An observational study of changes in cervical inter-vertebral motion and the relationship with patient-reported outcomes in patients undergoing spinal manipulative therapy for neck pain

Jonathan Branney BN(Hons), RN, MChiro, PgCert

A thesis submitted in partial fulfilment of the requirements of Bournemouth University for the degree of Doctor of Philosophy (PhD)

Collaborating Establishment:
Institute of Musculoskeletal Research & Clinical Implementation,
Anglo-European College of Chiropractic, Bournemouth

School of Health & Social Care
Bournemouth University

July 2014

This copy of the thesis has been supplied on condition that anyone who consults it is understood to recognise that its copyright rests with its author and due acknowledgement must always be made of the use of any material contained in, or derived from, this thesis.

Abstract

An observational study of changes in cervical inter-vertebral motion and the relationship with patient-reported outcomes in patients undergoing spinal manipulative therapy for neck pain, by Jonathan Branney

Spinal manipulation is a commonly sought therapy for neck pain. The present work examined sagittal plane cervical inter-vertebral kinematics in patients and healthy volunteers to explore whether motion is different in patients with neck pain, if manipulation is associated with changing cervical kinematics, and if changes are related to patient-reported outcomes.

A standardised quantitative fluoroscopy (QF) image acquisition protocol for the cervical spine was developed and tested. A model of a cervical segment with a rigidly fitted digital inclinometer was rotated in the sagittal plane whilst being fluoroscopically imaged and QF results were compared for accuracy to that of the inclinometer. QF imaging sequences from ten subjects were analysed twice, six weeks apart, to assess repeatability. Finally, 30 patients and 30 age/gender-matched healthy volunteers had two cervical spine QF assessments four weeks apart. Only patients received spinal manipulation and completed patient-reported outcome measures (PROMs). Kinematic variables of interest included IV-RoM, segmental hypo-mobility, paradoxical motion, instantaneous axis of rotation (IAR) location, and laxity/attainment rate.

The acquisition protocol allowed for imaging sequences to be achieved in a manner acceptable to participants. QF was found to be accurate to 0.5° for rotational range of motion. Intra- and inter-observer repeatability studies revealed substantial agreement and reliability for the QF measurement of C1 to C6 rotational motion (largest standard error of measurement (SEM) = 1.14°, lowest intra-class correlation coefficient (ICC) = 0.895) but not for IAR location (largest SEM = 7.66mm, lowest ICC = -0.080). Agreement and reliability were moderate-substantial for laxity/attainment rate (largest SEM = 0.04, lowest ICC = 0.70).

There were no significant differences at baseline between patients and healthy volunteers in IV-RoM, or in the number of hypo-mobile, paradoxical or lax motion segments. Spinal manipulation was weakly associated with IV-RoM increases above the minimum detectable change calculated from healthy volunteers, in a dose response manner (Rho = 0.39 (95% CI: 0.014 to 0.663) p = 0.04). While the majority (87%) of patients reported clinically significant reductions in pain and disability, changes in IV-RoM were not correlated with any of the PROMs measured.

Contents

List of Tables

List of Figures

List of Appendices

Acknowledgements

Gordon Waddell put it better than I could in his introduction to 'The Back Pain Revolution'; "*I claim this book as my own, and I did write it, but such as this could never be a solo effort*". There is no more apt a quote for me to emphasise that without the help and guidance of the following people, this thesis would not have happened.

First of all, I cannot overstate my gratitude to my first supervisor, Professor Alan Breen, for unlimited access to your time, expertise, wisdom and enthusiasm. Your support and approachability made an onerous task more bearable, and you have shown me the model of a professional researcher for me to aspire to.

Huge thanks to Professor Jenni Bolton for your generosity and advice especially your clarity of thought (which always helped me to think more clearly!) and organisational skills, which were especially invaluable in the final stages of the thesis.

Many thanks to Dr Sarah Hean for always challenging me to present my work more clearly for an audience less familiar with spine kinematics and the treatment of neck pain, and for helping me to identify all the thesis content that represented the original contributions to knowledge. And thank you for always travelling to AECC for our meetings!

Thank you to Dr Gert Bronfort, Northwestern Health Sciences University, for your invaluable expertise and comments in the early stages of this project – and thank you for your continuing world-class contributions to the spinal manipulation research base.

To all the staff at IMRCI, thanks for being such great people to work with. To Fi, Alex and Alister, thanks for the regular discussions and constructive criticism over the past 3 ½ years and for being generous with your time and knowledge. To Linda, thank you for always being able to get those research papers I couldn't get my hands on and for maintaining my ever-increasing demands for caffeine!

To the Maintenance Department at AECC particular thanks must go to Lee Murphy, Timon Kelly and Peter Giles for constructing the model for the accuracy study, great workmanship.

To all the AECC chiropractors and interns who participated in this study, thank you so much for being willing to help me and for providing your skilled hands in delivering the treatment to patients. Special mention for Dr Andrew Vitiello DC for your helpful comments on my MPhil transfer document – many thanks.

Thanks to all the AECC staff who showed an interest in the study and provided encouraging words, which were usually needed!

To Sean Branney, whose critical faculties know no bounds, for your ability to sniff out grammatical errors like a shark can smell a drop of blood in the ocean from two miles away, I owe you one, thank you. Thanks also to Victoria Wheeldon DC, who would not tolerate a split infinitive or a missing hyphen – I have obeyed. Any grammatical errors remaining are my fault alone!

To the European Chiropractors' Union, thank you for making available the financial assistance that made this project possible in the form of a Doctoral Research Fellowship. Thanks also are due to the TAM Club at AECC, for covering the costs of patients' treatment fees, and to the Graduate School, Bournemouth University, for their awards of funds to allow me to present my work at important conferences.

Finally, thank you to all the healthy volunteers and patients who gave up their time to participate in this study. If this thesis contributes in any way, however small, to improving the treatment of people with neck pain, it will have been worth it.

Jonny Branney

Author's Declaration

Content from this thesis has been published and presented at conferences as follows:

Branney J and Breen A (2014) Does inter-vertebral range of motion increase after spinal manipulation? A prospective cohort study. *Chiropractic and Manual Therapies* 22:24 (See page 286).

Conference proceedings

• "The objective measurement of continuous cervical inter-vertebral motion in living subjects" poster presentation - World Federation of Chiropractic Biennial Congress, Durban, South Africa, April 2013 [2nd prize Best Student Poster Award]
Abstract published in Journal of Chiropractic Medicine (2013) 12(2): 111-112

• "Measurement of cervical inter-vertebral motion with quantitative fluoroscopy: Observer and intra-subject repeatability" virtual poster presentation – NIHR Statistics Group – Imaging in Translational Research, Pembroke College, University of Oxford, October 2013

• "Does spinal manipulation change cervical inter-vertebral motion?" – BritSpine, University of Warwick, April 2014
Abstract published in European Spine Journal (2014) 23(Suppl 1): S128

• "Cervical spine manipulation is associated with increased inter-vertebral motion", European Chiropractors' Union Convention, Dublin, May 2014 [Best New Researcher prize]
Abstract to be published in Chiropractic & Manual Therapies

Abbreviations

AANTTA – American Academy of Neurology Therapeutics and Technology Assessment subcommittee

AECC – Anglo-European College of Chiropractic

CI – Confidence interval

CID – Clinically important difference

CROM – Cervical range of motion

EQ-5D-5L – EuroQuol-five dimensions-five levels questionnaire

GBD – Global Burden of Disease

HVLA- High-velocity low-amplitude [also referred to as thrust manipulation]

IAR - Instantaneous axis of rotation (2D)

ICC – Intra-class correlation coefficient

ICR – Instantaneous centre of rotation (3D)

IV-RoM – Inter-vertebral angular/rotational range of motion; also, inter-segmental motion

IQR – Inter-quartile range

LBP – Low back pain

LOA – Limits of agreement

MDC – Minimum detectable change

NDI – Neck Disability Index

NRS- - Numerical rating scale

OSMIA – Objective Spinal Motion Imaging Assessment – name for QF image analysis system at AECC

PGIC – Patient global impression of change

PROMs – Patient-reported outcome measures

QF - Quantitative fluoroscopy

RCT – Randomised clinical trial

RMS – Root mean square

ROM - Range of motion

RSA – Radiostereometric analysis (also called radiostereophotogrammetric analysis)

SEM – Standard error of measurement

SEP – Somatosensory-evoked potential [dermatomal]

SMT - Spinal manipulative therapy; also, spinal manipulation

VAS – Visual analogue scale

VBA – Vertebro-basilar arterial [stroke]

VBU - Vertebral body unit

Dedication

This thesis is dedicated to:

My parents and siblings

To Kathleen, Michael, Sean and Rachel

Thank you so much for your continuing and unerring support, encouragement, generosity and love throughout. Particular thanks to you, Mum, for your extended visits which made writing this thesis achievable and maintained our sanity.

My wife and children

To Deborah, Owen and Iris

I think this might be the hardest section of the thesis to write. It is impossible to adequately express my love for you all and my gratitude for your total support through what has been an extremely challenging process for our family. I am so lucky to have you all in my life, thank you.

Here, finally, is Daddy's book; hope you like the pictures.

PART I: Background

"Is it time to discard the term 'diagnosis' when examining a person with uncomplicated axial neck pain?" (Haldeman 2011)

"Spinal manipulation for neck pain does not work" (Bogduk 2003)

Chapter 1. Introduction

1.1 Statement of the problem

Many people get neck pain and the best way of managing this problem is unknown. Findings from the World Health Organisation's Global Burden of Disease (2005) study showed one-year incidence rates of neck pain ranging from 10.4% (Canada) to 21.3% (Finland) and one-year prevalence rates ranging from 17.1% (Finland) to as high as 73% (Sweden) (Hoy et al. 2010). In the UK one-year incidence and prevalence rates are reported as 17.9% (Croft et al. 2001) and 33.7% (Palmer et al. 2001) respectively. The more recent Global Burden of Disease (2010) study suggests that the prevalence of neck pain-related disability is higher than previously estimated and that the burden it places on society and healthcare can be expected to rise with an ageing world population (Murray et al. 2012). Rates do vary between individual studies and countries depending on the age range of study participants (most studies indicate an increasing risk of neck pain until the age-group 35-49 after which the risk decreases) and the survey methods used. However, taken as a whole the data indicate that, particularly in high-income countries, neck pain represents a global source of suffering (Hoy et al. 2010; Murray et al. 2012).

Despite the technological advances of the late 20th and early 21st centuries in medicine, neck pain remains something of an enigma regarding accurate diagnosis with no tests demonstrating clear validity (Nordin et al. 2008), and, without a diagnosis, prescription of the correct treatment amounts to a lottery. Thankfully in spite of this situation most sufferers recover with little intervention, at least to the point of being able to get on with their lives without too much disruption. The overwhelming majority of neck pain is considered to be of postural or mechanical origin rather than due to specific disease (Binder 2008). However, the typical course of neck pain is now seen to be an episodic one over a person's lifetime (Guzman et al. 2008b) rather than a discrete event that ultimately resolves, and for around 10% of sufferers a problem that becomes chronic (Binder 2008).

For those neck pain sufferers who seek care there are a number of healthcare options. Neck pain is mostly managed in primary care and the common port of call is the general practitioner (Wermeling et al. 2011) who may typically prescribe self-care advice, pain-relieving medication, or refer to a physiotherapist or, less often, a medical specialist (Borghouts et al. 1999a; Vos et al. 2007). Available privately for neck pain treatment are chiropractic, osteopathy and physiotherapy, amongst others.

At present the various treatments employed by healthcare professionals show generally only modest benefit (Carragee et al. 2008; Hurwitz et al. 2008) and this may be in part due to the lack of accurate diagnosis, coupled with a lack of understanding of the mechanism of action of commonly available treatments.

Spinal manipulation, commonly utilised by chiropractors, osteopaths and musculoskeletal physiotherapists in the treatment of neck pain, is thought to have as a mechanism of action the restoration of motion to restricted spinal joints with consequent reduction of pain (Cassidy et al. 1992; Martinez-Segura et al. 2006). However, this theory has never been adequately tested, largely due to the lack of reliable means of measuring spinal joint motion in the first place. Improving the understanding of the biomechanical effects of spinal manipulation and the relationship between these and patient outcomes has been highlighted as an important research aim (Cramer et al. 2006; Khalsa et al. 2006). A new technology, quantitative fluoroscopy, has recently become available which allows, for the first time, reliable measurement of motion between the vertebrae (Breen et al. 2006) and therefore can be used to explore this theory. Improving our understanding of the mechanism of this treatment might lead to better targeting of this therapy to those expected to benefit from it, and thereby contribute to the improved management of neck pain.

1.2 Purpose of the study

This study sought firstly to determine the accuracy, observer repeatability and intra-subject reproducibility of measuring cervical inter-vertebral motion with quantitative fluoroscopy as this technology has only been previously researched in the lumbar spine. The second purpose was to determine whether spinal manipulation was associated with changes in cervical inter-vertebral motion as measured by quantitative fluoroscopy in patients with neck pain, and whether any changes in motion were related to patient-reported outcomes.

1.3 Organisation of the thesis

This thesis is structured into three parts:

Part I includes a review of the related literature (Chapter 2), the aims and objectives (sections 2.9 and 2.10) of the study, and the questions that this research sought to answer (section 2.11).

Part II is concerned with the development of a quantitative fluoroscopy acquisition protocol for the measurement of cervical inter-vertebral motion (Chapter 3). Chapter 4 describes an accuracy study intended to validate QF measurement for the cervical spine and Chapter 5 presents observer repeatability studies of the analysis of the fluoroscopic imaging sequences. These studies were intended to determine which kinematic parameters might be reliably measured in living people to inform the clinical studies in Part III.

Part III begins with a cross-sectional study intended to identify differences in cervical inter-vertebral motion between patients and matched healthy volunteers (Chapter 6). Chapter 7 is an intra-subject reproducibility study that sought to determine the extent to which angular inter-vertebral motion changes over four weeks in healthy volunteers. Chapter 8 is a prospective cohort study of patients with neck pain receiving spinal manipulative therapy over four weeks. Informed by the results of the two preceeding chapters, this final chapter sought to observe changes in cervical angular inter-vertebral motion and their relationship with patient-reported outcomes.

The thesis is concluded by a summary of the key findings and recommendations for future work.

Chapter 2. Literature review

2.1 Methodology of the literature review

Biomedical literature databases were searched to identify the current knowledge base in the areas of neck pain epidemiology, diagnosis and management, cervical spine biomechanics, and spinal manipulative therapy for neck pain. From the extensive reference database held at IMRCI relevant papers were identified using the following key words: “Neck Pain”, “Cervical” AND “Biomechanics” OR “Kinematics”, “Reliability” OR “Reproducibility” OR “Repeatability”, “Validity” and “Spinal Manipulation” OR “Spinal Manipulative Therapy”. Several hundred articles were identified which were hand searched for relevance and reference lists were checked for important papers not contained in the database. Search engines were used to obtain additional citations using these same key words and by utilising the “related citations” option for articles related to seminal papers. The search engines employed were Pubmed, Index to Chiropractic Literature and CINAHL. Citations were obtained mainly through EBSCO, Ovid and ScienceDirect. Pubmed alerts were set up to provide a weekly update of articles published and linked with the following MeSH terms: “Neck Pain [Majr]”, “cervical vertebrae [Majr]”, “Validation studies [Publication type]” AND “Range of Motion, Articular”, “Reproducibility of Results” AND “Range of Motion, Articular”, “Biomechanics” AND “Neck” and “Manipulation, Spinal”.

