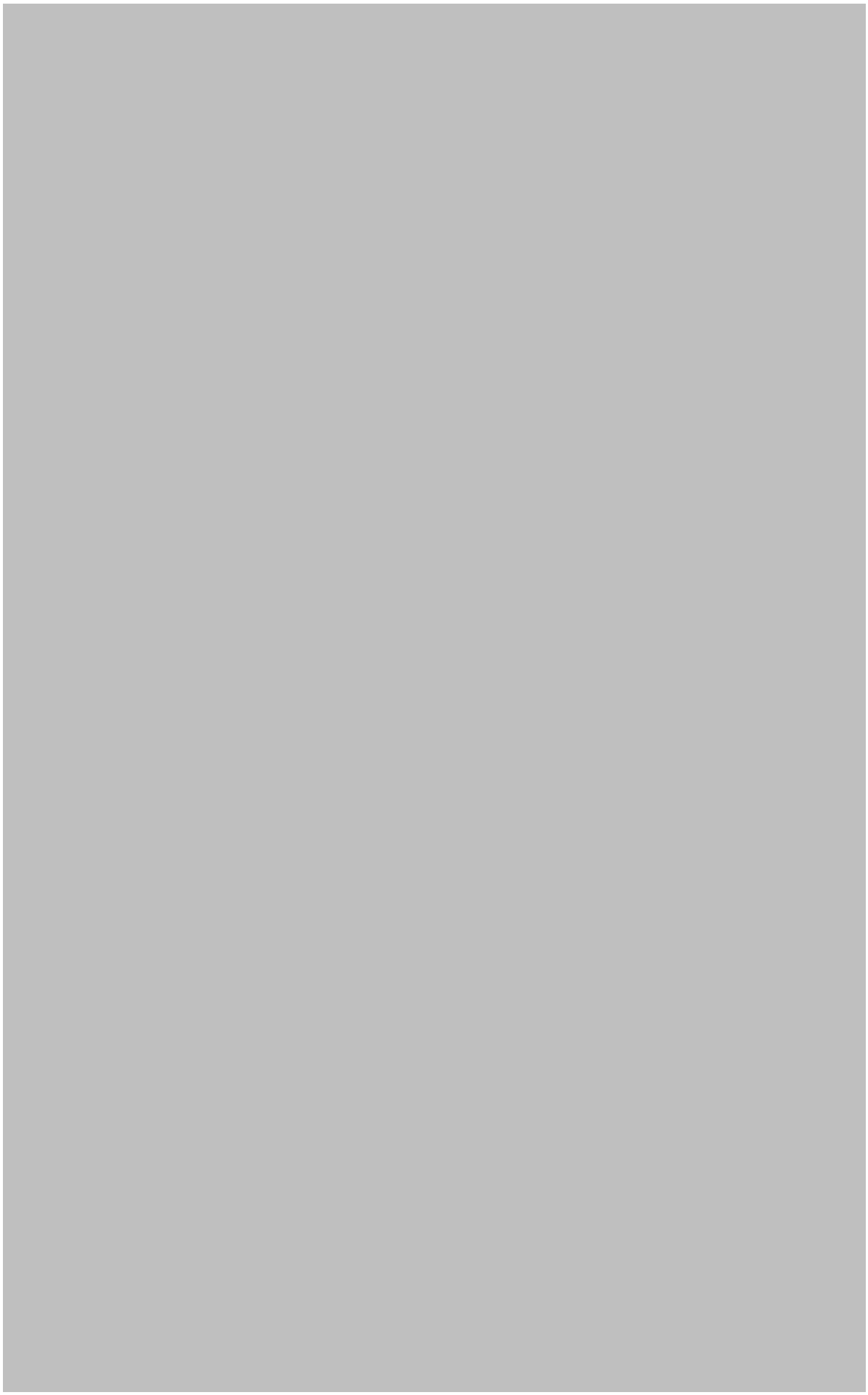


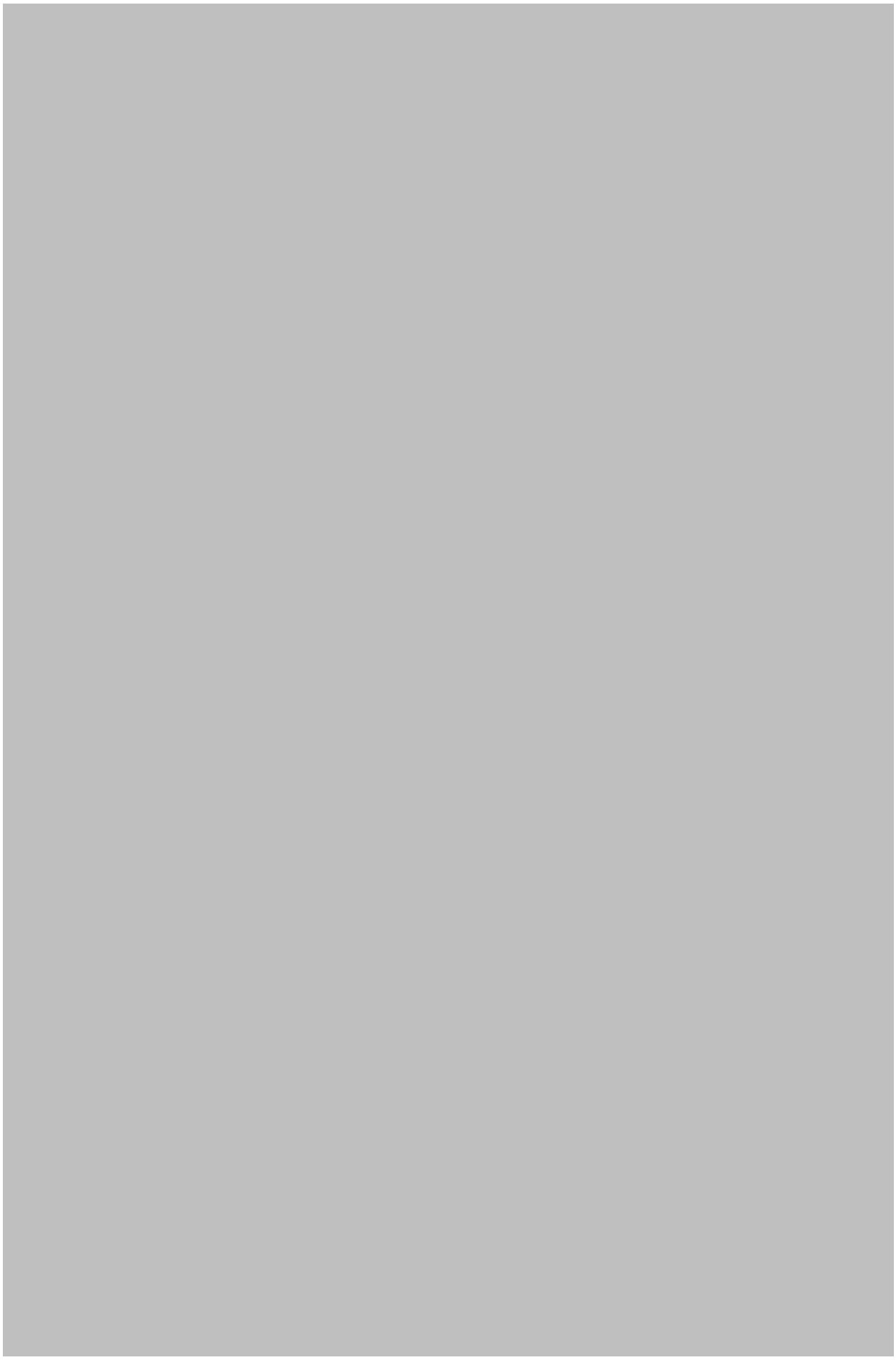












Appendix B: Medline search for systematic literature review used in thesis

Searches	Terms	Results
1	(cervico ADJ brachial).ti,ab	125
2	Cervicobrach*.ti,ab	318
3	(cervical ADJ radicul*).ti,ab	750
4	(cervical ADJ neuralg*).ti,ab	1
5	(neck ADJ3 arm ADJ pain) ti.ab	175
6	(trapezius ADJ myalgia).ti,ab	51
7	1 or 2 or 3 or 4 or 5 or 6	1382
8	management.ti,ab	550321
9	THERAPEUTICS/	7158
10	PHYSICAL THERAPY MODALITIES/ OR “PHYSICAL THERAPY (SPECIALITY)”/	25220
11	osteopath*.ti.ab	3562
12	exp CHIROPRACTIC/	2759
13	exp EXERCISE/ OR EXERCISE THERAPY/ OR EXERCISE MOVEMENT TECHNIQUES/	90579
14	PATIENT EDUCATION AS TOPIC/	61295
15	exp HEALTH EDUCATION/	121501
16	advice.ti.ab	27112
17	COGNITIVE THERAPY/ OR BEHAVIOR THERAPY/	34258
18	exp MUSCULOSKELETAL MANIPULATIONS/	12384
19	MANIPULATION, CHIROPRACTIC/OR MANIPULATION, ORTHOPEDIC/ OR MANIPULATION, OSTEOPATHIC/ OR MANIPULATION, SPINAL/	5295
20	mobili*.ti,ab	134244
21	exp MASSAGE/	4095
22	exp TRACTION/	5384
23	exp ELECTRIC STIMULATION THERAPY/	50907
24	exp TRANSCUTANEOUS ELECTRIC NERVE STIMULATION/	5221
25	interferential.ti,ab	289
26	ULTRASONIC THERAPY/	7701
27	SHORT-WAVE THERAPY/ OR DIATHERMY/	2657
28	(laser ADJ therap*).ti,ab	5083
29	exp HYDROTHERAPY/	1865
30	(aquatic ADJ physiotherapy*).ti,ab	5
31	exp CRYOTHERAPY/	18038
32	(heat ADJ treatment).ti,ab	8006
33	(heat ADJ therap*).ti,ab	148
34	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or17 or18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33	518328
35	(randomi* ADJ clinical ADJ trial).ti,ab	12262
36	(randomi* ADJ trial).ti,ab	150516
37	RANDOMIZED CONTROLLED TRIALS AS TOPIC/ OR RANDOM ALLOCATION/	140982
38	35 or 36 or 37	209009
39	7 and 34 and 38	27
40	Duplicate filtered: [7 and 34 and 38]	27

Appendix C: Participant information sheet and consent form

Participant Information Sheet (Version 2.2) (19/5/09)

1. Study title
Study to investigate the effectiveness of a lateral glide cervical spine mobilisation on cervicobrachial (neck and arm) pain.