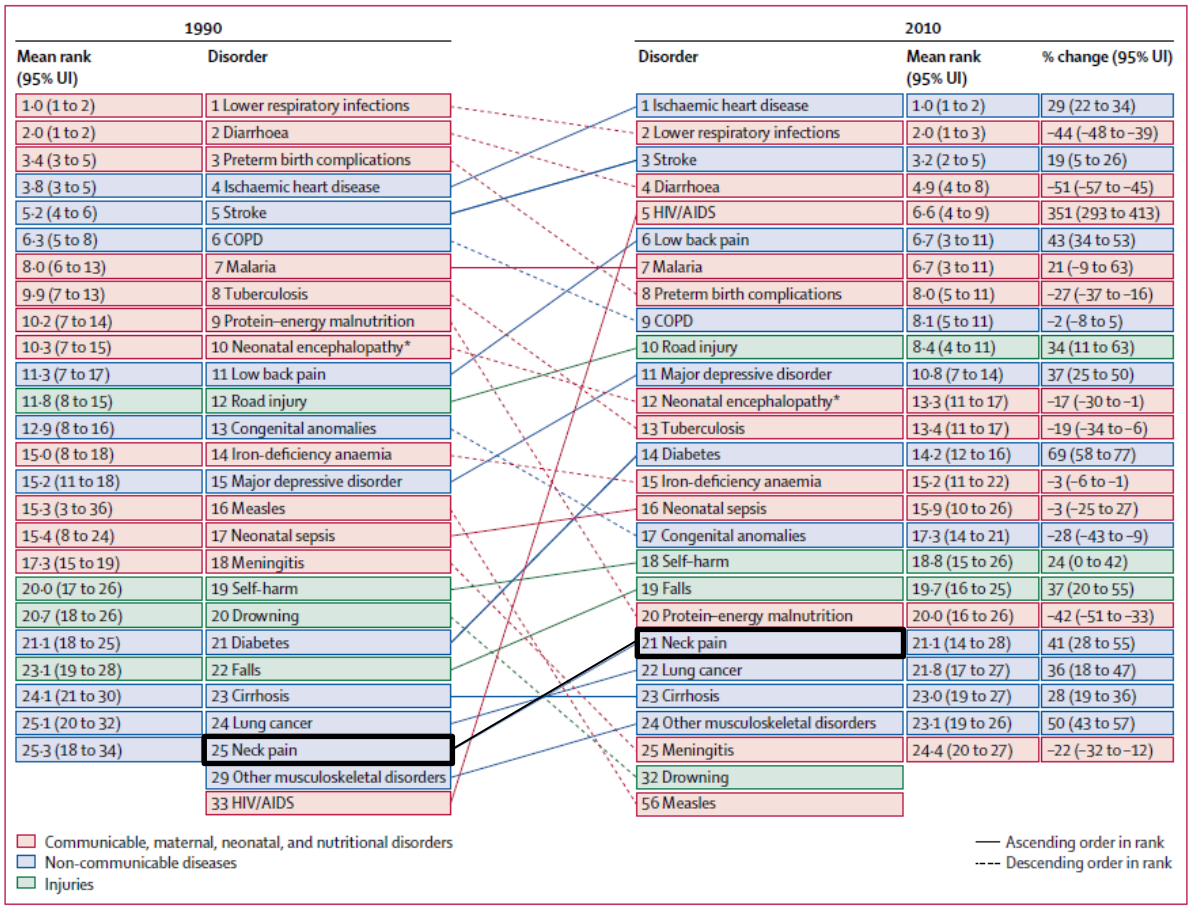
2.2 Neck pain - epidemiology

Neck pain is a common condition which most people experience at some point in their life, with self-reported incidence rates ranging from 15.5 to 213 per 1000 person years in the general population (Hogg-Johnson et al. 2008). The 12-month prevalence rates range around 30-50% with 1.7-11.5% of people experiencing activity-limiting pain annually (Hogg-Johnson et al. 2008). While most episodes of neck pain appear to be self-limiting, a systematic review and meta-analysis of inception cohort studies concluded that the prognosis of acute neck pain was poor (Hush et al. 2011). From the pooled analysis a rapid decrease in mean pain (-45%) and disability (-43%) over the first six and a half weeks of the neck pain episode was observed.

While this was expected to be clinically meaningful for some patients, the mean pain severity of 42% (95% CI, 39-45) at 12 months was considered to be sufficiently severe as to indicate continuing activity-limiting neck pain for others; the proportion affected was not calculated/reported (Hush et al. 2011).

Aside from the physical distress associated with this condition it can also be a source of significant human suffering both at the personal and societal levels through work absence (Cote et al. 2008b; HSE 2009) and healthcare costs (Borghouts et al. 1999b). In the UK in 2008/09 an estimated 9.3 million working days (full-day equivalent) were lost through musculoskeletal disorders reported as being caused by or made worse by work of which 3.8 million days were lost due to conditions mainly affecting the upper limb or neck (HSE 2009). More recent figures regarding time off work do not distinguish between different musculoskeletal disorders and suggest the number of days lost due to any musculoskeletal disorder may be declining (HSE 2012). While this might be an encouraging sign it is important to note that rates do fluctuate annually, and it could be that more people are working despite the pain, which presents the risk of reduced productivity (presenteeism) with subsequent negative impact on the national economy (Dagenais and Haldeman 2012).

With the global population aging and more national economies becoming industrialised, the burden of disease is shifting from being one of communicable to non-communicable diseases such as musculoskeletal disorders; it is a problem that has increased and is expected to grow in magnitude (Murray et al. 2012). Neck pain-related disability is a growing problem in many countries throughout the world. As indicated in Figure 1, neck pain has shifted from being the 25th leading cause of disability-adjusted life years worldwide in 1990 to being the 21st leading cause in 2010 as reported by the Global Burden of Disease (GBD 2010) survey (Murray et al. 2012). According to GBD 2010, in the United States neck pain ranks as the 11th leading cause of disability-adjusted life years and the 4th leading cause for years lived with disability (Murray and Lopez 2013).



95% UI,95% uncertainty index; [highlighting of neck pain made by this author]

Figure 1: Global disability-adjusted life year ranks with 95% UI for the top 25 causes in 1990 and 2010, and the percentage change with 95% UIs between 1990 and 2010 (Murray et al. 2012); Image reproduced with permission from Elsevier

2.3 The problem with diagnosing neck pain

Although neck pain can be defined in clinical terms, the underlying pathology and pathophysiology are largely unknown (Bogduk 2011). As is the case with chronic low back pain, research has not been able to demonstrate a consistent relationship between structural pathology and cervical-related pain (Friedenberg and Miller 1963; Heller et al. 1983; Gore et al. 1986; Boden et al. 1990; Pettersson et al. 1994; Marchiori and Henderson 1996). Typically, patients present with pain, muscle tension or stiffness in the posterior neck area, and may or may not have associated arm pain. Once serious or life-threatening (rare) causes of neck pain such as inflammatory arthritis, infection, tumour, fracture or vascular causes have been ruled out patients are then given a generic diagnosis of “non-specific neck pain” or its synonymous counterpart “mechanical neck pain” (Bogduk 1984; Guzman et al. 2008b).

This situation has led one author to consider, “Is it time to discard the term “diagnosis” when examining a person with uncomplicated axial neck pain?”, although he did not explicitly define when neck pain might be considered ‘uncomplicated’ (Haldeman 2011). Neck pain is a symptom, not a diagnosis, and the lack of an accurate diagnosis precludes being able to direct patients to one treatment or another, or identifying when new treatment approaches need to be developed.

There are many parallels between the problem of diagnosing and treating neck pain and low back pain (LBP). For many years LBP was seen through the lens of the disease model and therefore viewed as a specific, defined pathology (an injury), treatment of which was then expected to effect a cure (Waddell 2004). This medicalised approach failed to stem, and might even have contributed to, soaring levels of LBP disability in the latter half of the 20th century through ineffective treatment and management (Waddell 2004). The back pain problem prompted the re-focussing of research efforts which resulted in the disease model view of back pain being supplanted with that of the biopsychosocial model. Unlike the disease model, this more encompassing approach takes account of the multi-factorial nature of pain and acknowledges not just the physical nature of back [or neck] pain (bio-logical), but also how this pain is interpreted and acted upon (psycho-logical), as well as mediating factors within an individual’s social context, such as the behaviour of friends and family towards the person’s problem (social) (Waddell 2004).

The escalating LBP disability problem (Number 6 cause of global disability-adjusted life years in 2010, Figure 1) is a powerful explanation for the greater research interest there has been over that of neck pain (a search on Pubmed revealed that citations for “low back pain” [MeSH] (13,780) more than treble that of “neck pain” [MeSH] (4,315) [search date 18/05/14]). The relative lack of knowledge regarding neck pain prompted the launch, by the World Health Organisation, of an international ‘Task Force on Neck Pain and Its Associated Disorders’ (Neck Pain Task Force) whose remit it was to add to and gather together the existing scientific evidence regarding neck pain (Lidgren 2008). This resulted in the identification of strong evidence for a number of psychosocial factors that are important in someone recovering (positive prognostic factors) or continuing to suffer (negative prognostic factors) from neck pain (Carroll et al. 2008b). The American Physical Therapy Association recommends that the management of neck pain ought to take account of psychosocial factors (Childs et al. 2008), as is established in national and international clinical guidelines for back pain (Koes et al. 2010). However, references to the physical aspects of neck pain by the Neck Pain Task Force, the ‘bio’, are conspicuous by their absence.

This is perhaps indicative of the fact that research efforts to discover a clear mechanism(s) for neck pain (or back pain for that matter) to help inform diagnosis and, therefore, treatment, have not been fruitful (Bogduk 2011). Thus the emphasis in neck pain (Sterling 2009) and back pain research (Waddell 2004) has tended more towards the psychosocial side of the biopsychosocial model. While psychosocial factors such as fear avoidance (Carroll et al. 2008b) and work dissatisfaction (Carroll et al. 2008a) are important considerations in the management of neck pain they explain peoples' responses to pain rather than the pain itself (Adams et al. 2013). As Waddell (2004) asserted, the biopsychosocial model is not a causal model but one that "seeks to crystallise thinking regarding management" (Waddell 2004). While the model might be useful in reminding clinicians to consider various aspects impacting on a patient's condition, it does not get one any closer to a diagnosis which is required to direct treatment, and perhaps this is one reason why the model has yet to be widely and consistently adopted by clinicians (Pincus et al. 2013).

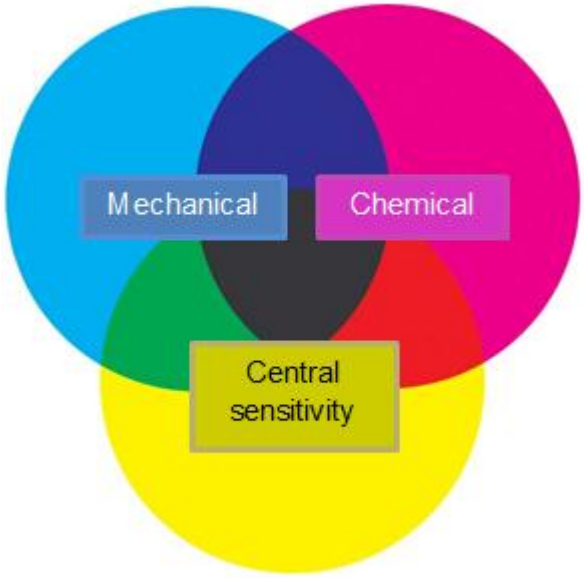


Figure 2: A proposed model for the biological component of non-specific spinal pain (Breen 2013); Image reproduced with permission

Complicating the clinical picture, it is possible that the biological component of the biopsychosocial model is itself multifactorial within any given patient. Rather than patients exclusively exhibiting features of mechanical pain, there may be, in varying degrees of importance, chemical or central sensitisation components also present, as suggested by the model in Figure 2.

While the detection of vertebral endplate oedema with MRI is evolving the understanding of the relationship between chemical changes in the spine and 'non-specific' spinal pain (Jensen et al. 2008; Mann et al. 2014), and reference values have been established for pain-pressure and thermal thresholds to aid diagnosis of central sensitisation (Neziri et al. 2011), none of the three components have biomarkers sufficient for accurate diagnosis at this time (MacDermid et al. 2009a).

Considering only the 'mechanical', there are numerous tissues in the neck that are innervated and therefore potential pain sources; all of the muscles, ligaments, synovial joints, inter-vertebral discs, cervical dura mater and the vertebral artery. Experimental evidence further implicates the synovial joints and inter-vertebral discs as pain sources while the role of the other tissues as pain generators remains unclear (Bogduk 2011). The pattern of pain produced by an anatomical structure is generally dictated by the nerve supply, not the location of the structure. Thus, discogenic pain cannot be distinguished from facet joint pain with clinical certainty due to the shared cervical segmental innervations (Bogduk 2011). Further, the lack of reliable and objective tests currently means that potential pain sources cannot be confirmed as sources (Nordin et al. 2008). Even if it were possible to identify the pain-producing tissue, consideration needs to be given as to why it is producing pain. In the absence of disease or trauma, postural and/or movement impairments are the main causes implicated, whereby anatomical structures are thought to become overloaded or stressed (Sahrmann 2002) and with neck pain movement impairment might include dysfunctional breathing through impaired mobility of the thorax (Wirth et al. 2014). However, it is not clear whether the movement impairment or the pain comes first.

While exercise in general appears to be an effective strategy for mechanical neck pain (Kay et al. 2012), the effectiveness of the assessment and treatment of movement impairments is yet to be properly evaluated. The management of neck pain is unlikely to be optimised until understanding of the biological component is improved, in relation, and in addition to, psychosocial factors (Hancock et al. 2011).

2.4 Subgrouping

Since patients with neck pain are grouped based on a common symptom it is likely that patients with neck pain are not a homogeneous group but rather consist of a variety of, as yet unidentified, subgroups, each of which may benefit from a different approach to management (Childs et al. 2004b). Approaches to subgrouping include classification models and clinical prediction rules. [A prerequiste to both forms of subgrouping is that the procedures used to evaluate patients i.e. in the physical assessment, are sufficiently reproducible to give clinically meaningful information. The manual examination of the cervical spine is discussed in section 2.7.1].

2.4.1 Mechanistic classification

"Mechanistic classification" is the more typical approach to subgrouping where the identification of joint impairments or spinal motion dysfunction during examination is used to inform what therapy should be used and where it should be directed (Huijbregts 2007). The majority of classification systems are concerned with LBP (Karayannis et al. 2012) and the main criticisms of these is they are largely influenced by tradition or unsystematic observations, or are evidence-informed hypotheses (Hebert and Fritz 2012). None have been sufficiently tested to evaluate their utility in clinical practice (Slater et al. 2012). Two classification systems for neck pain have been proposed in the literature (Figure 3 and Figure 4).