2. Invitation
You are being invited to take part in a research study. Before you decide it is important to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish. Ask us if there is anything that is not clear or it you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.

3. What is the purpose of this study?
Cervicobrachial pain is the name for symptoms in the arm which originate from the neck. Symptoms usually include pain and sometimes include pins and needles (tingling), numbness and weakness in the arm. Physiotherapy often aims to help these problems by using advice, exercises and a variety of other treatments. The extent to whether any treatments are more helpful than others is unclear. This study will aim to establish if one commonly used treatment for this condition is better than another.
This study is part of a research degree.

4. Why have I been chosen?
You have symptoms affecting your neck and arm which have been identified as suitable to receive physiotherapy. If you agree, you will be one of 96 patients to be involved in this study.

5. Do I have to take part?
No. It is up to you to decide whether or not to take part. If you do, you will be given this information sheet to keep and be asked to sign a consent form. You are still free to withdraw at any time and without giving reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

6. What will happen to me if I take part?
Sometimes we don't know which way of treating patients is best. To find out, we need to make comparisons between the different treatments. We put people into groups and give each group a different treatment; the results are compared to see if one group is better. To try to make sure the groups are the same to start with, each patient is put into a group by chance (randomly). You will be randomised to either manual therapy with standard physiotherapy or standard physiotherapy alone and this allocation will not be changed. However, we would like to ask whether you do have a preference so that we can explore this in relation to treatment.

You will receive your treatment at the physiotherapy department. Treatment will occur at weekly intervals (approximately) for between 1 to 6 weeks which is normal for treatment in a physiotherapy department. Each appointment will take up to 30 minutes.

In each appointment the physiotherapist will ask you about your symptoms and perform some physical tests on your neck and arm. If you are in the standard physiotherapy group you will receive an up to date booklet consisting of self treatments and advice which the physiotherapist will go through with you so you are clear about what you need to do. If you are in the manual therapy with standard physiotherapy group, you will also receive the booklet, but in addition have small pressures applied to the bottom of your neck whilst lying down.

7. What do I have to do?
You will need to be able to attend the physiotherapy department at the hospital for up to six weekly attendances once your treatment has started as would be expected for your normal physiotherapy care.
Additional requirements that are not part of standard physiotherapy practice include the following:

- You will be asked to sign the consent form (attached to the back of this paper).
- You will be required to fill in a questionnaire (so don't forget your reading glasses if you need them) which will ask you questions about your neck and arm pain and how your function and general health are affected. It is best to fill this in by yourself rather than having your friends, relatives or the physiotherapist help, to ensure that we have your view of your problems rather than someone else's. It will probably take you 20 minutes to complete the questionnaire.
- You will be required to return to the physiotherapy department for follow up appointments at six weeks, six months and one year following the start of your treatment. These appointments are important for us to evaluate how the treatment you previously received has affected your problem over a period of time. At each of these follow up appointments, you will be required to fill in another questionnaire (very similar to this first one) and have measurements taken of how much you can move your neck and the physiotherapist will measure how much she can move your arm. If you do not attend these appointments we will contact you by phone to arrange an alternative appointment time, unless you ask us not to. You will be entitled to £2.00 for each visit at 6 weeks, 6 months and one year to pay for transport and parking fees.

8. What are the possible disadvantages and risks and side effects of taking part?
There are no anticipated disadvantages, risks or side effects.

9. Will my taking part in this study be kept confidential?
All information that is collected about you during the course of the research will be kept strictly confidential. Any information about you that leaves the hospital will have your name and address removed so that you cannot be recognised from it.

With your consent your GP will be informed of your participation in the study.

10. What if there is a problem?
In the unlikely event that you are harmed by taking part in this research project, there are no special compensation arrangements. If you have any comments, concerns or complaints regarding the care you receive please contact the Patient Liaison Service (PALS) on 01283 511 511 extension 5284 or 3112 (email: pals@burtonh-tr.wmids.nhs.uk). If you wish to complain about any aspect of the way you have been approached or managed relating to the study, please contact Dr Brendan Laverty 0121 414 7618 (email: b.w.laverty@bham.ac.uk).

11. What will happen to the results of the research study?
They will be presented within the university, and used for conference presentations or publication in academic journals.

It is hoped that this work will contribute to a better understanding of how physiotherapists can effectively treat cervicobrachial (neck and arm) syndrome.

Please contact either Emma Salt or Sue Kelly on the contact numbers below if you would like to obtain a summary of the studies findings.

12. Who is organising and funding the research?
Researchers at the University of Birmingham.

13. Who has reviewed the study?
NHS Research Ethics Committee

14. Contacts for Further Information

Emma Salt	01283 566 333 x5255	EJS495@bham.ac.uk
Dr Sue Kelly Research Supervisor	0121 415 8081	s.m.kelly@bham.ac.uk

Thank you.

Participant Consent Form (version 2.2) 19/5/09

Study to investigate the effectiveness of a lateral glide cervical spine mobilisation on cervicobrachial (neck and arm) pain.

NAME OF LEAD RESEARCHER: _____

TRIAL ID : _____

HOSPITAL NUMBER: _____

		Please initial box
1	I confirm that I have read and understand the information sheet dated 19/05/09 (version 2.2) for the above study and have had the opportunity to ask questions and had these answered satisfactorily.	☐
2	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	☐
3	I understand that sections of any of my medical notes may be looked at by responsible individuals from the study team or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.	☐
4	I give permission for my GP to be informed of my participation in this study.	☐
5	I agree to take part in the above study.	☐
6	I am happy to be contacted following completion of the study to provide feedback to the research team.	☐

_____	_____	_____
Name of Subject	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature
_____	_____	_____
Researcher	Date	Signature

1 copy for subject; 1 for researcher; 1 (original) to be kept with hospital notes

Appendix D: REC letter of approval for main trial

NHS

National Research Ethics Service
South Staffordshire Local Research Ethics Committee

Medical Institute
Hartshill Road
Hartshill
Stoke-on-Trent
Staffordshire
ST4 7NY

Telephone: 01782 714980
Facsimile: 01782 714975

12 May 2009

Dear Ms Salt

Full title of study: **A Randomised Controlled Trial to assess the effectiveness of a lateral glide cervical spine mobilisation on cervicobrachial (neck and arm) syndrome. (CBS Trial)**

REC reference number: **09/H1203/45**

The Research Ethics Committee reviewed the above application at the meeting held on 06 May 2009.

Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission at NHS sites ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Other conditions specified by the REC

Approval with conditions:

- The Information Sheet needs INVOLVE or PALS details adding as an independent contact.

- The researcher has allowed £4 per visit in the Information Sheet, yet only £2 per visit in the application. This information needs to be correct in the Information Sheet.

Suggestion:
To get more robust results to enhance this potentially ground breaking important research it would be useful to gain additional review or funding from an Arthritis Association or MRC. It is recommended that Keele Musculoskeletal Department be contacted. The applicant could also apply for assistance through the local CLRN, details will be available from the Research & Development Department.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Supervisor's CV		
Participant Consent Form	2.1 Appendix A	18 March 2009
Participant Information Sheet	2.1 Appendix A	18 March 2009
GP/Consultant Information Sheets	2.1 appendix D	18 March 2009
Questionnaire: validated		
Summary/Synopsis	2.1	
Covering Letter		18 March 2009
Protocol	2.1	18 March 2009
Investigator CV		18 March 2009
Application		09 April 2009

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments

- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

09/H1203/45	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

Janet Clarke pp

Dr Nitin Gupta
Vice Chair

Email: Sandra.Halden@uhns.nhs.uk

Enclosures: *List of names and professions of members who were present at the meeting and those who submitted written comments*
"After ethical review – guidance for researchers"

Copy to: Dr B Laverty, Assistant Director, Research & Commercial Services,

[redacted]

This Research Ethics Committee is an advisory committee to West Midlands Strategic Health Authority

The National Research Ethics Service (NRES) represents the NRES Directorate within the National Patient Safety Agency and Research Ethics Committees in England

Appendix E: Self-management booklet

Burton Hospitals NHS Trust

Patient Information

from Queen's Hospital - www.burtonhospital.com - telephone: 01283 566333

Department of Physiotherapy

Self-treatment for neck and arm pain

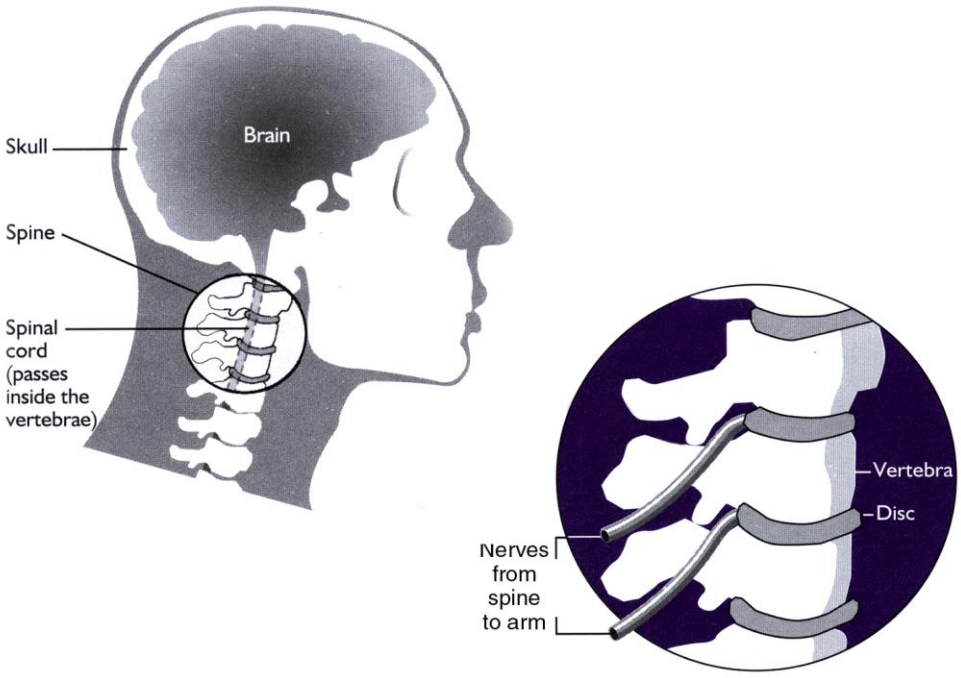
Neck and Arm Pain

-Self-Treatment-

This leaflet has been written to help you to understand the causes of your neck and arm pain and to give you suggestions as to how you can treat it yourself.

What Causes Neck and Arm Pain?

Pain in the neck and arm can be caused by irritation of the nerves as they come out through the spaces between the bones of the neck.



Illustrations reproduced (in modified form) by kind permission of the Arthritis Research Campaign (www.arc.org.uk)

Who Gets Neck and Arm Pain?

It is unclear why this should happen, and often there is no good reason, but it is known that it is more common in people:

- of working age
- who sit at desks/computers for long periods
- who do repetitive activities (such as data inputting)
- who lift heavy loads

Being female, having poor posture or being under emotional stress can also be factors which lead to symptoms.

What investigations should be done?

In most instances your condition will have been diagnosed by the doctor or physiotherapist from information you have given them and the physical tests they have performed on you.

Further investigations such as X-rays, scans and nerve and muscle tests are not usually required.

STEP ONE

Identify at least three key activities that can make *your* symptoms worse:

1.)

2.)

3.)

Pace yourself
It is usually a good idea to try and pace the activities that make you worse by

- having regular breaks
- breaking them up with other activities that affect your symptoms less, or better still, make them feel better.

This is logical, but it is surprising how much difference simple changes can help towards reducing your symptoms significantly.

Your physiotherapist will be able to help you with this.

Write below modifications to these activities or changes you can make to improve your symptoms when carrying out your three key activities.

1.)

2.)

3.)

As your symptoms settle, you should find that you can gradually return to all the things you want to do, without them causing you so much of a problem.

STEP TWO

Self-Treatments - What to expect

- Try to practise self-treatments three times a day to start off with.
- If these treatments are making you feel a bit sore initially, reduce them to once or twice a day.
- If you do not feel they are making a difference, try and do them a bit more regularly.
- You may feel some discomfort when you do these treatments, however this should reduce with time and practise. If discomfort increases, speak to your physiotherapist rather than just giving up on them.
- If one treatment in particular is a problem, but the others are fine, try eliminating that treatment for a week (whilst continuing with the others) then return to it.

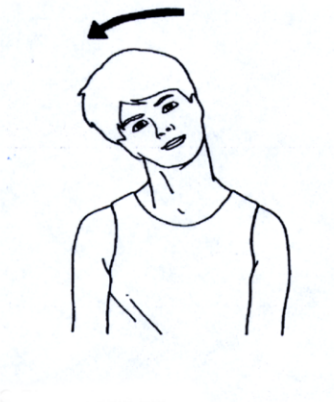
Treatment 1

Pull your chin in slowly whilst keeping your neck and back straight. Try not to tip your head down. hold at the end position for between 5 to 10 seconds. Repeat 5 times.

Treatment 2

Bend your head forward until you feel a stretch behind your neck.
Repeat slowly 5 times

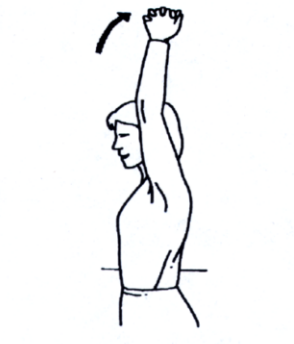
Treatment 3
Slowly and smoothly tilt your head towards one shoulder until you feel the stretch on the opposite side. Try not to raise either shoulder. Repeat on other side.
Repeat 5 times on both sides.



Treatment 4
Slowly and smoothly turn your head to one side until you feel a stretch. Repeat on other side.
Repeat 5 times on both sides.

Treatment 5
Slowly and smoothly bend your head backwards as far as is comfortable.
Repeat 5 times.

Treatment 6
Sit or stand with hands clasped in front of you. Lift your hands above your head and stretch your arms as far as possible. Repeat between 5 and 10 times.



STEP THREE

Be more physically active

Recent research shows that the more physically active you are, the more the pains in the neck and arm will reduce. Not only will simple exercise help your neck and arm pain, it will also help your general physical and mental well being.

General Exercise Advice

- If you are not used to exercise, then start off slowly.
  For example, simply take a walk around the block, then progress by increasing the speed and/or distance.
- Once you become more confident, you could progress onto other forms of exercise to improve your fitness.
- If you have problems staying motivated with exercise, it is sometimes worth joining an exercise group, perhaps with a friend or relative.
- Keep a chart of your exercise somewhere obvious (like the fridge door) and keep a diary of how frequently you are doing exercise.
- Walk or cycle to work rather than taking the car.
- If you find exercise is aggravating your problem, you should discuss ways in which you can modify it with your physiotherapist.

Occasionally, you may need to change to a different type of exercise until your symptoms start to settle.

- For example, swimming breast stroke can make your neck sore if you swim with your head lifted out of the water. If this is the case, then a different stroke may not cause neck soreness, but still enable you to continue swimming, which is very beneficial.
- It is important to continue exercising for the benefits to last, so try to include it in your lifestyle as much as possible.
- You should find the more you have done, the better you feel.

Above all -
Do not be afraid to exercise

ADVICE

Postural advice

- Maintain a good posture whenever possible.
- Slouching can put a strain down through the neck which may contribute to your symptoms.

Sitting

- Sometimes placing a rolled up towel behind your lower back when you are sitting can help gain a better position for your neck.
- Try to adopt a good position, particularly if you spend a lot of time sitting, e.g. at a table or computer.
- Ideally, your back should be upright and supported and your head should remain in a neutral position (neither bent forward nor tilted back).

- Your hands should be close by your body and positioned slightly lower than your elbow level.
- We are not designed to sit for long periods of time, so every 20 minutes or so it is important to get up, move around, loosen up and stretch, before continuing with your task.
- If you struggle to remember to do this, it may help to download a free software package (available on the internet) onto your computer system which frequently prompts you to change position.
- If you are planning to take a long car journey, it is best to break up the journey by regular stops along the way where you can get out of the car and move around.

Sleeping

- Sleep in a good position where your head is neither twisted nor tilted.
- You may need to try different pillow combinations or heights to find what suits you best. Everyone's neck is a different shape, and what works for one person won't necessarily work for another.
- It is generally advisable **NOT** to sleep face down as this causes your neck to twist. It is common to wake up with numb arms and hands when sleeping in this position.

Stress

- Exercise has been shown to be of great benefit if you are feeling stressed, anxious or depressed.
- Relaxation and rest is also beneficial under these circumstances.
- You may find it useful to take some time out of your hectic schedule and lay down for 20 minutes or so with some relaxing music.
- Deep breathing techniques can also help.

What to expect

- Do not panic if the self-treatment doesn’t work immediately.
- Often it takes a few weeks or more before you see any results from the efforts that you put in, so try and stick with it.
- Do not worry if the neck pain is getting worse, providing the arm symptoms are getting easier. This is often a sign of recovery.

Collar use

- Do not wear a collar for long periods as this can make symptoms worse in the long run.
- If you do have relief from wearing a collar, try to only wear it only when your symptoms are really bad, and then for no more than an hour at a time.
- It is important to continue to keep your neck mobile.

Heat and Cold

- Heat and cold can be used for short term relief of symptoms. You should discuss with your physiotherapist if this is a suitable home treatment for you and be guided by them on how to apply heat and cold treatments.