Classification	Examination Findings	Proposed Matched Interventions
Mobility	• Recent onset of symptoms • No radicular/referred symptoms in the upper quarter • Restricted range of motion with side-to-side rotation and/or discrepancy in lateral flexion range of motion • No signs of nerve root compression or peripheralization of symptoms in the upper quarter with cervical range of motion	• Cervical and thoracic spine mobilization/manipulation • Active range of motion exercises
Centralization	• Radicular/referred symptoms in the upper quarter • Peripheralization and/or centralization of symptoms with range of motion • Signs of nerve root compression present • May have pathoanatomic diagnosis of cervical radiculopathy	• Mechanical/manual cervical traction • Repeated movements to centralize symptoms
Conditioning and increase exercise tolerance	• Lower pain and disability scores • Longer duration of symptoms • No signs of nerve root compression • No peripheralization/centralization during range of motion	• Strengthening and endurance exercises for the muscles of the neck and upper quarter • Aerobic conditioning exercises
Pain control	• High pain and disability scores • Very recent onset of symptoms • Symptoms precipitated by trauma • Referred or radiating symptoms extending into the upper quarter • Poor tolerance for examination or most interventions	• Gentle active range of motion within pain tolerance • Range of motion exercises for adjacent regions • Physical modalities as needed • Activity modification to control pain
Reduce headache	• Unilateral headache with onset preceded by neck pain • Headache pain triggered by neck movement or positions • Headache pain elicited by pressure on posterior neck	• Cervical spine manipulation/mobilization • Strengthening of neck and upper quarter muscles • Postural education

Reproduced with permission from Childs et al (2004b) Proposal of a Classification System for Patients with Neck Pain Journal of Orthopaedic & Sports Physical Therapy 34(11), 686-700 doi: 10.2519/jospt.2004.34.11.686. Copyright ©Journal of Orthopaedic & Sports Physical Therapy®.

Figure 3: Proposed classification system for patients with neck pain: Overview of classification categories with key examination findings and proposed matched interventions (Childs et al. 2004b)

While the model proposed by Childs et al (2004b) focuses on making treatment decisions based on physical signs and symptoms (Figure 3), the clinical decision rule or guide proposed by Murphy and Hurwitz (2007) is more in keeping with the biopsychosocial model and incorporates assessment of oculomotor dysfunction, central sensitisation, and the identification of psychological prognostic variables in addition to physical spinal examination findings (Figure 4). Deficits in oculomotor control have been associated with neck pain, particularly whiplash-associated disorders, but it remains uncertain whether attempting to correct this may contribute to symptomatic improvements in neck pain (Treleaven and Takasaki 2014).

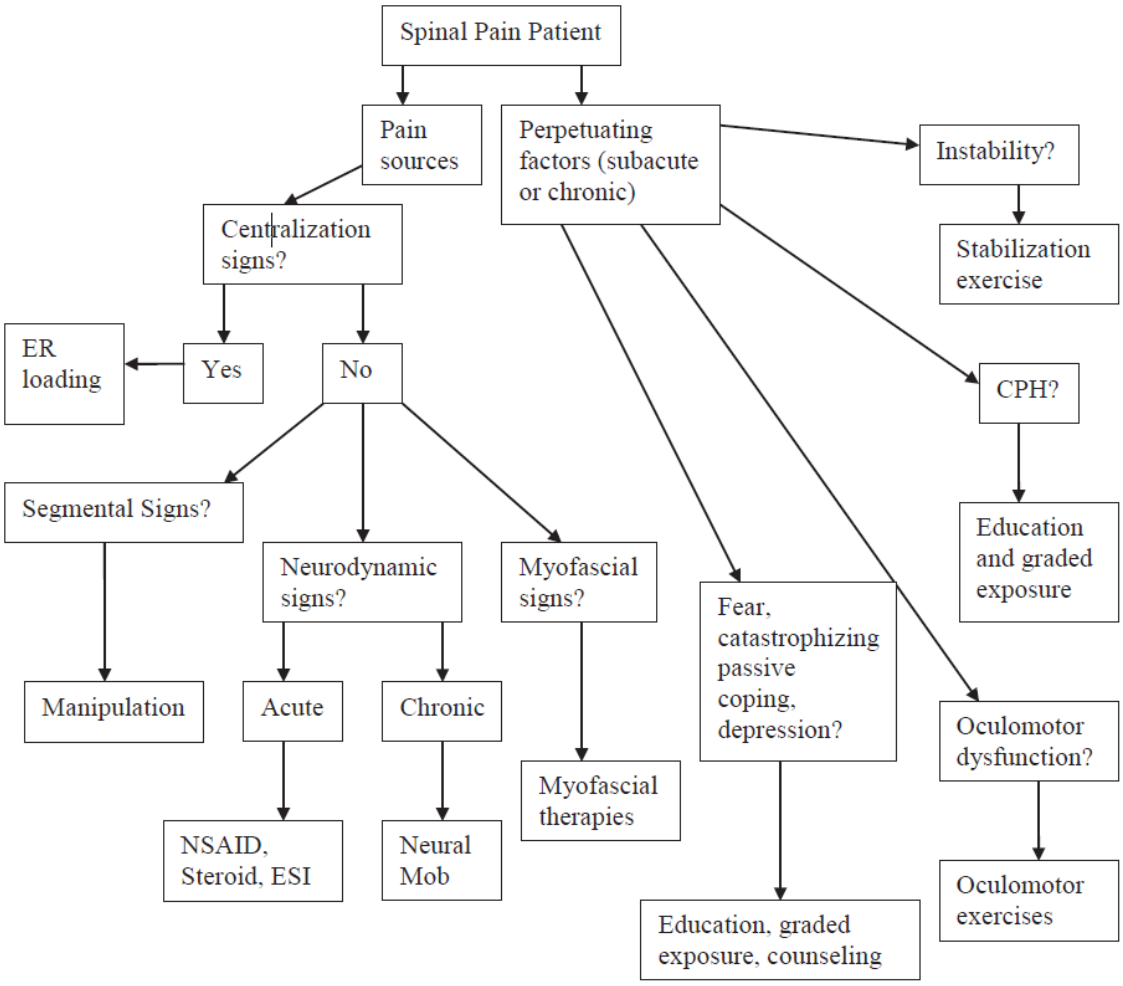


Figure 4: Management algorithm for the application of the Diagnosis-based Clinical Decision Rule[1] for the management of patients with spinal pain (Murphy and Hurwitz 2007)

While the two proposed classification systems are perhaps useful as guides for clinicians the model proposed by Murphy and Hurwitz (2007) has only been evaluated in a prospective cohort study (Murphy and Hurwitz 2011) and that proposed by Childs et al (2004b) has not been evaluated at all. Additionally, as alluded to previously in Figure 2, it is unlikely to be common for patients to exhibit features of only one of the above proposed diagnostic categories and until their utility is assessed in randomised clinical trials (RCTs), the ability of mechanistic classification to improve patients' outcomes will remain unknown.

[1] The use of the term 'Diagnosis–based Clinical Decision Rule' has been criticised for not adhering to the conventional use of the term 'clinical decision rule', which is an alternative term for clinical prediction rule (Hebert and Fritz 2012). There is an accepted process of derivation and validation for clinical prediction rules whereas the 'rule' presented by Murphy and Hurwitz (2007) was an evidence-based hypothesis. Perhaps by way of clarification, in a follow-up study the authors substituted the word 'rule' with 'guide' (Murphy and Hurwitz 2011).

2.4.2 Clinical prediction rules

The lack of any consistently identifiable mechanism(s) for neck [or back] pain to help inform treatment choices has prompted some investigators to develop clinical prediction rules (Huijbregts 2007). Clinical prediction rules are intended to aid clinical decision-making by identifying potential predictors of diagnostic test outcome, prognosis or therapeutic response (Hebert and Fritz 2012). In the rehabilitation literature clinical prediction rules are most commonly used to predict a patient's response to treatment whereby a cluster of signs and symptoms from the patient history and examination is used to sub-group patients based on the anticipated outcome from one treatment versus another (Hebert and Fritz 2012).

Most research in this area has involved the identification of predictors for response to spinal manipulation for LBP (May and Rosedale 2009). While some initial results appeared to be promising (Childs et al. 2004a; Cleland et al. 2009) a systematic review of clinical prediction rules in LBP research concluded that none of the rules, for any of the back pain treatments researched, had been sufficiently validated for implementation into routine practice (May and Rosedale 2009). A more recent systematic review came to the same conclusion (Haskins et al. 2012).

Similar prediction rules regarding manual therapy have also been proposed for sub-grouping neck pain patients. In a study seeking to identify predictors for an immediate favourable response to cervical manipulation, high-velocity low-amplitude (HVLA) manipulation was delivered to 100 patients with neck pain (Tseng et al. 2006). Six predictors were identified to significantly predict who the immediate responders were.[2] There were, however, problems with this study that limit its conclusions. First of all, the sample was heterogeneous. Patients included had diagnoses of cervicogenic headache, myofascial pain syndromes, herniated cervical disc or spondylosis ±radiculopathy, and some had traumatic-onset neck pain. Furthermore, "responders" were defined by improvement in one of three outcomes: PGIC of ≥4 ("much improved") on 15-point Likert scale (-7 to + 7) or, ≥50% pain reduction or, simply, "very satisfied" (Tseng et al. 2006). Patients could well have been "very satisfied" that a therapist had given time and attention to their neck problem, irrespective of any clinically meaningful improvement (Evans et al. 2014).

[2] The six predictors were: neck disability score < 11.5, "bilateral involvement pattern", not performing sedentary work > 5 hours/day, feeling better while moving the neck, neck extension not aggravating, the diagnosis of spondylosis without radiculopathy (Tseng et al. 2006).

The non-responders exhibited a greater prevalence of factors which are negatively prognostic for recovery from neck pain, irrespective of any intervention. Non-responders were much more likely to work >5hrs/day in a sedentary occupation which is a known occupational risk factor for neck pain (Cote et al. 2008a) that can hamper recovery (Carroll et al. 2008a) and, although not statistically significant, the proportion of females was higher in the non-responder group.

Furthermore, non-responders were more likely to have radiculopathy, which is a condition patho-physiologically and prognostically distinct from mechanical neck pain (Bogduk 2011) and the efficacy of manipulation for this is unknown (Guzman et al. 2008a).[3] The two groups might well have been similarly assimilated from case histories alone. Notably, no differences were found in regional cervical range of motion (ROM) nor in the proportions of palpated hypo-mobile segments prior to manipulation between responders and non-responders (Tseng et al. 2006), further suggesting factors other than spinal mobility were of prognostic importance.

Manipulation delivered to the thoracic spine has evidence of efficacy in the treatment of neck pain (Cross et al. 2011). In a prospective cohort of 78 patients with neck pain referred for physical therapy, Cleland et al (2007) developed a clinical prediction rule to help determine which neck pain patients might benefit from thoracic manipulation (Figure 5).

Predictors of a successful outcome from thoracic manipulation*
Symptoms < 30 days
No symptoms distal to shoulder
Looking up does not aggravate symptoms
FABQPA score < 12
Diminished upper thoracic spine kyphosis
Cervical extension ROM < 30°

*If ≥ 3 of these attributes were present the probability of experiencing a successful outcome increased from 54% to 86%; *FABQPA*, Fear-Avoidance Beliefs Questionnaire physical activity scale

Figure 5: Proposed clinical prediction rule to identify patients with neck pain likely to benefit from thoracic thrust manipulation (Cleland et al. 2007)

[3] In an earlier proposal for a classification system for patients with neck pain (Figure 3), it was proposed that patients with radicular pain specifically do not receive manipulation but rather, cervical traction and/or repeated movements to centralise pain (Childs et al. 2004b).

Unfortunately, the validity (please see Glossary for definition, page 284) of this rule was not supported when put to the test in RCTs. In the first RCT, 140 patients with neck pain were randomised to receive exercise only or exercise plus thoracic manipulation (Cleland et al. 2010). Regardless of the patients' baseline status according to the clinical prediction rule, those who received thoracic manipulation in addition to exercise had superior outcomes (Cleland et al. 2010). In a different RCT, patients with acute neck pain who met four out of six of the above-named criteria (Figure 5) were randomly assigned to receive either thoracic or cervical manipulation in addition to exercise (Puentedura et al. 2011). While confidence in the results of the study are limited by the small convenience sample (n=24), patients who received *cervical* manipulation reported greater improvements in pain and disability (Puentedura et al. 2011).

More recently a clinical prediction rule has been developed to predict success from cervical manipulative treatment for neck pain (Puentedura et al. 2012a). The predictors are shown in Figure 6.

Predictors of a successful outcome from cervical manipulation*
Symptoms < 38 days
Positive expectations that manipulation will help
Side-to-side deficit of ≥10° neck rotation
Pain with posterior to anterior springing of the middle cervical spine

*If ≥ 3 of these attributes were present the probability of experiencing a successful outcome increased from 30% to 90%

Figure 6: Proposed clinical prediction rule to identify patients with neck pain likely to benefit from cervical thrust manipulation (Puentedura et al. 2012a)

Despite some encouraging findings in the study by Puentedura et al (2012a) only 32/82 of the patients (39%) reported a favourable outcome defined as + 5 ("quite a bit better") or higher on a 15-point Likert scale (-7 to + 7), a higher threshold for success than that set by Tseng et al. (2006) (see page 14). Patients received only three treatment visits which, as acknowledged by the authors, meant the threshold for success was set rather high (Puentedura et al. 2012a). This is a small treatment frequency compared to usual clinical practice or that in found in clinical trials of manipulation (Childs et al. 2008).

Aside the lack of validation, a substantial problem with the two rules proposed above is the presence of prognostic factors that predict improvement independent of the treatment delivered.

A shorter duration of symptoms and the absence of symptoms in other body areas are predictors of improvement independent of manipulation or anything else (Carroll et al. 2008b). For now, this approach to sub-grouping is not the answer.

2.4.3 Which treatment, and for whom?

Reflecting the inability to accurately diagnose neck pain is the variety of treatments that have emerged over the years and it is perhaps not surprising that no one intervention for neck pain has so far shown strong effectiveness and clear superiority over the others (van der Velde et al. 2008). It has been pointed out that designing trials of treatments around patients sharing a symptom, not a diagnosis, might all but preclude finding real effects of any specific intervention (Childs et al. 2004a). Spinal manipulation, mobilisation, exercise, analgesics, acupuncture and low level laser have all been shown to provide at least some degree of short-term relief of neck pain in the absence of trauma (Guzman et al. 2008a). Spinal manipulation or mobilisation, particularly combined with exercise, appears to exhibit marginal benefit over other interventions (Hurwitz et al. 2008; Miller et al. 2010). Both manipulation and mobilisation are generally predicated on the idea that cervical spine motion is altered (dysfunctional) in patients with neck pain and that the motion can be changed with therapy.

2.5 Neck pain and cervical spine motion

2.5.1 Regional motion dysfunction

Several studies have found cervical spine (neck) regional motion to be different (typically decreased) in patients with neck pain, particularly whiplash, compared to persons without neck pain (Revel et al. 1991; Feipel et al. 1999; Dall'Alba et al. 2001; Antonaci et al. 2002; Grip et al. 2003; Ohberg et al. 2003; Vogt et al. 2007; Sjolander et al. 2008). Although decreased range of motion has been associated with spinal pain (Hagen et al. 1997), it is unknown whether it is a cause or an effect. The aetiology of abnormal motion of the spine is poorly understood. However, several explanations have been offered, such as decreased compressibility or elasticity of the inter-vertebral disc (Nachemson et al. 1979), disc herniations (Begg and Falconer 1949; Schalimtzek 1954), altered elasticity of ligaments and joint capsules (Froning and Frohman 1968) and muscle dysfunction (Stokes et al. 1981; Woodhouse and Vasseljen 2008).

It is possible that all of the above phenomena play a part in abnormal biomechanics to different degrees and in varying combinations.

2.5.2 Inter-vertebral motion dysfunction

Less is known regarding motion dysfunction at the inter-vertebral level. The normal movement of a motion segment (two vertebrae and their associated soft tissues) is a combination of rotation and translation described with reference to the three planes of human anatomy (Bogduk and Mercer 2000). Static radiographs taken at the end-range of flexion and extension (Figure 7) are established clinical practice to help identify abnormalities in inter-vertebral motion in patients with suspected cervical spine disorders (e.g. instability) (Yochum and Rowe 2004). Reference ranges of normal cervical inter-vertebral motion, which are needed for comparison with patients' inter-vertebral motion to determine if any motion can be classed as abnormal, have been published based on findings from a number of studies using this method in asymptomatic subjects (Aho et al. 1955; Bhalla and Simons 1969; Dvorak et al. 1988; Lind et al. 1989; Frobin et al. 2002). These studies have typically calculated the quantity (angular range in degrees, translation in mm) of inter-vertebral motion.

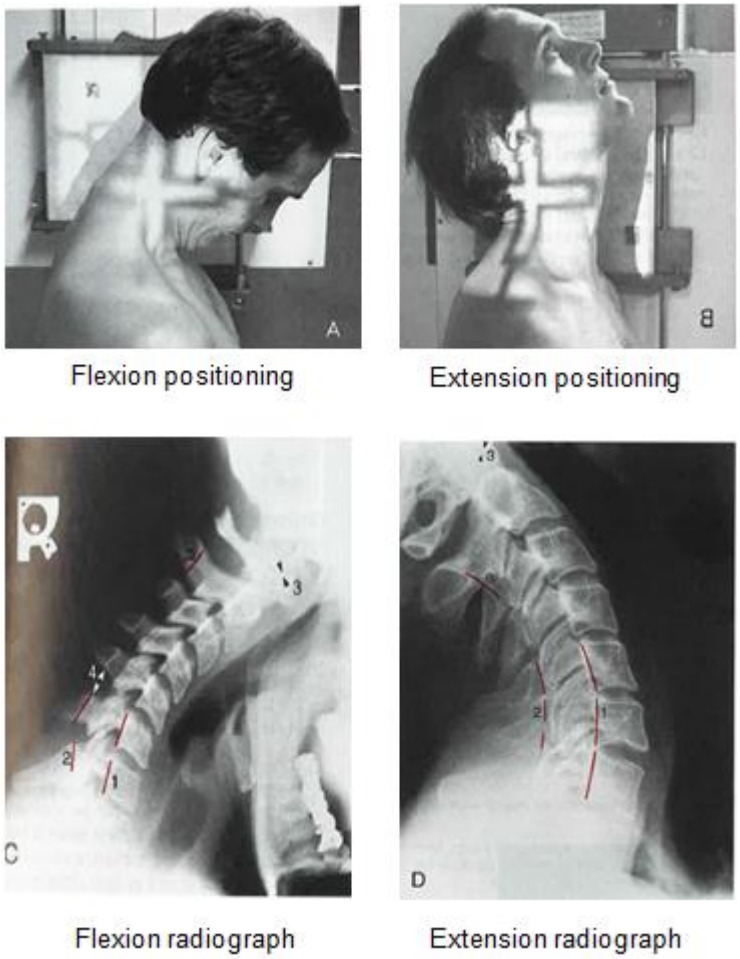


Figure 7: Plain-film flexion-extension study (Yochum and Rowe 2004, p. 36-37); Image adapted and reproduced with permission from Lippincott Williams & Wilkins

In contrast, the instantaneous axis of rotation (IAR) is considered to describe the quality of inter-vertebral motion (Bogduk and Mercer 2000). This kinematic parameter is the hypothetically stationary location somewhere below the superior vertebra in a motion segment about which this superior vertebra is rotating in an arc above the inferior one (White and Panjabi 1990).

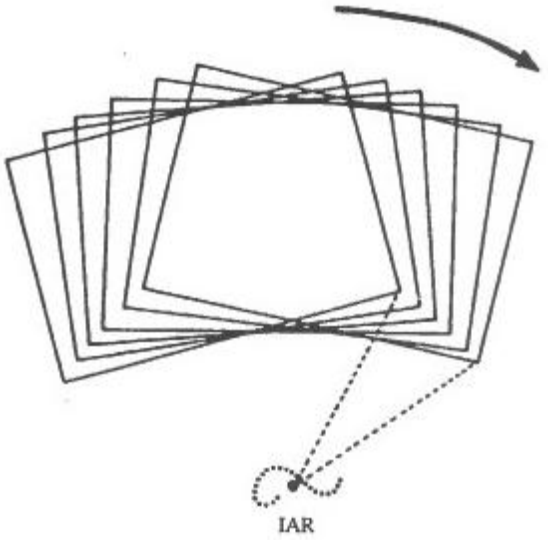


Figure 8: Vertebral motion approximated to a single, uniform arc around the instantaneous axis of rotation (IAR) (Bogduk et al. 1995); Image reproduced with permission from SAGE Publishing

In reality, due to the translation motion accompanying the rotation of vertebrae, the IAR can be expected to change location as the superior vertebra moves through different arcs (but at any one instant in time can be conceptualised as being at a stationary point). This cluster of IARs constitutes the centrode of motion.

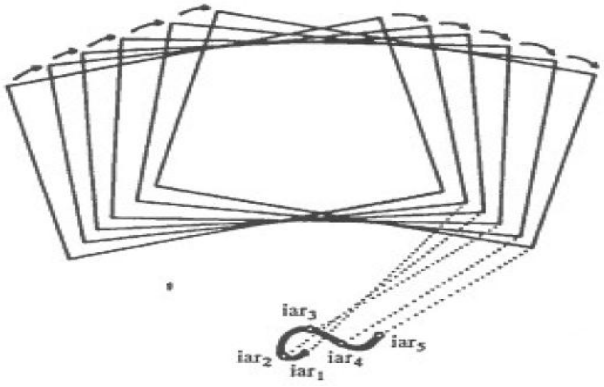
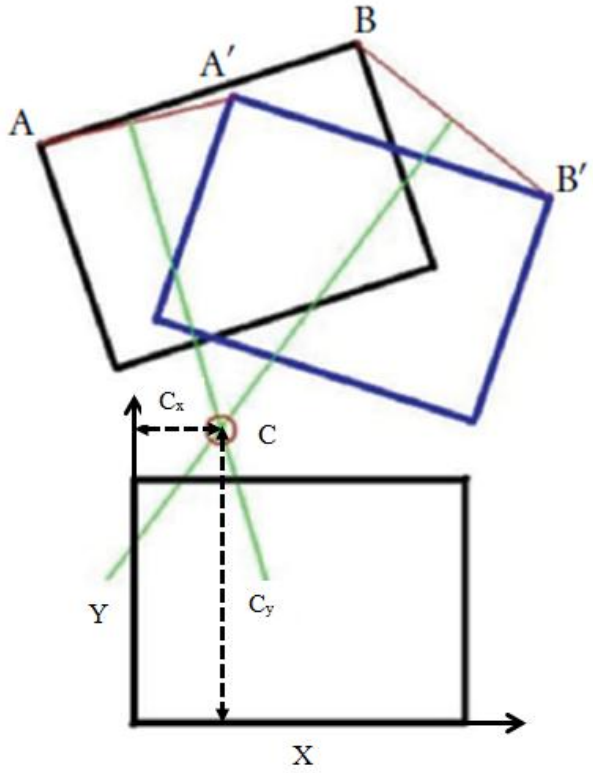


Figure 9: Vertebral motion along a series of different arcs around the centrode of motion (Bogduk et al. 1995); Image reproduced with permission from SAGE Publishing



A and B are points located at the superior corners of the superior verterbra and A' and B' represent the new locations of these points after the rotation. The centre of rotation, C (C_x, C_y), is at the intersection of the perpendicular bisectors of the lines of translation AA' and BB'.

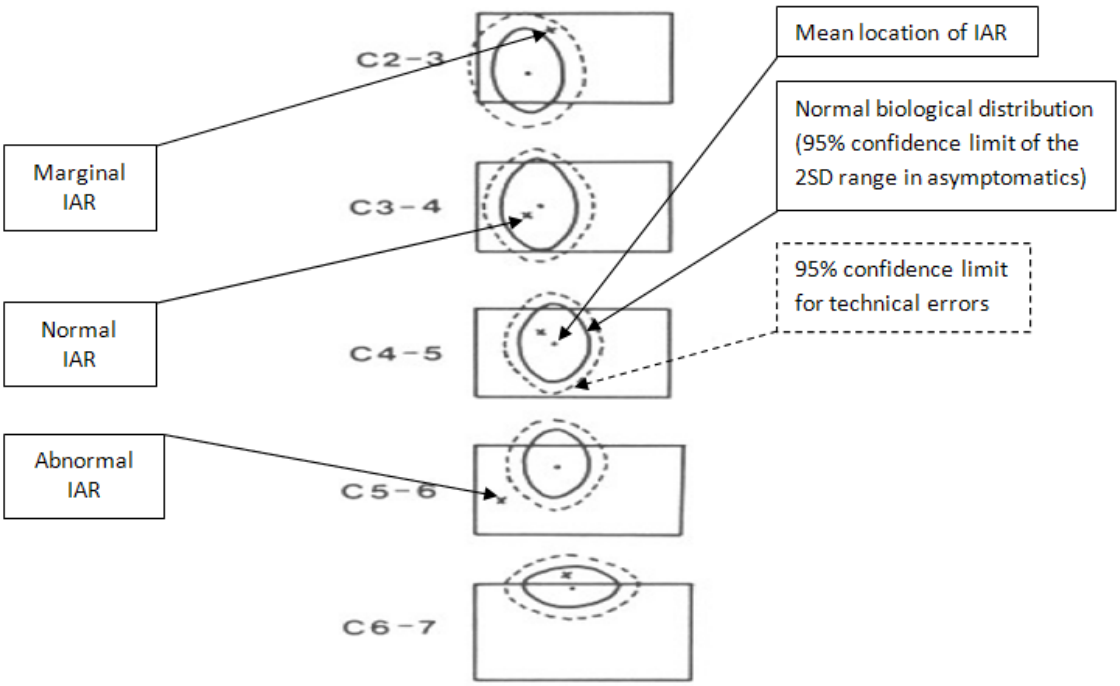
Figure 10: Block diagram illustrating the determination of IAR location

The determination of IAR location requires the measurement of coordinates from a minimum of two points identified on the superior vertebra of a pair, in at least two positions (Panjabi 1979), as illustrated above in Figure 10. Point C is the centre of rotation, usually called the axis of rotation (essentially analogous to IAR) when measured from two-dimensions, as from a plain-film x-ray.

Measurement of IAR location from plain-film flexion-extension studies can be subject to large errors due to difficulties in identifying anatomical landmarks consistently (Dimnet et al. 1982) and where only a small amount of rotation has taken place. Pearcy and Bogduk (1988) found generally large errors in locating IARs from lumbar spine plain-films which were unacceptable if rotation was less than 5°. Errors were also found to be largest at the uppermost (L1/2) and lowermost (L5/S1) levels because the radiographic beam was centred on the mid-lumbar spine (Pearcy and Bogduk 1988).

Therefore, these vertebrae were less well defined due to the divergence of the beam and therefore more difficult to the tracing and superimposition over the second film associated with that technique. The error locating the IAR may be reduced when there are not only two radiographs but a series of multiple radiographs taken throughout the flexion-extension motion (Dimnet et al. 1982). However, in a cineradiography study where many images are recorded IAR location errors were found to be large when rotation was less than 7° (van Mameren et al. 1990), further suggesting that measuring IARs may only be useful when the magnitude of motion is large.

It was suggested over 100 years ago that inter-vertebral dysfunction (subluxation [sic]) might be associated with an abnormally located centre/axis of rotation (Smith et al. 1906) but this idea was not investigated until much later. Cervical flexion-extension radiographs of patients with and without neck pain were analysed and compared by Amevo and colleagues for differences in IAR locations, (Amevo et al. 1992). They found the majority of patients with neck pain had evidence of abnormal inter-vertebral motion as determined by identification of abnormal IAR locations (Amevo et al. 1992) when compared to those without neck pain (Amevo et al. 1991c) (Figure 11).



x – IAR locations from a neck pain patient; *Marginal IAR at C2-3*: the IAR falls outside the biological distribution but within the technical error range; *Normal IAR at C3-4*: the IAR falls within the biological distribution range (mean±2SD of IAR locations from 40 people without neck pain); *Abnormal IAR at C5-6*: the IAR falls outside the technical error range; *2SD* – two standard deviations.

Figure 11: Examples of abnormal, marginal and normal IARs (Amevo et al. 1992); Image adapted and reproduced with permission from Lippincott Williams & Wilkins

Despite the limitations of plain-film radiography the findings from this study suggest IAR might be an important parameter in neck pain.

Using this statistical approach to defining abnormal motion, where abnormal is that defined as motion out-with the mean±2SD range from a representative asymptomatic population (assuming a normal distribution), is an approach that was adopted in a low back study by Abbott et al. 2006 for analysing motion data calculated from lumbar flexion-extension radiographs (Abbott et al. 2006).

This was done in two different ways; first, what was termed a “between-subjects Gaussian approach” [where reference intervals of normal motion (mean±2SD) were calculated from a sample of 30 asymptomatic volunteers]. Where inter-vertebral motion in patients with LBP was found to be out-with that reference range, the motion segment in question was considered to be “rigid” (hypo-mobile) if motion was below the 2nd percentile whereas “instability” (hyper-mobility) was deemed present if motion was above the 98th percentile (Abbott et al. 2006). This is shown graphically in Figure 12.

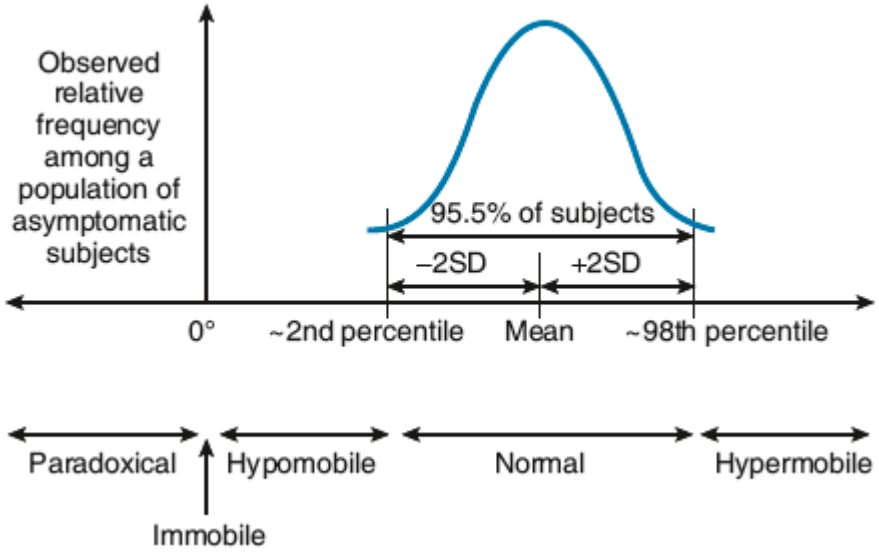


Figure 12: Theoretical framework for the categorisation of inter-vertebral motion (Deitz et al. 2011); image adapted and reproduced with permission from Elsevier

In the second approach, “within-subject normalised values” the authors calculated the proportion of motion that each inter-vertebral level contributed to the total inter-vertebral motion in each asymptomatic individual. Any motion segment whose proportional contribution to the total inter-vertebral motion in patients with back pain that fell out-with these normal limits could then be considered abnormal, as previously described.