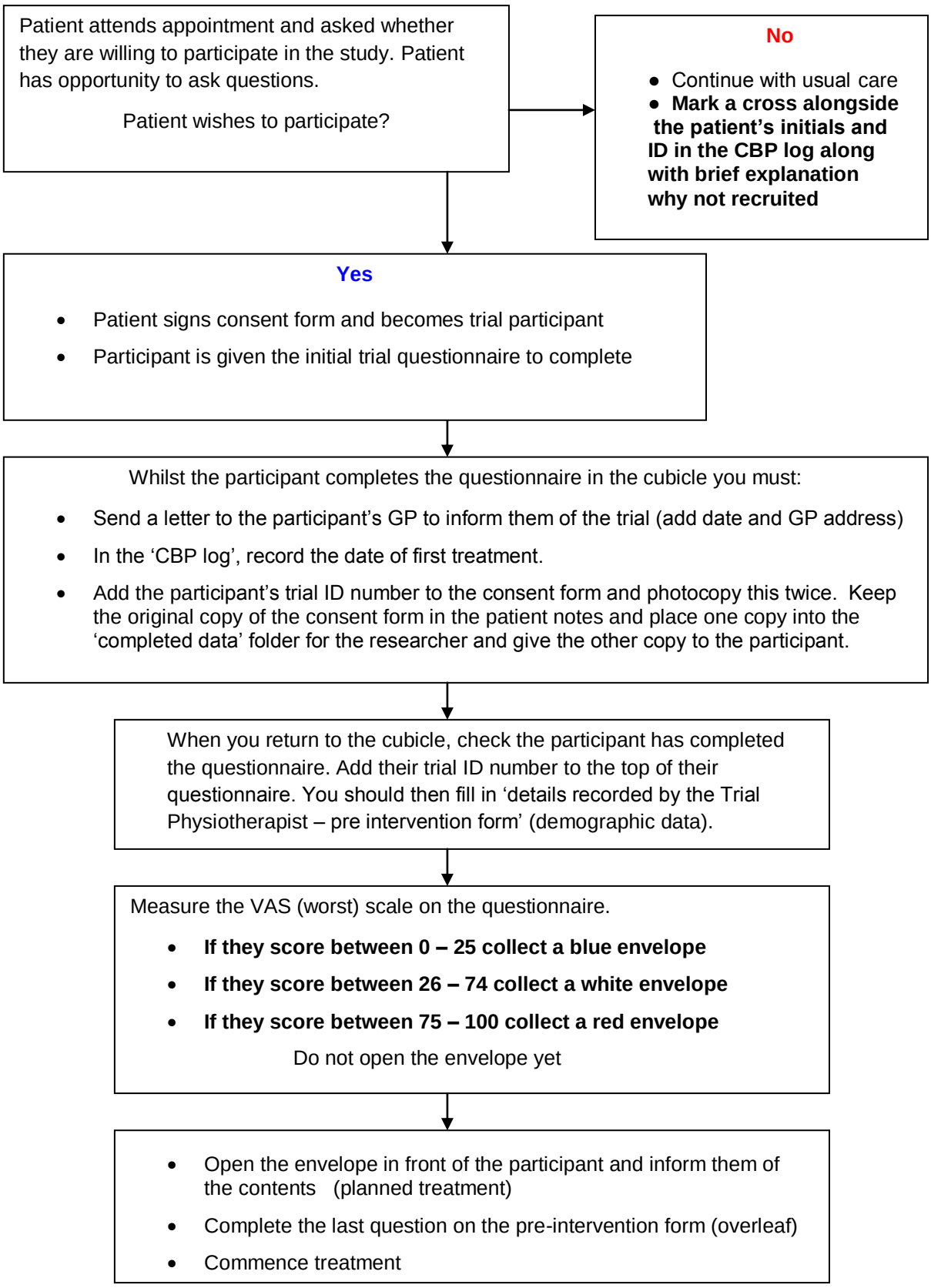
Maintaining the Improvement in your Neck and Arm

- Your symptoms should at least reduce to a manageable level by following the advice and self-treatments suggested in this leaflet, however, it is possible for the problem to recur.
- You can avoid the likelihood of it recurring by keeping up with your general fitness and following the simple steps to look after your neck.
- Continuing self-treatments can be used to help prevent a future problem, but it is often difficult to continue with the suggestions when it seems that the symptoms have subsided.
- Some people find it useful to re-start the self-treatments at the first sign of the problem recurring, to nip it in the bud!

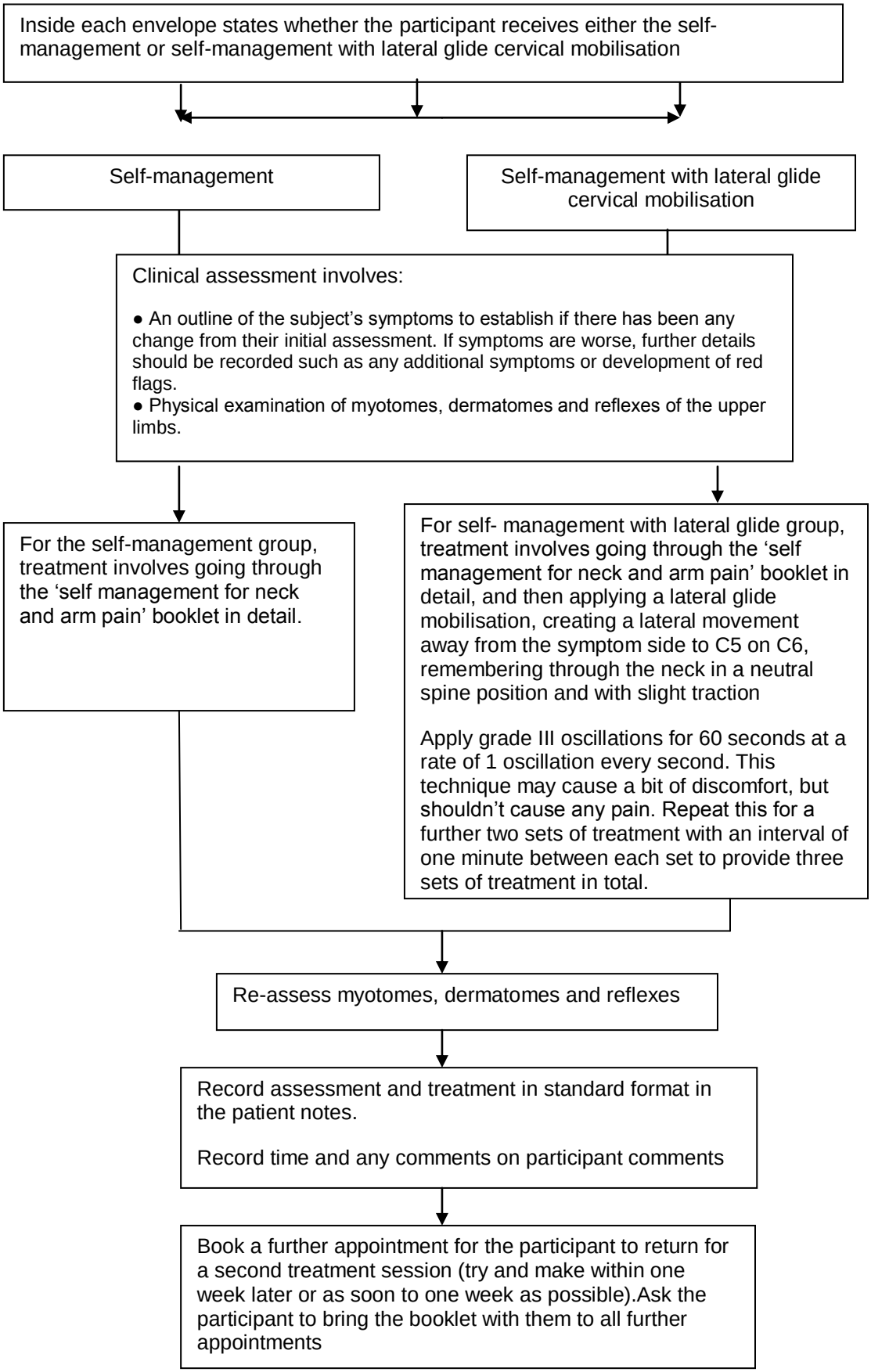
Keep this booklet in a safe place in case you need it again in the future.