Lumbar segmental “rigidity” was found with statistically significant prevalence in patients with recurrent or chronic LBP. The prevalence of abnormal motion at both the segmental and individual level were generally higher using the normalised within-subjects model compared to the conventional Gaussian model (Abbott et al. 2006). These findings are limited however by not considering measurement error.

The flexion-extension method, despite having been considered the gold standard of inter-vertebral motion assessment (Frobin et al. 2002) is prone to error (Amevo et al. 1991a; Amevo et al. 1991b; Panjabi et al. 1992) and most studies have not adequately reported technical errors or means and standard deviations which are required for the data to be meaningfully used (Bogduk and Mercer 2000).

Hino et al. (1999) measured normal and pathological inter-vertebral motion patterns in the cervical spine through the analysis of continuous motion by cineradiography (Hino et al. 1999) a method considered to be an improvement on flexion-extension studies (Bogduk and Mercer 2000). Differences in motion patterns between normal and pathological cervical spines were found based on the order that motion segments contributed to the overall movement. Kaneoka et al (1999) have reported similar observations with cineradiography. They studied healthy volunteers, exposing them to a minor whiplash injury or loading and then evaluated their cervical spines. The research showed that during a whiplash injury, the cervical spine is forced to move from the lower vertebrae first, opposite to what is thought to occur in normal extension motion (Kaneoka et al. 1999). It is not yet clear how useful these observations may prove to be clinically.

2.5.3 Measuring changes in inter-vertebral motion

It has been typical for inter-vertebral motion to be measured in individuals on only one occasion so the stability or variability of inter-vertebral motion over time is poorly understood. The stability of inter-vertebral measurements over time has been investigated by Van Mameren et al. (1990) using cineradiography. Using this technique Van Mameren et al. (1990) took up to 25 high-speed exposures per flexion-extension sequence in each participant from which to calculate inter-vertebral motion, in contrast to the two end-range radiographs of a flexion-extension study (van Mameren et al. 1990). Of the ten healthy volunteers aged 19-22 years involved in the study two subjects were imaged at baseline and two-week follow-up, while the remaining eight were imaged at these time intervals and at ten weeks.

Inter-vertebral motion within and between participants was found to be highly variable, and from this it was concluded that inter-subject variability of inter-vertebral motion was too large to be useful for diagnosing abnormal cervical spine motion and intra-subject variability too high to be sure if changes in motion after treatment might be related to a manual therapy intervention or to normal physiological variation. However, as the authors concede, these changes could be accounted for, at least in part, by participants moving in a slightly different way at each measuring session.

According to the paper, the movement of participants seems not to have been standardised beyond the fact they were seated and imaged from a position of maximum extension into flexion and vice-versa (van Mameren et al. 1990). Intra-subject variability might be reduced by improving the standardisation of the acquisition procedure. In contrast to the variability in ranges of motion, the order of maximum contribution of motion segments consistently showed the same pattern between measurement sessions within subjects, particularly in the lower cervical spine (van Mameren et al. 1990). Between subjects, the order of contribution of segments only varied in the mid-cervical spine (C2-4).

This same research group also calculated IARs on the same sample of ten participants (van Mameren et al. 1992). They did this by calculating “averaged” IARs, defined as the mean of a cluster of IARs, and “standard” IARs, defined as IARs calculated from only the two extreme frames of the cineradiographic film (similar to a plain-film x-ray flexion-extension study). These were calculated only for inter-vertebral levels that rotated a minimum of 7° as measurements below this were subject to large errors (van Mameren et al. 1992). IAR locations in the cervical spine were found to be stable over time at all levels, and the “averaged” method was found to be more reproducible (van Mameren et al. 1992). However, these findings are not from a sample sufficiently large and representative from which to derive normal reference values. Normal data from healthy volunteers are required to calculate the minimum detectable change (MDC) (Bland and Altman 1996a); changes that might be attributable to an intervention need to be larger than this MDC. Studies of the MDC of cervical regional motion as measured with external methods suggest the MDC is large (Appendix 1), but might be reduced with improved standardisation of the measurement procedure (Dunleavy and Goldberg 2013).The limitations with measuring IAR previously discussed highlight the importance of conducting repeatability/reproducibility studies on any measurement method to inform its use in a clinical study. However the apparent stability of IAR location over time in healthy individuals makes it an attractive parameter for any study aiming to measure changes in a biomechanical parameter in response to a therapeutic intervention for neck pain.

Limitations notwithstanding, the above studies suggest that inter-vertebral motion parameters might be used to biomechanically sub-group neck pain.

2.6 Spinal manipulative therapy

2.6.1 Proposed mechanisms for spinal manipulative therapy

Spinal manipulation appears to have been performed in one form or another almost throughout documented human history. The first known evidence of a manual technique used in the treatment of the spine is the ancient Indian epic *Srimad Bhagwat Mahapuranam*, estimated to have been written between 3,500 and 1,800 B.C. (Naderi et al. 2007). Hippocrates performed spinal manipulation and his techniques were later advocated by Galen whose teachings influenced medicine for hundreds of years (Naderi et al. 2007).

A modern re-emphasis on spinal manipulation occurred in the 19th century in the United States with the emergence of osteopathy and chiropractic, when the HVLA approach to manipulation appears to have become popularised. This appears to be the prevalent form of spinal manipulative therapy (SMT) among practitioners of manipulation in modern times (Maitland 2005; Peterson and Bergmann 2011).

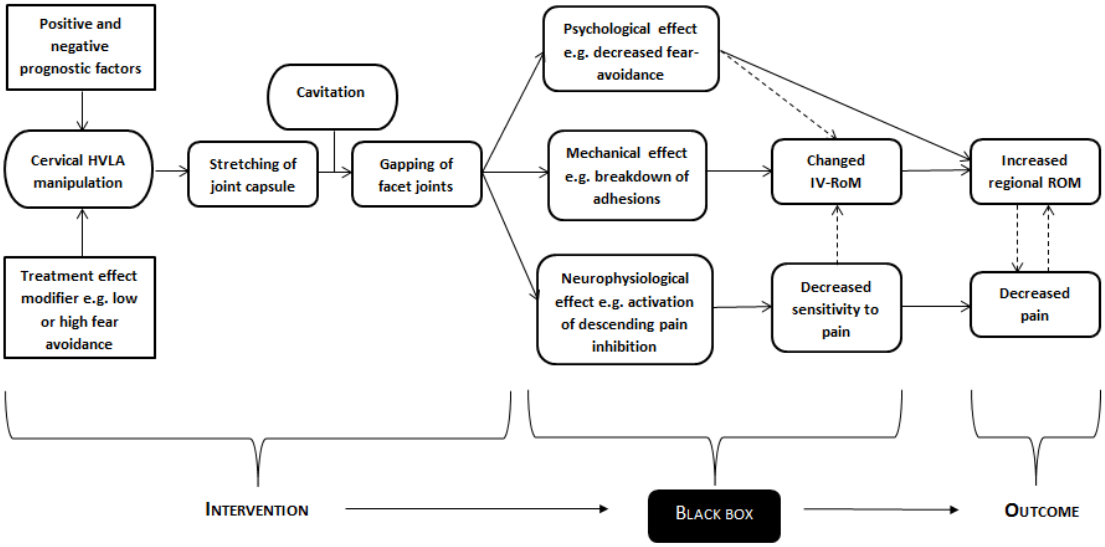
SMT is a frequently used therapy for neck pain (Wolsko et al. 2003) yet, despite a long history, little is known about its' mechanism(s) of action. There are many competing theories attempting to explain the clinical effects of SMT (see Figure 13). Historically biomechanical models have served as the primary basis for the mechanistic explanation of manipulation; for example, the correction of inter-vertebral "aberrant motion" (Peterson and Bergmann 2011). More recent evidence suggests that the effects of manipulation may be mediated by neurophysiological mechanisms; for example, inhibition of pain signals from the nervous system (Souvlis et al. 2004).

	Proposed mechanism*
1	Restore vertebra to normal position
2	Straighten the spine
3	Relieve interference of blood supply
4	Reduction of compressive or irritative insults to neural tissues
5	Relieve irritation of sympathetic chain
6	Mobilise fixated vertebral units
7	Shift a fragment of inter-vertebral disc
8	Mobilise posterior joints
9	Remove interference with cerebrospinal fluid circulation
10	Psychological effect of laying on of hands
11	Correct abnormal somato-visceral reflexes
12	Stretching or tearing of adhesions around the nerve root
13	Reduce distortion of the annulus
14	Inhibition of excessive muscular reflex activity and/or facilitation of inhibited muscle activity
15	Alleviation of an entrapped facet joint inclusion or meniscoid
16	Alleviation of stiffness induced by fibrotic tissue from previous injury or degenerative changes that may include adaptive shortening of fascial tissue
17	Activation of pain–inhibiting mechanisms
18	Unbuckling of motion segments that have undergone disproportionate displacements

*Collation of the mechanisms listed by: (Haldeman 1976; Shekelle 1994; Meeker and Haldeman 2002; Souvlis et al. 2004)

Figure 13: Proposed biomechanical and neurophysiological mechanisms of spinal manipulation

The clinical effects of SMT are thought to occur in response to mechanical, neurophysiological or psychological mechanisms (Zusman 1986; Maigne and Vautravers 2003) but it might be helpful to consider that mechanisms associated with all three of these conceptual models could be simultaneously at play to varying extents, at different times. In Figure 14, one mechanistic chain of events is suggested to explain decreased pain and increased regional ROM in a patient who has received cervical HVLA manipulation.



The '*black box'* represents the (unknown) underlying mechanisms that account for the outcome after an intervention (Howick et al. 2010). In the above black box are mechanical, neurophysiological and psychological effects (mechanisms) that may be considered to act in isolation or in concert in producing the clinical outcome. '*Changed IV-RoM'* includes the possibility of a change (increase) in range, or change in another kinematic variable, e.g. IAR location, with or without a change in range.

Figure 14: A suggested mechanistic chain to explain the clinical effects of spinal manipulative therapy

A similar but more detailed model has been proposed for the mechanisms behind the clinical effects associated with any manual therapy and is shown in Figure 15 (Bialosky et al. 2009).

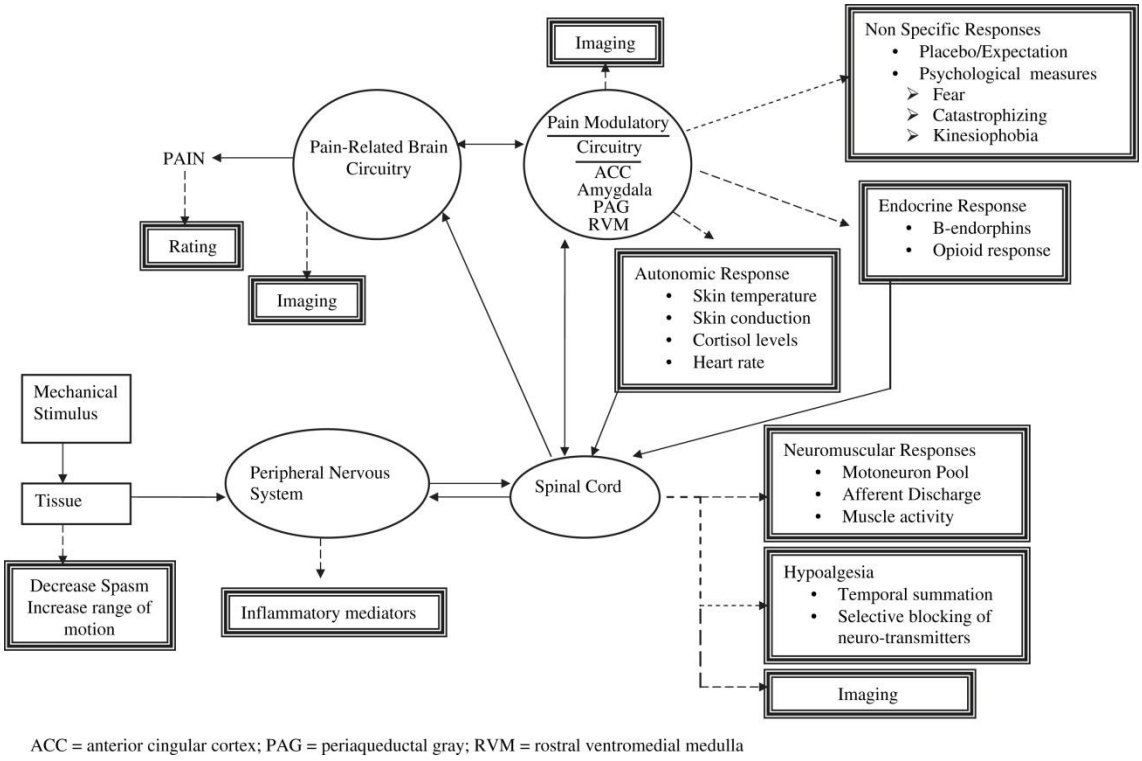


Figure key: The model suggests that a transient, mechanical stimulus to the tissue produces a chain of neurophysiological effects. Solid arrows denote a direct mediating effect. Broken arrows denote an associative relationship which may include an association between a construct and its measure. Bold boxes indicate the measurement of a construct.

Figure 15: Model of proposed mechanisms of manual therapy (Bialosky et al. 2009); Image reproduced with permission from Elsevier

Simply put, this model (Figure 15) proposes that a 'mechanical stimulus', like SMT, sets off a chain of neurophysiological [including pyschological] responses that are ultimately responsible for the clinical outcomes (Bialosky et al. 2009).[4] A number of the mechanisms postulated by this model have been investigated, but mostly theorised, in relation to SMT. Most investigative research has used cadavers, animal models or asymptomatic volunteers which can provide useful information to inform patient studies but the findings from such studies are in themselves not immediately clinically useful. Further, when mechanisms are explored in patients they are rarely considered in relation to symptomatic changes, and study designs rarely include a control group.

[4] It is inferred from this model that there may be little difference or at least significant overlap in the neurophysiological effects, irrespective of the manual therapy. While no manual therapy intervention has been shown to have unambiguous efficacious superiority for neck pain or any other musculoskeletal condition (Gross et al. 2010; Clar et al. 2014) it does not necessarily follow that they all work through the same mechanisms. Further to the model by Bialosky et al. (2009) it has been proposed that diverse manual therapy techniques may achieve similar outcomes due to common effects on the fascial tissues (Simmonds et al. 2012) but this remains to be investigated.

Finally, most research has concerned the effects of SMT on the lumbar spine (LBP), and caution is warranted in extrapolating findings to a different condition (neck pain) and the biomechanically distinct cervical spine (Sterling 2004).

2.6.2 Mechanical mechanisms

• **Facet joint gapping**

The facet joint capsule opposite the side contacted by the practitioner is assumed to have been stretched during the manipulative thrust as the facet joints are gapped. Static positional changes have been demonstrated, but only in the lumbar spine. Cramer et al. (2013) found that SMT increased separation (gapping) of lumbar facet joints as measured by MRI in patients with LBP and was associated with immediate decreases in pain. However, controls who did not receive SMT but were lying on their side while being imaged exhibited the largest amount of gapping at visit one, while those receiving SMT and remained on their side while being imaged exhibited most gapping at visit two, making the link between gapping and pain relief uncertain (Cramer et al. 2013).