Appendix F: Protocol for Trial Physiotherapists

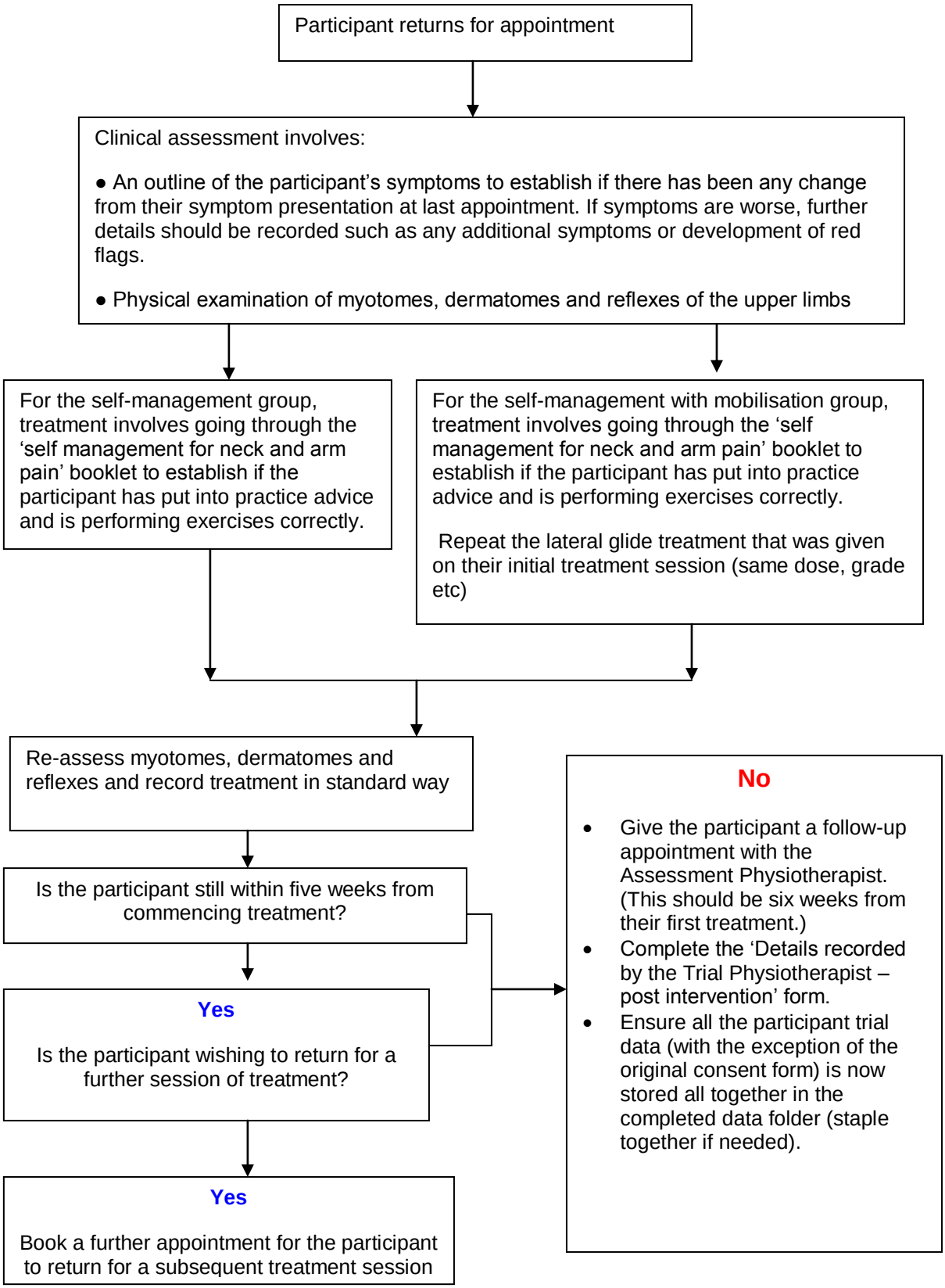
Flow diagram for 'Trial Physiotherapists'



Flow diagram for 'Trial Physiotherapists' - Initial treatment pathway



Flow diagram for 'Trial Physiotherapists' - 2nd – 6th treatment pathway



Missed appointments and cancellations
In instances where treatment appointments are missed or cancelled, further appointments will be made based on usual departmental protocols.

It is important for the Trial Physiotherapist to be able to arrange the 6 week re-assessment, and complete the participant data post-intervention form regardless of whether the participant has attended all agreed treatment sessions or not.

The research lead will be responsible for overseeing that all participants have been contacted for their follow-up appointments.

Indications for participants who discontinue the trial
If a participant decides not to continue with being part of the trial, they are at liberty to do so. In these instances participants will not be required to attend the follow-up assessments, however, please make sure you still fill in the 'Details recorded by the Trial Physiotherapist – post intervention' form and make sure it is clear that they received alternative treatment and if possible, the reasons for this.

Adverse incidents for subjects during the trial
If an adverse reaction occurs and it is suspected that this is as a direct result from any of the treatment given in the trial, this must be recorded on both the 'Adverse incidents during the CBS trial' sheet and a Trust incident form. Please let the research lead know as soon as possible if this occurs.

Appendix G: Comments sheet

Participant Trial No:

	Comments of Trial physiotherapists i.e. any deviations from basic protocol	Comments from participant i.e. treatment response
Treatment session 1		
Treatment session 2		
Treatment session 3		
Treatment session 4		
Treatment session 5		
Treatment session 6		

Appendix H: Serious adverse incidents log

Subject trial number	Date of incident	Nature of incident	Outcome	Incident form filled?

Appendix I: Participant feedback survey with covering letter

16th February 2009

Dear

Re: Feedback from participating in research trial

Last year you kindly agreed to be involved in a pilot research study in the Physiotherapy Department at Queen's Hospital, Burton regarding your neck and arm pain.

We are now looking to evaluate how you felt about being involved in the trial to inform us what measures we need to address before involving other patients in future research trials.

I would be very grateful if you could spend a few minutes to complete the survey and return it by post in the pre-paid envelope. Alternatively, you can contact the research lead, Emma Salt either by phone or email.

Yours sincerely,

Emma Salt MSc, MMACP, Grad dip phys.
MSK Physiotherapy Lead.

Survey of involvement in physiotherapy research trial

1. Did you feel you were given enough information about what to expect from being involved in the research trial? (please circle appropriate answer)

Yes No

If no, then please comment on which aspects you would like to have known more about.
…….
…….

2. Did you feel obliged to be involved in the trial? (please circle appropriate answer)

Yes No

If yes, then please comment at which point you felt obliged and how this could have been avoided.
…….
…….

3. Do you have any comments to make about the questionnaires you filled in?
……
……

4. Please comment on how useful you found the information booklet you received
……..
……..

5. If you received any mobilisation (manipulation) treatment, please comment on how you found this.
……
……

6. Were you aware that you were free to withdraw from the trial at any point in time? (please circle appropriate answer)

Yes No

7. Based on your experience of this trial, would you be happy to participate in another health research trial? (please circle appropriate answer)

Yes No

Please add any further information you feel would be useful for researchers to know when planning trials in physiotherapy.
……
……
……
…….

Thank you.

Appendix J: Follow-up questionnaire

Trial ID ……

(Version 2.1)
(18/3/09)

To be completed by Assessment Physiotherapist

Date of one year assessment……

Has the participant needed further treatment following completion of the 6 month follow up?

☐ Yes ☐ No

If 'yes' please give further details

☐ More physiotherapy/osteopathy etc

☐ Acupuncture

☐ Injections to the cervical spine for this problem

☐ Surgery

☐ A combination of treatment

Days off sick due to this problem within last month of work :

☐ none ☐ 1- 5 days ☐ 6-10 days ☐ 11-15 days ☐ > 15 days ☐ Not applicable

Ipsilateral ULNE

The test should be performed in supine lying in the following sequence:
scapular depression, shoulder abduction, forearm supination, wrist and finger extension, shoulder lateral rotation, elbow extension and contralateral cervical side bend.
The test was considered positive if any of the following criteria are positive:
1) symptoms reproduced
2) side to side differences of >10 degrees elbow extension
3) contralateral neck side-bending increased symptoms or ipsilateral side-bending decreased symptoms when in upper limb tensioned position.

Positive ipsilateral (same side as symptoms) ULNE? ☐yes ☐no

AROM Cervical spine

The test should be performed in sitting using an inclinometer on participants head. Only one measure per movement is needed and this is to be recorded in degrees.

Flexion	
Extension	
Right side bend	
Left side bend	
Right rotation	
Left rotation	

To be completed by the participant

This questionnaire is divided into four parts. The first part asks what the severity of your pain is in the neck and arm and any additional symptoms you may be suffering with. The second part aims to identify how your symptoms affect your health in general. The third part aims to establish how your symptoms are affecting your function and the last part asks if there have been any changes since you started your physiotherapy treatment. Some of the questions may be similar, but please try and answer every question. This is not a test and there are no right or wrong answers. It will take you approximately 20 minutes to complete.

The Severity of your pain

The following scales help to identify the severity of your pain.

For example if you were feeling moderately high severity of pain/discomfort you would indicate it on the line below with an **x** as such:

example:

no pain — **worst pain imaginable**

However if you were only feeling moderately low pain/discomfort you would indicate it on the line like this:

no pain — **worst pain imaginable**

On the scale below mark an **x** to indicate the **average** pain in your neck and arm over the **last week**

no pain — **worst pain imaginable**

On the scale below mark an **x** to indicate the **worst** pain in your neck and arm over the **last week**

no pain — **worst pain imaginable**

Below are 7 questions about any additional symptoms you may have.
- Think about how your neck and arm symptoms have felt **over the last week**.
- Only circle responses that describe your pain.

1. In the area where you have pain, do you also have 'pins and needles', tingling or prickling sensations?

a) NO - I don't get these sensations (0)

b) YES - I get these sensations often (5)

2. Does the painful area change colour (perhaps looks mottled or more red) when the pain is particularly bad?

a) NO - The pain does not affect the colour of my skin (0)

b) YES - I have noticed that the pain does make my skin look different from normal (5)

3. Does your pain make the affected skin abnormally sensitive to touch? Getting unpleasant sensations or pain when lightly stroking the skin might describe this.

a) NO - The pain does not make my skin in that area abnormally sensitive to touch (0)

b) YES - My skin in that area is particularly sensitive to touch (3)

4. Does your pain come on suddenly and in bursts for no apparent reason when you are completely still? Words like 'electric shocks', jumping and bursting might describe this.

a) NO - My pain doesn't really feel like this (0)

b) YES - I get these sensations often (2)

5. In the area where you have pain, does your skin feel unusually hot like a burning pain?

a) NO - I don't have burning pain (0)

b) YES - I get burning pain often (1)

6. Gently rub the painful area with your index finger and then rub a non-painful area (for example, an area of skin further away or on the opposite side from the painful area). How does this rubbing feel in the painful area?

a) The painful area feels no different from the non-painful area (0)

b) I feel discomfort, like pins and needles, tingling or burning in the painful area that is different from the non-painful area (5)

7. Gently press on the painful area with your finger tip then gently press in the same way onto a non-painful area (the same non-painful area that you chose in the last question). How does this feel in the painful area?

a) The painful area does not feel different from the non-painful area (0)

b) I feel numbness or tenderness in the painful area that is different from the non-painful area (3)

Your Health in General

Please answer every question. Some questions may look like others, but each one is different. Please take the time to read and answer each question carefully by filling in the bubble that best represents your response.