Gapping is confirmed clinically by an audible release or cavitation (Herzog et al. 1993). It has been suggested that the cavitation is a hallmark feature that distinguishes HVLA manipulation from other manual techniques (Evans and Lucas 2010). However, the role of cavitation in the clinical effects of manipulation is uncertain. In the lumbar and thoracic spines cavitation has been shown to take place at the target segment only half of the time, and multiple cavitations were common from only one manipulation (Ross et al. 2004). Multiple cavitations have also been associated with manipulation to the upper cervical spine, with cavitation occurring unilaterally (on either side of the spine) or bilaterally (Dunning et al. 2013). Thus, manipulation does not appear to accurately target the intended inter-vertebral level. Further, in a study of manipulation in patients with LBP, cavitation was not found to be necessary for a successful outcome (Flynn et al. 2003).

Facet joint gapping is an important feature of a number of proposed mechanical theories for the clinical effects of SMT. Gapping of the joint may lead to mechanical breakdown of capsule adhesions, although adhesions have not been shown to be a dominant factor for restricted segmental motion (Zusman 1986); similarly uncertain is the extent to which the synovial folds (meniscoids) are involved in neck pain, and whether they might be un-trapped during facet gapping (Webb et al. 2011).

It is also theorised, but unknown, that facet joint capsule stretching will facilitate the inhibition of paraspinal muscle spasm (Maigne and Vautravers 2003). Inhibition of reflex muscle contraction about a joint is thought to disperse irritative metabolites which have accumulated due to muscle ischaemia. Further, there may be reduced muscular tension on periarticular structures with a subsequent decrease in peripheral afferent discharge (Zusman 1986). Corroborating the role of muscle spasm in spinal pain, Zhu et al (2000) measured cortical-evoked potentials on magnetic stimulation of lumbar paraspinal muscles in patients with LBP (Zhu et al. 2000). After two weeks of SMT, palpable muscle spasm was decreased in 11/13 patients, and decreases in pain were significantly correlated with increased cortical-evoked potentials (Zhu et al. 2000). Due to the lack of a control group however, it is unknown whether the muscle spasm changed due to treatment, or natural history.

• Diffusion of water in the inter-vertebral disc

Oscillatory mobilisation to the lumbar spine has been associated with producing a significant increase in the diffusion of water in the degenerated L5/S1 inter-vertebral disc in patients with activity-limiting LBP (Beattie et al. 2009), but the clinical significance of such changes, and whether they might occur in the cervical spine or with HVLA manipulation, are unknown. It is also said to be unlikely that manipulation repositions fragments of disc (Evans 2002).

• Relief of joint stiffness

Muscle guarding or splinting has been observed in patients with LBP and it is suggested that mechanical deformation of pain receptors in the soft tissues may activate the paraspinal muscles, causing the motion segment to stiffen (Solomonow et al. 1998). One study has linked immediate decreases in measured lumbar spine stiffness with decreases in pain and increased regional ROM after one session of Grade III rhythmic mobilisation to the fourth lumbar vertebra in patients with LBP (Shum et al. 2013). Patients could also tolerate greater mechanically applied loading to the spine immediately after treatment, but the longer-term benefits of this remain unknown. The study also showed that rather than the target segment alone receiving the mechanical loading, the whole region of spine was mobilised (Shum et al. 2013). Similar three-point bending has been shown to occur with posteroanterior mobilisation of the cervical spine but in that study stiffness and pain were not measured (Lee et al. 2005).

Another study similarly measured lumbar stiffness and in addition measured multifidus recruitment by ultrasound after two SMT sessions over one week (Fritz et al. 2011). Pain-related disability was significantly decreased at one-week which the authors concluded was mediated by improved multifidus recruitment (measured during a submaximal contraction) and immediate decreases in lumbar stiffness, suggesting a link between joint stiffness, muscle activity and pain (Fritz et al. 2011).

• Increasing spinal motion

The previous theories of the repositioning of vertebra or straightening of the spine have been shown to be untrue (Evans 2002). However, despite the lack of accurate clinical measures of inter-vertebral motion, there is evidence to suggest that SMT can increase regional cervical spine motion and decrease pain. Nansel et al. (1989a) showed that a single manipulation could reduce asymmetry of passive regional cervical spine motion (Nansel et al. 1989a). Cassidy et al. (1992) and Martinez-Segura et al. (2006) independently found manipulation both reduced neck pain and increased regional range of neck motion immediately after treatment (Cassidy et al. 1992; Martinez-Segura et al. 2006). There is also evidence from RCTs of neck pain/headache that SMT increases cervical regional range of motion (Nilsson et al. 1996a; Whittingham and Nilsson 2001; Hemmila 2005). However, little is known about changes in cervical inter-vertebral motion resulting from SMT as intended.

Hviid et al (1965) took flexion-extension radiographs before and after a course of SMT in 50 patients with neck complaints and observed that in cases judged to have regional cervical hypo-mobility, 10/10 patients (flexion) and 10/13 patients' (extension) hypo-mobility was returned to normal (Hviid 1965). However, the timing of radiographs was not standardised, with follow-ups taking place at different time intervals between patients, and identification of hypo-mobility was qualitative, not quantitative. When the authors subsequently measured the motion from the radiographs they found the majority of patients had increased mobility; but this was not measured segmentally (Hviid 1965). Neither measurement error nor the MDC of measurements from radiographs were taken into account, so the meaningfulness of these results is unknown.

In a case series of 58 patients with neck pain or headache the motion at each vertebra was measured on radiographs before and after SMT but while vertebral motion was shown to increase, measurements were not standardised and changes in motion were less than the measurement error from plain-film radiography, so were in fact not detectable (Yeomans 1992).

In order to detect true changes in inter-vertebral motion the acquisition procedure must be standardised, and interpretation of the results need to take account of the inherent measurement limitations of the method.

2.6.3 Neurophysiological mechanisms

• Descending pain inhibition

A systematic review and meta-analysis concluded that SMT has a greater effect on increasing pressure-pain thresholds (PPT) compared to other interventions, suggesting an influence on central descending pain inhibition (Coronado et al. 2012). However, most of the studies included had been carried out on asymptomatic participants, there was a lack of studies linking changes in pain sensitivity to changes in clinical outcomes, and most studies only assessed short-term or immediate PPT changes (Coronado et al. 2012). Finally, this systematic review appears not to have taken account of the MDC in assessing changes in PPT.

In a study that assessed immediate changes in patients with neck pain after cervical or thoracic manipulation, while pain and PPT improved significantly, changes in PPT did not exceeded the MDC (Martinez-Segura et al. 2012). In another study that assessed immediate changes after cervical or thoracic SMT, PPT threshold was again increased post-intervention (Molina Ortega et al. 2014). Levels of nitric oxide and substance P were also measured pre and post-intervention. Nitric oxide remained unchanged while the largest increase in substance P occurred in the cervical SMT group (Molina Ortega et al. 2014). However it is unknown whether this change would last beyond the two hours post–SMT time point at which it was measured, and the role of substance P in pain modulation is not fully understood.

• Somatosensory activation

In an experimental study, dual peripheral nerve stimulation somatosensory evoked potentials (SEP) were recorded after median and nerve stimulation at the wrist in 11 asymptomatic subjects (Haavik-Taylor and Murphy 2010). This was done as a means of assessing somatosensory processing before and after a 20 minute typing task (Haavik-Taylor and Murphy 2010). SEPs were measured again after the typing task was repeated, this time preceded by cervical SMT. Changes in SEPs were detected after the task post-SMT that were not present after the task only, and the authors concluded that this was suggestive of altered central nervous system activity (Haavik-Taylor and Murphy 2010).

Unfortunately, there is no evidence to support the use of dermatomal SEPs as an outcome measure for any condition (AANTTA. 1997). Importantly, there was no control group to compare changes with. Altered muscle firing patterns have been found in patients with chronic neck pain while performing a functional task (Tsang et al. 2014) and it would be desirable to see if muscle firing patterns were altered post-treatment, the implications of which are more clinically obvious that changes in SEPs. A review paper on SMT somatosensory activation reveals that this is an area of investigation that is still at the experimental stage (Pickar and Bolton 2012).

• Sympathetic nervous system

A recent systematic review of research into effects of spinal mobilisation on the sympathetic nervous system found seven randomised controlled trials that the authors rated as high quality. These studies found consistent increases in sympathetic nervous system activity across all outcome measures, indicative of sympathetic excitation, irrespective of the segments mobilised (Kingston et al. 2014). However, only one study evaluated changes in a symptomatic population and, since changes were not linked to outcomes, the clinical utility of changes in skin conductance, decrease in skin temperature, and especially of increases in respiratory rate, blood pressure and heart rate, are unknown and questionable (Kingston et al. 2014).

• Endocrine system

Despite the role it plays in pain modulation, there has been little research of the effects of SMT on the endocrine system. In a small prospective case series (n=9, assumed to be asymptomatic) serum cortisol levels were not significantly different after four treatment visits for SMT (region of spine not stated) (Tuchin 1998). A second study compared salivary cortisol levels in a cervical SMT group, a sham group and a control group before and after treatment, and found no differences in cortisol changes between the (asymptomatic) groups (Whelan et al. 2002). Finally, despite the author's tenuous claims to the contrary, Padayachy et al (2010) similarly found no differences in serum cortisol levels five minutes after lumbar manipulation in 30 asymptomatics (Padayachy et al. 2010).

• Inflammation

In a cross-sectional study patients (n=27) with chronic and recurrent neck pain were found to have significantly higher levels of serum inflammatory mediators compared to controls with no neck pain (Teodorczyk-Injeyan et al. 2011). The presence of an inflamed joint is generally considered a contra-indication to manipulation, at least in the case of spondyloarthopathies (Assendelft et al. 1996).

However, in an earlier study the same research group found that a single *thoracic* manipulation was associated with a greater decrease in inflammatory cytokines compared to sham or venepuncture controls (Teodorczyk-Injeyan et al. 2006). While experiments with an animal model suggest SMT might decrease inflammation associated with the inter-vertebral foramen (Song et al. 2006), the mechanism behind these decreases in inflammation, the duration of action and the importance of this in mediating patients' clinical outcomes in neck pain or any other condition remains unknown.

The use of functional MRI to monitor brain changes in response to lumbar mobilisation has been investigated recently (Meier et al. 2014). This appears to be feasible and might be a more promising avenue for investigating the neurophysiological effects of SMT.

2.6.4 Psychological mechanisms

Finally, a psychological effect may occur in isolation or in tandem with mechanical and neurophysiological effects, such as a decrease in fear avoidance, by breaking the pain-spasm-pain cycle (Maigne and Vautravers 2003). Fear avoidance is a good example of a psychological variable that can function as both a treatment effect modifier (baseline variable that influences the relationship between an intervention and the outcome) or as a treatment mediator (factors that have an intermediary role in the link between treatment and outcome) (Hill and Fritz 2011).

The expectations that patients have before commencing treatment can have an influence on recovery. In a clinical trial of 140 patients, patients who believed that manipulation would help, and received manipulation, had better odds of recovery at one month than those who received manipulation, but did not think it would help (OR 0.33; 95%CI: 0.11 to 0.99) (Bishop et al. 2013). In a randomised trial of 346 patients receiving physical therapy treatments for neck pain, low treatment expectation was a predictor of poor outcome at six months (Hill et al. 2007). Despite expectations appearing to be important, early positive response to treatment appears to ultimately be a better predictor of improvement than any baseline variable (Bolton and Hurst 2011; Peterson et al. 2012).

Despite the identification of a number of potential mechanisms these have rarely been linked to patient-reported outcomes, and when they have, only in patients with LBP (Fritz et al. 2011; Koppenhaver et al. 2011). The value in discovering a mechanism will only be fully realised when the extent to which it is associated with reducing pain and disability is also discovered.

2.6.5 Clinical trials of spinal manipulative therapy for neck pain

A systematic review of spinal manipulation for neck pain published in 2003 concluded, on the basis of four randomised clinical trials, that spinal manipulation (performed by chiropractors) was not more effective than control treatment and inferior to exercise treatment (Ernst 2003). Letters written to the journal editor in response to this review's findings highlight some of the issues regarding the evidence base for spinal manipulation in general, issues which have still yet to be completely resolved. The view of two correspondents was that the review was methodologically flawed, for example, by omitting certain electronic databases, only focusing on one manual therapy profession and being conducted by a solo author rather than a team (Peloso and Gross 2003); another correspondent concluded that there were no major methodological flaws, for example, by suggesting that the inclusion of more journal searching would not have identified any additional trials that may have altered the review's conclusion (Bogduk 2003). While both these letters highlighted that the biggest problem with the evidence was the lack of it, Peloso and Gross's (2003) response to this was, "Further studies are needed to assess the competing therapies for neck pain" while, in contrast, Bogduk (2003) concluded, "Spinal manipulation for neck pain does not work". Since then, the evidence base has grown considerably, but some views on spinal manipulation for neck pain remain polarised.

In 2008 the Neck Pain Task Force conducted a Best Evidence Synthesis of non-invasive treatments for neck pain (Hurwitz et al. 2008) and the 13 trials on spinal manipulation or mobilisation which met their inclusion criteria are listed in Table 1, pages 34-36 . In summary, what this table shows is that trials investigating spinal manipulation for neck pain produce conflicting results. However, the Neck Pain Task Force concluded that, on balance, the evidence was supportive of the effectiveness of spinal manipulation in the treatment of neck pain (Hurwitz et al. 2008).

Trial	Sample	Episode duration	Intervention	Outcomes	Last follow-up	Comparator(s)	Outcome of comparison
(Koes et al. 1992; Koes et al. 1993)	64 GP patients	≥ 6 weeks	Manipulation/mobilisation [manual therapist]	Pain, disability, global effect	52 weeks	Placebo or sham	=
						Usual GP care	=
						Physiotherapy (exercise, massage, modalities)	=
(Sterling et al. 2001)	30 Manual. PT patients	> 3 months	Mobilisation [PT]	Pain, pressure pain threshold	Immed-iate	Placebo or sham	+
						No care	+
(Hoving et al. 2002; Korthals-de Bos et al. 2003; Hoving et al. 2006)	183 GP patients	≥ 2 weeks	Mobilisation [manual therapist]	Pain, disability, perceived recovery Cost (cost effectiveness)	52 weeks	Usual care	+ (7 and 13 weeks) +/= (26 and 52 weeks) + (CE)
						Physiotherapy (sessions of exercise)	+ (7 weeks) = (13 and 52 weeks) + (CE)
(Jull et al. 2002; Stanton and Jull 2003)	200 PT patients	One HA/week for ≥ 2 months	Manipulation/mobilisation [PT]	HA frequency, length, neck pain, perceived effect	52 weeks	No care	+
						Sessions of exercise therapy	=
						Sessions of exercise therapy + manipulation/ mobilisation	=
(Brodin 1984)	71 patients	?	Salicylates, advice +/- mobilisation	Pain	4 weeks	Salicylates only	+
						Salicylates + advice, massage, electrical stimulation and traction	+

(continued)

Trial	Sample	Episode duration	Intervention	Outcomes	Last follow-up	Comparator(s)	Outcome of comparison
(Dziedzic et al. 2005)	350 GP patients referred to PT	> 3 months	Advice about coping, individualised home exercise + manipulation/mobilisation	Disability, global improvement, sick leave	26 weeks	Advice about coping, individualised home exercise	=
						Advice about coping, individualised home exercise + shortwave diathermy	=
(Martinez-Segura et al. 2006)	71 primary care referrals to PT/Osteo	≥ 1 month	Manipulation [PT/Osteo]	Pain	5 minutes	Mobilisation [PT/Osteo]	+
(Hurwitz et al. 2002)	336 chiro patients	Any length	Manipulation [Chiro]	Pain, disability, harms	26 weeks	Mobilisation [Chiro]	= [pain, disability] - [harms]
(Wood et al. 2001)	30 Chiro patients, general population	≥ 1 month	Manipulation [Chiro]	Pain, disability	8 weeks	Instrumental manipulation [Chiro]	=
(Jordan et al. 1998)	119 patients referred to orthopaedic department	> 3 months	Advice, home exercise, manipulation [Chiro]	Pain, disability, perceived effect, physician global assessment	52 weeks	Advice, home exercise, intensive training of cervical muscles	=
						Advice, home exercise, mobilisation and traction	=
(Bronfort et al. 2001; Evans et al. 2002)	191 general population	≥ 12 weeks	Manipulation [Chiro]	Pain, disability	104 weeks	Strengthening exercises	-
						Strengthening exercises + manipulation	-

(continued)

Trial	Sample	Episode duration	Intervention	Outcomes	Last follow-up	Comparator(s)	Outcome of comparison
(Skillgate et al. 2007)	265 workers	≥ 2 weeks	Naprapathy (manipulation, mobilisation, massage, stretching) [Naprapath]	Pain, disability, perceived recovery	12 weeks	Physician-provided advice and support to stay active	= (3 weeks) + (7 and 12 weeks)
(McReynolds and Sheridan 2005)	58 emergency department patients	< 3 weeks	Manipulation, muscle-energy and soft tissue techniques [Osteo]	Pain, patient perceived effect	1 hour	Intramuscular ketorolac tromethamine, 30mg	+/=

=, equal, a clinically relevant difference was not observed between intervention and comparator; +, better or - , worse, denotes clinically relevant differences between intervention and comparator; *PT*, physiotherapist; *Osteo*, osteopath; *Chiro*, chiropractor; *HA*, headache; *CE*, cost-effectiveness

Table 1: Clinically relevant differences in pain or disability outcomes between manipulation intervention [equal (=), better (+), worse (-)] and comparator included in efficacy or effectiveness studies, or relative effectiveness studies, of non-specific neck pain or associated disorders reported by the Neck Pain Task Force. Table adapted from the Best Evidence Synthesis by Hurwitz et al. (2008)

Since the Neck Pain Task Force, seven systematic reviews on spinal manipulation/mobilisation have been published and summaries of these reviews' conclusions are listed in Table 2. With the exception of the systematic review of systematic reviews (Posadzki and Ernst 2011), these conclusions further support those of the Neck Pain Task Force but they serve to highlight the continuing lack of high quality evidence and contradictory trial results. As concluded by the most recent review, the evidence suggests manipulation and/or mobilisation produce similar improvements compared to other "active" [sic] treatment, however, some trials also found no improvement in comparison to a control group (Clar et al. 2014). Three RCTs published more recently (Bronfort et al. 2012; Evans et al. 2012; Maiers et al. 2014), listed in Table 3, provide additional evidence for the efficacy of manipulation as part of a treatment package but the absence of control groups in these studies precludes the determination of whether manipulation had a specific treatment effect or not. These studies also failed to show clear superiority of SMT over exercise, rather, they add to the conclusion of one systematic review that SMT and exercise appear to be most efficacious when combined (Miller et al. 2010).

Another systematic review (Cross et al. 2011) concluded that thoracic manipulation alone could be effective for neck pain (Table 2). The findings from another recent RCT (Saavedra-Hernandez et al. 2012), included in Table 3, are limited by only following-up participants at one week but suggest the combination of cervical and thoracic manipulation may be more effective than cervical alone; it is the case in most RCTs of spinal manipulation for neck pain for SMT to be restricted to the neck. What the research base into manipulation for neck pain has so far not been able to indicate is which neck pain patients might be expected to derive most benefit from manipulation and for whom an alternative management strategy is indicated. It is further unknown which exercises or soft tissue technique(s) are most effective, and the ideal dosage that is required to produce clinically meaningful benefit is unknown for any manual therapy intervention.[5]

[5] Manual therapy dose-response studies are few. In an RCT evaluating SMT for cervicogenic headache, 8 versus 16 treatment sessions yielded small dose effects (Haas et al. 2010). In a study evaluating the dose-response of SMT for chronic LBP, 400 patients were randomised to receive 0 (light massage), 6, 12 or 18 sessions of spinal manipulation. At 12 weeks, the greatest differences from the control group were found for 12 sessions over 6 weeks; at 24 weeks differences were negligible, at 52 weeks the greatest group differences were seen for 18 visits (Haas et al. 2014); any dose effects were small. In another study 228 individuals with chronic neck pain were randomised to one of four groups receiving various doses of massage over four weeks or to a waiting list control group (Sherman et al. 2014). It was concluded that participants who received 30-minute treatments, regardless of their frequency, did not do significantly better than controls, while 60-minute treatments two and three times/week significantly increased the chance of clinically significant improvement over controls at five weeks (relative risk = 2.30 and 2.73; p = 0.007 and 0.001, respectively) (Sherman et al. 2014).

Summary conclusions of systematic reviews regarding the treatment of neck pain with spinal manipulation/mobilisation
Manual therapy and exercise for neck pain: A systematic review (Miller et al. 2010) • High quality evidence (3 pooled trials, 320 participants) suggests greater short-term pain relief from manual therapy (manipulation or mobilisation) (pooled standardised mean difference -0.50 (95% CI: -0.76 to -0.24) than exercise alone, but no longer-term differences for pain (pSMD -0.10 (95% CI: -0.42 to 0.21) or for any other outcomes (function, disability, quality of life, global perceived effect or patient satisfaction) are evident for any duration of neck pain • Moderate quality evidence (2 pooled trials, 178 participants) suggests manual therapy + exercise is superior to manual therapy alone for the reduction of pain [pSMD – 0.48 (95% cI: -0.78 to -0.18)] and improvement of quality of life for chronic neck pain • Low quality evidence (2 pooled trials, 111 participants) suggests manual therapy + exercise produces greater long-term pain reduction (absolute benefit 23-37/100mm, number needed to treat = 5, treatment advantage 27%) when compared to no treatment for chronic neck pain and subacute/chronic neck pain with cervicogenic headache
Manual therapy with or without physical medicine modalities for neck pain: A systematic review (D'Sylva et al. 2010) • Moderate quality evidence (1 trial, 221 participants) suggests greater short and medium-term pain reduction and patient satisfaction from the combination of mobilisation + manipulation + soft tissue techniques versus short-wave diathermy for a new episode of neck pain. When different arms in the same trial were compared (209 participants) mobilisation + manipulation + soft tissue techniques resulted in greater improvements in global perceived effect, patient satisfaction and quality of life, but similar changes in pain and function, when added to advice and exercise for a new episode of neck pain • Low to very low quality evidence from seven stand alone trials that a combination of mobilisation + manipulation + soft tissue techniques is no more effective than a variety of other treatments for pain, function, return-to-work, satisfaction at any time-point for subacute or chronic neck pain *(continued)*

Summary conclusions of systematic reviews regarding the treatment of neck pain with spinal manipulation/mobilisation
• Low quality evidence suggests a statistically non-significant but clinically significant benefit favouring manipulation + mobilisation for pain relief (1 meta-analysis of 2 trials, 112 participants), improved function and global perceived effect (1 trial, 94 participants) for chronic cervicogenic headache compared to a control at medium and long-term follow-up • Low quality evidence (1 trial, 25 participants) suggests no difference in pain relief and global perceived effect between manipulation + mobilisation versus detuned electrotherapy placebo for subacute/chronic neck pain in the short-term • Evidence for manipulation and mobilisation is conflicting (5 trials, 240 participants) when compared to physiotherapy, GP care or exercise for subacute/chronic neck pain +/- cervicogenic headache • Low quality evidence (6 stand alone trials) shows no difference in pain, function or global perceived effect when manipulation or mobilisation are added to various physical medicine modalities and compared to placebo, exercise and various other manual and modality treatment combinations • *Cost* – moderate quality evidence favoured reduced costs for manual therapy for acute/subacute/chronic neck pain with or without headache or radicular involvement
Manipulation or mobilisation for neck pain: A Cochrane Review (Gross et al. 2010)
• Moderate quality evidence (2 trials, 369 participants) suggests that cervical manipulation is not superior for pain, function or patient satisfaction when compared to mobilisation for subacute or chronic neck pain at short and medium-term follow-up • Low quality evidence (3 trials, 130 participants) suggests that cervical manipulation may provide immediate and short-term relief of acute and chronic neck pain compared to control [pSMD -0.90 (95% CI: -1.78 to -0.02)] • Low quality evidence supportive of thoracic manipulation for reduction of pain (NNT = 7) and improved function (NNT = 5) for acute neck pain and immediate pain reduction in chronic neck pain (NNT = 5) • Very low quality evidence (3 trials, 88 participants) suggests one manipulation technique is not superior to another for short-term relief of subacute neck pain
(continued)

Summary conclusions of systematic reviews regarding the treatment of neck pain with spinal manipulation/mobilisation
• Very low quality evidence suggests cervical manipulation is equivalent to certain medications (2 trials, 69 participants), acupuncture (2 trials, 81 participants), soft-tissue treatments (1 trial, 53 participants) or certain combined treatments for subacute and chronic neck pain, but may be superior to TENS (1 trial, 64 participants) for chronic cervicogenic headache
Effectiveness of manual therapies: the UK evidence report (Bronfort et al. 2010) • Moderate quality (positive) evidence for spinal manipulation/mobilisation + exercise for chronic neck pain • Moderate quality (positive) evidence for thoracic spinal manipulation/mobilisation for acute/subacute neck pain • Inconclusive (favourable) evidence for cervical spine manipulation/mobilisation alone for neck pain of any duration
Spinal manipulation: an update of a systematic review of systematic reviews (Posadzki and Ernst 2011) • Data from five systematic reviews (one positive, three negative, one neutral or unclear) fail to convincingly demonstrate that spinal manipulation is an effective intervention for the treatment of neck pain NB: One of the three 'negative' systematic reviews (Gross et al. 2004) was updated six years later (Gross et al. 2010). This time Posadzski and Ernst (2011) categorised its conclusions as 'neutral or unclear'
Thoracic spine thrust manipulation improves pain, range of motion, and self-reported function in patients with mechanical neck pain: A systematic review (Cross et al. 2011) • A limited body of evidence of varying quality (6 trials, 358 participants) suggests that thoracic spinal manipulation for the treatment of neck pain reduces pain and improves function in the immediate and short-term, and in the medium-term (1 trial, 140 participants) *(continued)*

Summary conclusions of systematic reviews regarding the treatment of neck pain with spinal manipulation/mobilisation
Clinical effectiveness of manual therapy for the management of musculoskeletal and non-musculoskeletal conditions: systematic review and update of UK evidence report (Clar et al. 2014) • Inconclusive (favourable) evidence for cervical spine manipulation/mobilisation alone • Inconclusive (favourable) evidence for cervical spine manipulation and mobilisation +/- soft tissue treatment

Table 2: Summary conclusions of systematic reviews of spinal manipulation/mobilisation for neck pain published since the reporting of the Neck Pain Task Force in 2008

Trial	Sample characteristics	Intervention and Outcomes	Number of treatment visits	Last follow-up	Comparator(s)	Outcome of comparison
(Saavedra-Hernandez et al. 2012)	82 chronic neck pain patients referred to private manual PT, 50% female, aged 45±9years (mean±SD)	Cervical thrust manipulation [PT] Pain, disability, cervical ROM	One	One week	Cervical and thoracic thrust manipulation	*Pain*: decreased in both groups with no significant between-group difference *Disability*: greater reduction in the cervical+thoracic manipulation group *Cervical ROM*: Increased similarly in both groups
(Evans et al. 2012)	270 chronic neck pain participants recruited from general population aged 18-65 years	High dose supervised strengthening exercise (predominantly neck and upper body strengthening with low-tech methods, partially individualised according to tolerance) [exercise therapist] + SMT [manipulation±light massage] [Chiro] Pain, disability, global improvement, medication use, satisfaction, general health status (SF-36 subscales)	*High dose supervised exercise [+ SMT]* – 20, one-hour sessions [+ 15-20min SMT session]; *Home exercise and advice* – 2, one hour sessions	52 weeks	High dose supervised strengthening exercise alone [exercise therapist]	*Pain*: no significant differences; *All other outcome measures*: no significant differences
					Low dose home exercise and advice (simple self-mobilisation of the neck and shoulder joints, partially individualised according to tolerance) [exercise therapist]	*Pain*: significant difference in favour of +SMT group; *All other outcome measures*: no significant differences except for global perceived effect and satisfaction in favour of +SMT group

(continued)

Trial	Sample characteristics	Intervention and Outcomes	Number of treatment visits	Last follow-up	Comparator(s)	Outcome of comparison
(Bronfort et al. 2012)	272 acute neck and subacute neck pain participants recruited from general population aged 18-65 years	Cervical and thoracic SMT (manipulation±mobilisation± limited massage, stretching, hot and cold packs, advice regarding activity) [Chiro] Pain, disability, global improvement, medication use, satisfaction, general health status (SF-36 subscales), cervical ROM	*Medication group* - Mean(range) 4.8(1-8); *SMT group* - 15.3(2-23) determined by treating practitioner over period of 12 weeks; *Home Exercise group* – 2.0(1-2) fixed duration for study	52 weeks	Medication group – brief history and examination; 1st line: NSAIDs±paracetamol; 2nd line: narcotics, muscle relaxants	*Pain*: statistically significantly reduced in short and long-term and greater proportion with clinically significant decrease at 26 weeks in favour of SMT group; *All other outcome measures*: SMT superior for except for SF-36 measured mental function
					Home exercise with advice group - primarily focused on simple self-mobilisation exercise of the neck and shoulder joints, individualised to each participants' abilities	*Pain*: no significant differences; *All other outcome measures*: no significant differences for except patient satisfaction in favour of SMT in short and long-term *Cervical ROM*: changes greatest in home exercise group

(continued)

Trial	Sample characteristics	Intervention and Outcomes	Number of treatment visits	Last follow-up	Comparator(s)	Outcome of comparison
(Maiers et al. 2014)	241 acute and subacute neck pain participants recruited from general population aged over 65 years	SMT (manipulation and mobilisation±light massage±stretching, hot and cold packs) [Chiro] + home exercise (Information on pain management, postural and movement instruction, advice to stay active, exercises to improve flexibility, coordination, balance and strength – individualised to tolerance) Pain, disability, global improvement, medication use, satisfaction, general health status (SF-36 subscales	*SMT*: up to 20 visits at practitioner discretion; *Supervised rehabilitative exercise* – 20, one hour sessions *Home exercise* - Four, 45-60 min sessions of instruction	52 weeks	Home exercise alone [Chiro or exercise therapist]	*Pain*: significantly reduced pain in favour of SMT+home exercise in short and long-term; *All other outcome measures*: No significant differences except for global improvement and satisfaction in favour of SMT+home exercise in short and long-term
					Supervised rehabilitative exercise (similar to home exercise but included supplementary exercises individually tailored to each participant and encouragement) + home exercise	*Pain*: significantly in favour of SMT+home exercise in short but not long-term; *All other outcome measures*: no significant differences except duration of medication use in favour of SMT+home exercise in long-term

PT, physiotherapist; *Chiro*, chiropractor

Table 3: Recent randomised clinical trials of spinal manipulation for the treatment of neck pain

In addition to the lack of knowledge regarding dose, the manipulation or mobilisation techniques that are most effective, and in whom, are equally unknown (Dunning et al. 2012; Casanova-Mendez et al. 2014). The lack of an accurate diagnosis beyond the symptom of neck pain is precluding the identification of treatment effects in subgroups. In the systematic review of manipulation for neck pain in 2003 concern was expressed regarding the fact that neck pain was an ill-defined disorder (Ernst 2003); it continues to be.[6]

Another important feature of the SMT evidence base is the difficulty in designing and conducting methodologically sound RCTs for manual therapies. RCTs are the accepted standard for determining treatment effects, making them necessary for the evaluation of the effectiveness of SMT; non-RCT evidence rarely provides data that are sufficiently robust from which to infer treatment causation (Howick et al. 2009). However, RCTs are better suited to evaluating the likes of pharmaceutical (homogeneous) interventions rather than the more complex manual therapy (heterogeneous) encounter (Bolton 2001). While the delivery of a pharmaceutical can be closely controlled (the appearance of the drug e.g. colour and shape, the method of delivery e.g. oral versus intravenous) the delivery of SMT is difficult to control as there are differences in the level of skill and experience between practitioners (Cattrysse et al. 2009) and SMT may not be uniformly delivered by the same practitioner between treatment sessions (Dugailly et al. 2014).