EXAMPLE

This is for your review. Do not answer this question. The questionnaire begins with the section ***Your Health in General*** below.

each question you will be asked to fill in a bubble in each line:

How strongly do you agree or disagree with each of the following statements?

	Strongly agree	Agree	Uncertain	Disagree	Strongly disagree
a) I enjoy listening to music.	○	●	○	○	○
b) I enjoy reading magazines.	●	○	○	○	○

Please begin answering the questions now.

In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
O_1	O_2	O_3	O_4	O_5

Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
O_1	O_2	O_3	O_4	O_5

During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a) Cut down on the **amount of time** you spent on work or other activities	O_1	O_2	O_3	O_4	O_5
b) **Accomplished less** than you would like	O_1	O_2	O_3	O_4	O_5
c) Did work or other activities **less carefully than usual**	O_1	O_2	O_3	O_4	O_5

During the past 4 weeks, to what extent has your physical health or emotional problems interfere with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
O_1	O_2	O_3	O_4	O_5

These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
a) did you feel full of life?	O_1	O_2	O_3	O_4	O_5	VT01
b) have you been very nervous?	O_1	O_2	O_3	O_4	O_5	MH01
c) have you felt so down in the dumps that nothing could cheer you up?	O_1	O_2	O_3	O_4	O_5	MH02
d) have you felt calm and peaceful?	O_1	O_2	O_3	O_4	O_5	MH03
e) did you have a lot of energy?	O_1	O_2	O_3	O_4	O_5	VT02
f) have you felt downhearted and depressed?	O_1	O_2	O_3	O_4	O_5	MH04
g) did you feel worn out?	O_1	O_2	O_3	O_4	O_5	VT03
h) have you been happy?	O_1	O_2	O_3	O_4	O_5	MH05
i) did you feel tired?	O_1	O_2	O_3	O_4	O_5	VT04

During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
O_1	O_2	O_3	O_4	O_5

How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a) I seem to get sick a little easier than other people	O_1	O_2	O_3	O_4	O_5
b) I am as healthy as anybody I know	O_1	O_2	O_3	O_4	O_5
c) I expect my health to get worse	O_1	O_2	O_3	O_4	O_5
d) My health is excellent	O_1	O_2	O_3	O_4	O_5

How your symptoms affect your function

This part of the questionnaire is divided into two further sections; in section A, you will rate your ability to do a variety of activities based on your condition in the last week, by circling the most appropriate number. For example, circle number "1" if you have no difficulty performing the activity, or circle number "7" if you are unable to do the activity, or circle any of the numbers in between depending on the amount of difficulty you have with the activity or situation in the question. If you did not have the opportunity to perform a certain activity in the past week, please make your best estimate on which response would be the most accurate. It doesn't matter which arm you use to perform the activity. Please answer based on your ability regardless of how you perform the task.

Questions 7 to 10 ask about your work and refer to your usual job tasks. If you do not have a job and were not working at the time of your symptoms starting, answer "not applicable" to these questions.

Note that section B (questions 12 to 20), the numbers "1" to "7" refer to how frequently you experience the situation in the question (e.g. "1" refers to "never" and "7" refers to all the time)

Please check "not applicable" if the question refers to an activity that you do not normally do or if the situation described in the question is not related to your neck or arm.

SECTION A

How much difficulty do you have or would you have *NOW* with the following activities or situations BECAUSE OF YOUR PROBLEM? *NOW* refers to the past 7 days.

1	2	3	4	5	6	7	NOT APPLICABLE
No difficulty at all	A little difficult	Somewhat difficult	Moderately difficult	Very difficult	Extremely difficult	Cannot do	Check "NOT APPLICABLE" if question does not apply to you or you don't know

1	Washing yourself, dressing, grooming or eating?	1	2	3	4	5	6	7	NOT APPLICABLE
2	Washing the top of your head or washing, drying or arranging your hair?	1	2	3	4	5	6	7	NOT APPLICABLE
3	Reaching behind your back (for example, to wash or dry your back, get your wallet out of your back pocket or do up a bra or back zipper)?	1	2	3	4	5	6	7	NOT APPLICABLE
4	Doing household chores or looking after your family?	1	2	3	4	5	6	7	NOT APPLICABLE
5	Opening cans, jars or turning keys, taps or door knobs?	1	2	3	4	5	6	7	NOT APPLICABLE
6	Carrying grocery bags, cases of beer or soft drinks, or garbage bags?	1	2	3	4	5	6	7	NOT APPLICABLE

SECTION B

How **often** is the following **true** for you *NOW* BECAUSE OF YOUR PROBLEM?
NOW refers to the past 7 days.

1	2	3	4	5	6	7	NOT APPLICABLE
Never	Rarely	Sometimes	Somewhat often	Often	Very often	All the time	Check "NOT APPLICABLE" if not related to your problem

12	Feeling anxious, nervous, worried or jumpy.	1	2	3	4	5	6	7	NOT APPLICABLE
13	Feeling sad, depressed or moody.	1	2	3	4	5	6	7	NOT APPLICABLE
14	Feeling irritable, frustrated or angry.	1	2	3	4	5	6	7	NOT APPLICABLE
15	Feeling less pleasure in life.	1	2	3	4	5	6	7	NOT APPLICABLE
16	Feeling like I can't take care of my family the same way I used to.	1	2	3	4	5	6	7	NOT APPLICABLE
17	Being afraid that in the future I will be unable to earn my living.	1	2	3	4	5	6	7	NOT APPLICABLE

How often is the following true for you *NOW* BECAUSE OF YOUR PROBLEM?
NOW refers to the past 7 days.

1	2	3	4	5	6	7	NOT APPLICABLE
Never	Rarely	Sometimes	Somewhat often	Often	Very often	All the time	Check "NOT APPLICABLE" if not related to your problem

18 Waking up during the night with pain, tingling or numbness.

1	2	3	4	5	6	7	NOT APPLICABLE

19 Sleeping badly.

1	2	3	4	5	6	7	NOT APPLICABLE

20 Having pain or discomfort from the physical examinations, treatments or therapy for my neck or upper limb problem.

1	2	3	4	5	6	7	NOT APPLICABLE

For the following 17 questions, please state your level of agreement if:

1 = strongly disagree
2 = disagree
3 = agree
4 = strongly agree

Please circle most appropriate answer

1. I'm afraid that I might injury myself if I exercise	1	2	3	4
2. If I were to try to overcome it, my pain would increase	1	2	3	4
3. My body is telling me I have something dangerously wrong	1	2	3	4
4. My pain would probably be relieved if I were to exercise	1	2	3	4
5. People aren't taking my medical condition seriously enough	1	2	3	4
6. My accident has put my body at risk for the rest of my life	1	2	3	4
7. Pain always means I have injured my body	1	2	3	4
8. Just because something aggravates my pain does not mean it is dangerous	1	2	3	4
9. I am afraid that I might injure myself accidentally	1	2	3	4
10. Simply being careful that I do not make any unnecessary movements is the safest thing I can do to prevent my pain from worsening	1	2	3	4
11. I wouldn't have this much pain if there weren't something potentially dangerous going on in my body	1	2	3	4
12. Although my condition is painful, I would be better off if I were physically active	1	2	3	4
13. Pain lets me know when to stop exercising so that I don't injure myself	1	2	3	4
14. It's really not safe for a person with a condition like mine to be physically active	1	2	3	4
15. I can't do all the things normal people do because it's too easy for me to get injured	1	2	3	4
16. Even though something is causing me a lot of pain, I don't think it's actually dangerous	1	2	3	4
17. No one should have to exercise when he/she is in pain	1	2	3	4

Since the last time you completed this form, would you say your pain has become:

A very great deal better
□ A great deal better
□ A good deal better
□ Moderately better
□ Somewhat better
□ A little better
□ Almost the same, hardly any worse or better at all
□ A little worse
□ Somewhat worse
□ Moderately worse
□ A good deal worse
□ A great deal worse
□ A very great deal worse

Please mark x in the box which describes your situation the best.

Since the last time you completed this form, have you needed to take medications for the neck and arm pain? Please mark an x in the box that is appropriate to your answer.

□ No pain medications

□ Different (weaker) pain medications

□ Same pain medications

□ Different (stronger) medications or I have needed to start taking medications for the neck and arm pain whereas I wasn't needing them before

Thank you for completing this questionnaire

Appendix K: Short-form postal questionnaire (with covering letter)

Version 2.2 (15.9.10)

Date:

Cervicobrachial Pain Trial
Final reminder

Dear

Thank you for participating in the above study.

We are sorry that you were unable to attend your last review appointment. We would be extremely grateful if you could answer the enclosed short questionnaire so that we are able to compare how you are now with when you joined the study. Once completed, please return the questionnaire in the stamped addressed envelope provided.

Your participation is very important so that the results provide physiotherapists with a better understanding of how to help people who have neck and arm pain. To achieve this goal, it is essential that we find out how people respond in the long-term to different physiotherapy treatments. This is why your information is of great value to us.

If you have any queries about the questionnaire or any other aspects of the trial, please contact Emma Salt on 01283 566 333 x5255 or by email: emma.salt@burtonh-tr.wmids.nhs.uk.

Yours sincerely,

Emma Salt
MSc, MMACP, MCSP, Grad dip phys.
Research lead

Trial ID ……

Short Component Questionnaire for Cervicobrachial Pain Trial

Date ……

The Severity of your pain

The following scales help to identify the severity of your pain.

Example:

For example if you were feeling moderately high severity of pain/discomfort you would indicate it on the line below with an x as such:

no pain — **worst pain imaginable**

However if you were only feeling moderately low pain/discomfort you would indicate it on the line like this:

no pain — **worst pain imaginable**

On the scale below mark an **x** to indicate the **average** pain in your neck and arm over the **last week**

no pain — **worst pain imaginable**

On the scale below mark an **x** to indicate the **worst** pain in your neck and arm over the **last week**

no pain — **worst pain imaginable**

Please turn over page

Since the last time you completed a trial form, would you say your pain has become:

□ A very great deal better
□ A great deal better
□ A good deal better
□ Moderately better
□ Somewhat better
□ A little better
□ Almost the same, hardly any worse or better at all
□ A little worse
□ Somewhat worse
□ Moderately worse
□ A good deal worse
□ A great deal worse
□ A very great deal worse

Please mark x in the box which describes your situation the best.

Since the last time you completed a trial form, have you needed further treatment for your neck and arm pain?

□ Yes □ No

If 'yes' please give further details
□ More physiotherapy/osteopathy/ chiropractic's
□ Acupuncture
□ Injections to the cervical spine for this problem
□ Surgery
□ A combination of treatment

Thank you for completing this questionnaire

Appendix L: Data check for accuracy of data inputting

1. Audit check on data – 10%
    a. If >10 % errors, check an additional 10%.
2. For each outcome measure, check the minimum and maximum values.
    a. If both minimum and maximum recorded values are within the limits for all outcome measures, then, proceed.
    b. If one or both extremes are outside the theoretical limits for one or more outcome measures:
        i. Check the inputted data against the original data sheets.
        ii. Correct any errors found.
        iii. If “errors” are still present, and there are no other data with which to cross-check values, set data outside the limits to “missing” (a blank in Excel).
3. Check “XXX” entries (i.e. missing data). For multi-item outcome measures:
    a. Does any subscale of any outcome measure (e.g. SF36, SLANSS) have more than 50% unanswered/missing items for any participant?
        i. If yes, for that participant, set the score on the subscale to “missing” in the Excel database
        ii. If no, for that participant, set the score on the subscale to the “mean” score across answered items on that subscale (as recommended by developers of the outcome measure).
    b. Does any outcome measure have more than 50% unanswered/missing items for any participant?
        i. If yes, for that participant, set the score on the outcome measure to “missing” in the Excel database.
        ii. If no, for that participant, set the score on the outcome measure to the “mean” score across answered items or use weightings as specified by the developers of that outcome measure.
4. Check XX entries (i.e. non-applicable items on multi-item outcome measures).
    a. These “non-applicable” items should correspond to items within outcome measures that do not necessarily apply to all participants (e.g. NULI):
        i. If the XX are consistent with point (a): compute score as recommended for the outcome measure
            1) Change XX to missing (blank cell) in the Excel database, if consistent with (i).
        ii. If the XX are not consistent with point (a): then, check inputted data against the original data sheets.
5. Following completion of the above checks, compute participant scores for each outcome measure following rules specified by the developers (or, latest published criteria, as appropriate)

   Independent person to check a sample of data.

Appendix M: Range of minimum and maximum scores per outcome measure

No recorded data items were outside the minimum or maximum values for any outcome measure:

Outcome measure scores at baseline

	VAS (average pain)	VAS (worst pain)	S-LANSS	NULI	TAMPA	SF36
min	0	0	0	0	23	17.65
max	89	97	24	88.33	60	91.67

Outcome measure scores at 6 week follow-up

	VAS (average pain)	VAS (worst pain)	S-LANSS	NULI	TAMPA	SF36	GROC
min	0	0	0	0	20	12.5	-5
max	93	100	24	95	53	94.74	6

Outcome measure scores at 26 week follow-up

	VAS (average pain)	VAS (worst pain)	S-LANSS	NULI	TAMPA	SF36	GROC
min	0	0	0	0	18	21.74	-6
max	81	93	24	83.33	50	94.74	6

Outcome measure scores at 52 week follow-up

	VAS (average pain)	VAS (worst pain)	S-LANSS	NULI	TAMPA	SF36	GROC
min	0	0	0	0	17	22.37	-6
max	94	97	21	68.63	52	97.06	6

Key: GROC= Global Rating of Change score; NULI= Neck and Upper Limb Index; SF36= Short-Form 36 (Mental component summary); S-LANSS= Self Leeds Assessment of Neuropathic Signs and Symptoms; VAS= Visual Analogue Scale.

Footnote*:*

Possible score range:

VAS:	0 to 100
S-LANSS:	0 to 24
NULI:	0 to 100
TAMPA:	17 to 68
SF36:	0 to 100
GROC:	6 to -6

Appendix N: Strategy for building the MLM

MLM was calculated using linear 'mixed models'on SPSS version 19

'Dependent variable' was the outcome measure of interest e.g. VAS(worst pain)

'Fixed factors' were defined as the intervention (group), baseline covariates that could affect outcome (e.g. age) and time in months post baseline at which data were collected for each particpant.

Follow-up time points were also identified as **'Random factors'** to model variation around the planned follow-up time points

The model was built in three phases:

1) Analysis across time

The dependent variable (e.g. VAS(worst pain) was modelled as a function of (i) time, (ii) time and time squared, and (iii) time, time squared and time cubed, to account for any underlying pattern of change in worst pain over time.

2) Adding covariates

Covariates were tested for addition to the model, one at a time, in the order of their "importance" as identified from the literature reviews. Non-significant covarites were not included in the model, so that only significant covaraiates were taken forward to stage three of the modelling.

3) Adding intervention

The intervention was the last variable to be added to the model, to assess intergroup differences after adjustment for time and effects of important covariates.

This approach was recommended by Field (2009) and compared the profile of change across the intervention groups, with adjustment for time and important covariates.

Appendix O: MLM example (dependent variable = VAS(worst pain))

Phase I- Analysis across time

VAS (worst pain) as a linear function of Time across baseline and all follow-up time points (i.e. modelling change over time as a straight line)

Tests of Fixed Effects

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	266.319	998.870	.000
TIME	1	167.325	23.718	.000

Estimates of Fixed Effects

Parameter	Estimate	Std. Error	df	t	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Intercept	56.503849	1.787819	266.319	31.605	.000	52.983790	60.023907
TIME	-.397717	.081666	167.325	-4.870	.000	-.558945	-.236489

Estimates of Covariance Parameters

Parameter	Estimate	Std. Error	Wald Z	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
Residual	569.553610	49.499889	11.506	.000	480.348795	675.324512
TIME [subject = ID]	.255197	.066067	3.863	.000	.153642	.423878

Information Criteria

-2 Log Likelihood	3360.262
Akaike's Information Criterion (AIC)	3368.262
Hurvich and Tsai's Criterion (AICC)	3368.376
Bozdogan's Criterion (CAIC)	3387.773
Schwarz's Bayesian Criterion (BIC)	3383.773

The information criteria are displayed in smaller-is-better forms.

Time as a quadratic function of time (a curve)

Tests of Fixed Effects

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	265.536	899.276	.000
TIME	1	308.569	28.340	.000
TIME * TIME	1	274.460	15.466	.000

Estimates of Fixed Effects

Parameter	Estimate	Std. Error	df	t	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Intercept	60.531394	2.018526	265.536	29.988	.000	56.557042	64.505746
TIME	-1.319023	.247771	308.569	-5.324	.000	-1.806557	-.831488
TIME * TIME	.017743	.004512	274.460	3.933	.000	.008861	.026624

Estimates of Covariance Parameters

Parameter	Estimate	Std. Error	Wald Z	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
Residual	539.373792	46.859377	11.510	.000	454.924878	639.499181
TIME [subject = ID]	.261716	.065383	4.003	.000	.160391	.427051

Information Criteria[a]

-2 Log Likelihood	3345.198
Akaike's Information Criterion (AIC)	3355.198
Hurvich and Tsai's Criterion (AICC)	3355.368
Bozdogan's Criterion (CAIC)	3379.586
Schwarz's Bayesian Criterion (BIC)	3374.586

Time as a cubic function of time (a curve)

Tests of Fixed Effects

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	264.764	771.246	.000
TIME	1	268.859	19.076	.000
TIME * TIME	1	265.856	10.551	.001
TIME * TIME * TIME	1	266.407	8.165	.005

Estimates of Fixed Effects

Parameter	Estimate	Std. Error	df	t	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Intercept	63.828283	2.298352	264.764	27.771	.000	59.302909	68.353657
TIME	-3.498383	.800974	268.859	-4.368	.000	-5.075363	-1.921404
TIME * TIME	.142090	.043745	265.856	3.248	.001	.055960	.228221
TIME * TIME * TIME	-.001612	.000564	266.407	-2.858	.005	-.002723	-.000501

Estimates of Covariance Parameters

Parameter	Estimate	Std. Error	Wald Z	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
Residual	522.959942	45.452063	11.506	.000	441.050044	620.081791
TIME [subject = ID]	.267611	.065495	4.086	.000	.165646	.432342

Information Criteria

-2 Log Likelihood	3337.160
Akaike's Information Criterion (AIC)	3349.160
Hurvich and Tsai's Criterion (AICC)	3349.400
Bozdogan's Criterion (CAIC)	3378.427
Schwarz's Bayesian Criterion (BIC)	3372.427

Phase II- Adding covariates

SF36(MCS) as covariate

Type III Tests of Fixed Effects

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	355.365	235.601	.000
TIME	1	268.794	20.057	.000
TIME * TIME	1	266.037	11.331	.001
TIME * TIME * TIME	1	266.588	8.872	.003
SF36t1	1	356.524	17.692	.000

Estimates of Fixed Effects

Parameter	Estimate	Std. Error	df	t	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Intercept	85.120502	5.545568	355.365	15.349	.000	74.214244	96.026759
TIME	-3.533629	.789018	268.794	-4.479	.000	-5.087071	-1.980187
TIME * TIME	.145096	.043104	266.037	3.366	.001	.060228	.229963
TIME * TIME * TIME	-.001656	.000556	266.588	-2.979	.003	-.002751	-.000561
SF36t1	-.343011	.081550	356.524	-4.206	.000	-.503390	-.182632

Estimates of Covariance Parameters

Parameter	Estimate	Std. Error	Wald Z	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
Residual	507.672864	44.107549	11.510	.000	428.183572	601.918789
TIME [subject = ID]	.231125	.059350	3.894	.000	.139723	.382318

Information Criteria[a]

-2 Log Likelihood	3242.891
Akaike's Information Criterion (AIC)	3262.891
Hurvich and Tsai's Criterion (AICC)	3263.534
Bozdogan's Criterion (CAIC)	3311.555
Schwarz's Bayesian Criterion (BIC)	3301.555

Chronicity as covariate

Type III Tests of Fixed Effects

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	352.814	115.480	.000
TIME	1	265.577	19.671	.000
TIME * TIME	1	262.896	11.231	.001
TIME * TIME * TIME	1	263.453	8.836	.003
SF36t1	1	352.012	16.401	.000
Chronicity	1	351.307	.067	.796

Estimates of Fixed Effects

Parameter	Estimate	Std. Error	df	t	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Intercept	84.000392	7.816797	352.814	10.746	.000	68.627014	99.373770
TIME	-3.538241	.797773	265.577	-4.435	.000	-5.109006	-1.967476
TIME * TIME	.146076	.043588	262.896	3.351	.001	.060249	.231902
TIME * TIME * TIME	-.001671	.000562	263.453	-2.972	.003	-.002778	-.000564
SF36t1	-.342776	.084641	352.012	-4.050	.000	-.509241	-.176311
Chronicity	.368080	1.421178	351.307	.259	.796	-2.427008	3.163167

Estimates of Covariance Parameters

Parameter		Estimate	Std. Error	Wald Z	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Residual		513.289538	44.862595	11.441	.000	432.479565	609.199073
TIME [subject = ID]	Variance	.229579	.059820	3.838	.000	.137765	.382583

Information Criteria[a]

-2 Log Likelihood	3285.791
Akaike's Information Criterion (AIC)	3301.791
Hurvich and Tsai's Criterion (AICC)	3302.210
Bozdogan's Criterion (CAIC)	3340.723
Schwarz's Bayesian Criterion (BIC)	3332.723

Gender as a covariate

Type III Tests of Fixed Effects

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	356.462	200.085	.000
TIME	1	268.404	20.121	.000
TIME * TIME	1	265.678	11.388	.001
TIME * TIME * TIME	1	266.232	8.924	.003
SF36 (baseline)	1	356.268	16.886	.000
Gender	1	355.011	.644	.423

Estimates of Fixed Effects

Parameter	Estimate	Std. Error	df	t	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Intercept	83.518633	5.904411	356.462	14.145	.000	71.906775	95.130491
TIME	-3.541355	.789489	268.404	-4.486	.000	-5.095735	-1.986975
TIME * TIME	.145553	.043131	265.678	3.375	.001	.060630	.230476
TIME * TIME * TIME	-.001662	.000556	266.232	-2.987	.003	-.002757	-.000567
SF36(baseline)	-.336643	.081922	356.268	-4.109	.000	-.497754	-.175532
Gender	2.297121	2.863332	355.011	.802	.423	-3.334105	7.928346

Estimates of Covariance Parameters

Parameter	Estimate	Std. Error	Wald Z	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
Residual	508.245183	44.188185	11.502	.000	428.615183	602.669192
TIME [subject = ID]	.226980	.058926	3.852	.000	.136461	.377543

Information Criteria

-2 Log Likelihood	3319.426
Akaike's Information Criterion (AIC)	3335.426
Hurvich and Tsai's Criterion (AICC)	3335.840
Bozdogan's Criterion (CAIC)	3374.448
Schwarz's Bayesian Criterion (BIC)	3366.448

Estimates of Covariance Parameters

Parameter	Estimate	Std. Error	Wald Z	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
Residual	508.245183	44.188185	11.502	.000	428.615183	602.669192
TIME [subject = ID]	.226980	.058926	3.852	.000	.136461	.377543

Age as covariate

Type III Tests of Fixed Effects

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	356.891	132.694	.000
TIME	1	268.880	19.188	.000
TIME * TIME	1	266.202	10.709	.001
TIME * TIME * TIME	1	266.747	8.350	.004
SF36(baseline)	1	356.250	18.406	.000
Age(years)	1	354.121	3.886	.049

Estimates of Fixed Effects

Parameter	Estimate	Std. Error	df	t	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Intercept	97.931094	8.501488	356.891	11.519	.000	81.211786	114.650403
TIME	-3.451461	.787928	268.880	-4.380	.000	-5.002755	-1.900167
TIME * TIME	.140848	.043040	266.202	3.272	.001	.056105	.225590
TIME * TIME * TIME	-.001604	.000555	266.747	-2.890	.004	-.002697	-.000511
SF36(baseline)	-.348025	.081122	356.250	-4.290	.000	-.507563	-.188488
Age(years)	-.264635	.134252	354.121	-1.971	.049	-.528667	-.000603

Estimates of Covariance Parameters

Parameter	Estimate	Std. Error	Wald Z	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
Residual	504.929349	43.880764	11.507	.000	425.850488	598.692862
TIME [subject = ID]	.221860	.057925	3.830	.000	.132997	.370098

Information Criteria

-2 Log Likelihood	**3316.215**
Akaike's Information Criterion (AIC)	**3332.215**
Hurvich and Tsai's Criterion (AICC)	3332.629
Bozdogan's Criterion (CAIC)	3371.237
Schwarz's Bayesian Criterion (BIC)	3363.237

Phase III- Adding intervention

Type III Tests of Fixed Effects

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	101.996	74.231	.000
TIME	1	202.255	26.637	.000
TIME * TIME	1	200.545	14.602	.000
TIME * TIME * TIME	1	200.746	11.270	.001
SF36(baseline)	1	97.623	9.995	.002
Age(years)	1	98.536	2.130	.148
Intervention	1	96.686	.060	.808

Estimates of Fixed Effects

Parameter	Estimate	Std. Error	df	t	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Intercept	97.836011	11.427608	102.307	8.561	.000	75.170221	120.501800
TIME	-3.434363	.665426	202.255	-5.161	.000	-4.746425	-2.122302
TIME * TIME	.139078	.036396	200.545	3.821	.000	.067310	.210847
TIME * TIME * TIME	-.001576	.000469	200.746	-3.357	.001	-.002502	-.000650
SF36(baseline)	-.353473	.111809	97.623	-3.161	.002	-.575364	-.131582
Age(years)	-.265687	.182055	98.536	-1.459	.148	-.626944	.095571
[Intervention=Comparator]	.956164	3.914184	96.686	.244	.808	-6.812728	8.725055
[Intervention=Mobilisation]	0[a]	0	.	.	.	.	.

Type III Tests of Fixed Effects

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	101.996	74.231	.000
TIME	1	202.255	26.637	.000
TIME * TIME	1	200.545	14.602	.000
TIME * TIME * TIME	1	200.746	11.270	.001
SF36(baseline)	1	97.623	9.995	.002
Age(years)	1	98.536	2.130	.148
Intervention	1	96.686	.060	.808

Estimates of Covariance Parameters

					95% Confidence Interval	
Parameter	Estimate	Std. Error	Wald Z	Sig.	Lower Bound	Upper Bound
Residual	353.068915	35.862645	9.845	.000	289.334007	430.843439
Intercept [subject = ID]	233.263658	54.143583	4.308	.000	148.003483	367.639553
TIME [subject = ID]	.118850	.045983	2.585	.010	.055676	.253706

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Information Criteria[a]

-2 Log Likelihood	3242.891
Akaike's Information Criterion (AIC)	3262.891
Hurvich and Tsai's Criterion (AICC)	3263.534
Bozdogan's Criterion (CAIC)	3311.555
Schwarz's Bayesian Criterion (BIC)	3301.555

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