The major weakness when researching manual therapy is the difficulty of blinding. While it is possible to blind the assessor of the primary outcome measure, practitioners cannot be blinded to the therapy they deliver, although they may be blinded as to the clinical status of the recipient and thereby not be influenced by a participant's symptomatic status. The blinding of participants as to whether they are receiving 'real' manipulation is not yet possible due to the lack of a suitable sham, although efforts are being made to develop one (Vernon et al. 2012). Therefore, when the evidence base for SMT is assessed the use of some scales such as the popular Jadad scale, developed to assess the quality of evidence of pain studies, are punishing due to the lack of blinding, despite studies being otherwise methodologically sound (Lundh and Gotzsche 2008).

[6] For Bogduk (2003), that manipulation might differentially affect pain associated with osteoarthritis, spondylosis, increased muscular tone, trigger points or myofascial pain is a "spurious concern" based on the assertion that "no one in clinical practice makes the distinction" (Bogduk 2003). While a recent survey of manual therapy practictioners largely supports this assertion (Carlesso et al. 2014) the lack of diagnostic accuracy is likely to be driving such an apparently uniform therapeutic approach to the treatment of the neck pain symptom. However, the data from the survey support the notion that manipulation is rarely delivered on its own but rather as part of a package of care, the components of which might vary considerably (Carlesso et al. 2014).

Unfortunately, avoidable methodological flaws such as the lack of appropriate concealment of allocation to an intervention or control group also continue to beset the confident interpretation of many studies, and variation between study designs prevents meta-analysis (D'Sylva et al. 2010; Gross et al. 2010; Miller et al. 2010).

Since the evidence base for the treatment of neck pain (with any intervention) remains equivocal (Walker and French 2012) it has been suggested that mobilisation be favoured over manipulation as an intervention for neck pain, at least as a first line manual therapy choice, since mobilisation appears to be equally effective (Miller et al. 2010) and is considered to be associated with a milder side-effects profile (Hurwitz et al. 2002; Leaver et al. 2010; Leaver and Maher 2012). The lack of clear effectiveness superiority has even led some to call for the abandonment of cervical manipulation for neck pain on the grounds of unnecessary risk to the patient (Wand et al. 2012). This is due to the concerns raised regarding the [rare] occurrence of VBA stroke (vertebrobasilar artery dissection) after SMT (Ernst 2002; Gouveia et al. 2009; Ernst 2010). The body of evidence on which these concerns are based (largely, case reports) has been criticized for a lack of adequate reporting (Wynd et al. 2013) which stymies the hypothesis that SMT causes VBA stroke.[7]

Case-control studies are the best study design for examining rare events such as VBA stroke. One case-control study found an association between VBA stroke and the likelihood of having visited a chiropractor within one week, but only in patients under 45 years (Rothwell et al. 2001). A second case-control study found VBA stroke to be independently associated with SMT received within 30 days (Smith et al. 2003). A third case-control (and case-crossover study), in the same population as the two preceding studies, found the incidence of VBA stroke to be the same irrespective of whether patients had consulted a chiropractor or a general practitioner for neck pain. This study concluded that VBA stroke is very rare, and that it was likely that patients were presenting to a healthcare provider with symptoms of an evolving VBA stroke i.e. neck pain (Cassidy et al. 2008). The highest quality prospective research studies have reported no occurrences of stroke in 4,891 treatments administered to 529 patients (Rubinstein et al. 2007) nor 28,109 treatment given to 19,722 patients (Thiel et al. 2007).

[7] A recent systematic review failed to find any epidemiological studies that measured the incidence of cervical SMT and internal carotid artery dissection nor any studies that suggested there was an association between the two (Chung et al. 2014).

Therefore, based on the best available evidence it would appear there is no strong foundation for a causal relationship between cervical manipulation and VBA stroke, rather, patients are seeking care from a chiropractor or other primary healthcare provider for relief of neck pain or headache that results from the VBA stroke (Murphy 2010).

Irrespective of this, while Thiel et al (2007) concluded the risk of serious adverse events from cervical manipulation to be ~0.01%, or low to very low, it is essential that practitioners remain vigilant in trying to identify those patients who are potentially at increased risk of stroke and manage them accordingly, but this is a challenge (Murphy 2010; Rushton et al. 2014). A review of case reports concluded that many adverse events associated with cervical SMT could potentially have been prevented by a sufficiently thorough history-taking and examination, but it was also highlighted that even this may fail to identify a large proportion of patients at risk of an adverse event like VBA dissection (Puentedura et al. 2012b).

While the balance of evidence is in favour of SMT for neck pain, its lack of superiority over alternative treatments and continuing controversy surrounding its safety provides fertile ground for trying to better understand the mechanisms behind its clinical effects. This could lead to better targeting of this therapy towards those expected to benefit, and away from those expected not to.

In the past, the emphasis on the success or otherwise of therapeutic interventions has typically been based on clinician-based outcomes (McCormick et al. 2013). This approach is rooted in the reductionist belief that, for example, the correction of a physical impairment will bring about the improvements desired by the patient, such as pain relief. Such an approach has not always been successful in the treatment of the complex phenomenon of pain which is underscored by the move away from this to the more encompassing biopsychosocial approach (see pages 8-9) to patient management (Gatchel and Theodore 2008). In recognition of the importance of the patient's perspective, patient-reported outcome measures now take prominence in clinical practice and trials. While objective measurable changes in a patient's health status post-intervention might be clearly desirable, the importance given to these changes should ultimately be determined by the patient.

In the literature related to the treatment of neck pain can be found a plethora of outcome measures used with no obvious standardisation (Gross et al. 2009). However there is a core set of outcome measures recommended by international consensus for the evaluation of the treatment of spinal disorders covering the following domains: *pain*, *back [neck] specific function*, *generic health status*, *work disability* and *patient satisfaction (Bombardier 2000)*. The specific outcome measures used in this thesis to address these domains are introduced and discussed in Chapter 8 (pages 164 - 166).

The measurement of cervical spine range of motion, which manual practitioners commonly use to inform the decision to deliver SMT to a patient and evaluate its outcome, is the topic of the next section.

2.7 The measurement of cervical spine motion

2.7.1 Manual examination of the cervical spine

It is established practice in the manual therapy professions to perform a physical examination to assess motion of the spine, typically to identify segments that appear to be restricted. In the literature different labels have been given to such motion restrictions, notably vertebral subluxation complex or joint complex dysfunction (Seaman 1997), spinal 'fixation' (Breen et al. 2002), joint 'hypo-mobility' (Fritz et al. 2007; Deitz et al. 2011) spinal 'stiffness' (Fritz et al. 2011) and "aberrant" motion (Howe 1974; Teyhen 2007). Spinal fixation has also been equated with both joint *hypo-mobility* (Peterson and Bergmann 2011) and joint *immobility* (Hooper 2005). While some definitions are not confined only to the motion of a vertebral pair but include reference to, for example, palpation findings of the surrounding soft tissues, these wider considerations are not required when it is the measurement of the vertebral movements that is of importance. Therefore, for the purposes of this thesis it is the term hypo-mobility that will be used throughout. It is reasonable to allow the term hypo-mobility to encompass immobility since it is questionable whether the two can be distinguished, especially given that the United States Food and Drug Administration considers inter-vertebral motion of up to 5° as effectively immobile for the purpose of evaluating arthrodesis status following spinal fusion surgery, due to the measurement limitations of flexion-extension x-rays (Deitz et al. 2011).

For clarity, spinal stiffness is best considered as distinct from these other entities. Joint hypo-mobility or immobility might be described as the lack of or no motion as perceived from motion palpation (where inter-vertebral motion is palpated while the examiner passively moves the patient) (Breen et al. 2002) or measured, for example, from a flexion-extension x-ray study (Fritz et al. 2005). In contrast stiffness refers more to the resistance to movement, for example as identified by applying downward palpatory pressure to the posterior aspect of a vertebra while a patient lies prone (static palpation) (Abbott et al. 2005; Fritz et al. 2011), or the resistance felt while applying extra pressure ("over-pressure") at the end-range of motion during motion palpation.

Motion palpation is used to assess the passive range of motion of an inter-vertebral motion segment, also classified as PPIVM (passive physiological inter-vertebral movement) while static palpation is said to assess accessory movement of the inter-vertebral motion segment, also termed PAIVM (passive accessory inter-vertebral movements) (Maitland 2005). For the purposes of this thesis the terms hypo-mobility, accessory motion and passive range of motion will be used.

While terminology might vary between the manual therapy professions the literature supports the statement that, for the most part, spinal manipulation is used with the intention of restoring motion to spinal hypo-mobility and thereby reducing symptoms. However, current techniques used by most manual therapy practitioners to identify spinal segments to which SMT should be applied (i.e. palpation) are unreliable and insufficient (Nansel et al. 1989b; Hestbaeck and Leboeuf-Yde 2000; Leboeuf-Yde et al. 2002; Haneline et al. 2008; Haneline and Young 2009). It is uncertain therefore whether this intention is translated into reality; an accurate (please see Glossary for definition, page 284) and reproducible method of measurement is required to determine this.

2.7.2 Reproducibility – agreement and reliability

When measurements are based on observations made by people they are prone to error; thus, reliability and agreement of a measurement method are important to know. The terms 'reliability' and 'agreement' are often used interchangeably but are technically two different concepts (de Vet 1998). Agreement parameters determine whether the same value is achieved if a measurement is performed twice and this estimates the measurement error (de Vet et al. 2006). Reliability coefficients are ratios of variances, and so express how well subjects can be differentiated from each other, despite measurement error. In this case the measurement error is related to the variability between subjects (de Vet et al. 2006).

The term reproducibility is established within the spinal kinematics literature (Madson et al. 1999; Hoving et al. 2005; Cattrysse et al. 2009) and means the degree to which repeated measurements by the same observer or two or more observers produce similar results and can be considered to encompass the concepts of agreement and reliability (de Vet et al. 2006).

2.7.3 Measurement of regional cervical spine motion

The development of computerized motion analysis devices over the last two decades has made it possible to simultaneously quantify, in real-time, coupled (inter-vertebral) motions associated with the primary regional movement (e.g. flexion) (Strimpakos et al. 2005). Most of the spinal research has focused on the lumbar spine. Early extensive work on surface motion in the lumbar spine involving more than 700 subjects by Marras et al. (1999) found that angular velocities in all 3 major planes of motion could distinguish with a high degree of sensitivity and specificity between individuals with LBP and those without (Marras et al. 1999). These authors also found that motion parameters (particularly velocity) could correctly predict patients according to the Quebec Task Force diagnostic classification system (Marras et al. 1995).

There has been a growing body of research on motion-related dysfunction of the cervical spine. Many investigators have concluded that abnormal cervical spine kinematics, measured non-invasively, provide important diagnostic information in the evaluation of patients with neck disorders. Reduced range of regional motion, slow movement, repositioning errors, reduced coordination of movement, and slower peak velocity have all been demonstrated in chronic neck pain patients compared to controls (Feipel et al. 1999; Herzog et al. 2001; Antonaci et al. 2002; Ohberg et al. 2003; Sjolander et al. 2008). Vogt et al. (2007) found that maximal cervical ROM was significantly lower and movement variability significantly higher in chronic neck pain patients compared to healthy age-matched controls (Vogt et al. 2007). More recently, Woodhouse and Vasseljen (2008) noted reductions in “conjunct” or coupled motions, motion contemporaneous in more than one plane that accompany the main (regional) motion in two groups of neck pain patients (Woodhouse and Vasseljen 2008). While these studies have identified what appear to be important motion differences in patients with spinal pain, the measurement methods used provide regional motion data, they do not reveal what is actually happening inside the neck (Bogduk and Mercer 2000).

2.7.4 Regional measurement tools for cervical inter-vertebral motion

There are a number of 3D regional measurement tools for inter-vertebral motion measurement. These include the CA6000 Spine Motion Analyzer, a device that registers motions using high-precision (please see Glossary for definition, page 284) potentiometers, and the Zebris CMS (ultrasonography) system which have both been shown to be reliable and valid and have high accuracy estimates (Mannion and Troke 1999; Malmstrom et al. 2003; Strimpakos et al. 2005; Dvir et al. 2006; Demaille-Wlodyka et al. 2007). Another class of non-invasive instrument is represented by electromagnetic devices such as the Fasttrack 3-Space (Woodhouse and Vasseljen 2008) or Polhemus Liberty (Horodyski et al. 2009). While 3D regional motion systems show some promise as research tools on the group level, it is uncertain if they can be used at the individual patient level (Mieritz et al. 2012) and they cannot assess inter-vertebral motion directly.

2.7.5 Cadaveric studies

The cervical spine has been researched used cadaveric spines, for example by applying external loads to observe where bending moments occur or the amounts of force required to cause tissue damage (Yoganandan et al. 2001). While such experiments have been useful for establishing what might be expected when individual vertebral segments come to be studied in-vivo and how it might best be measured, cadaveric studies are relatively artificial.

The movements of bone and soft tissue without muscles alas does not accurately reflect how intact living individuals move (Bogduk and Mercer 2000). Consequently, inter-vertebral motion needs to be visualised and measured within living subjects with medical imaging techniques.

2.7.6 In vivo dynamic radiographic methods

Direct assessment of inter-vertebral motion allows for a more full exploration of the mechanism of action of SMT, which is directed towards and attempts to affect inter-vertebral function. Although disorders of the cervical spine can affect motion in different geometric planes, abnormalities in sagittal plane motion have been the focus of most research relating to the cervical spine using invasive techniques such as plain film imaging and video-fluoroscopy. This is largely because physiological inter-vertebral motion i.e. that occurring in a living person, does not occur exclusively in these planes. For example, transverse rotation (also called axial rotation) in the cervical spine is "coupled" (Figure 16) with coronal rotation (Bogduk and Mercer 2000).

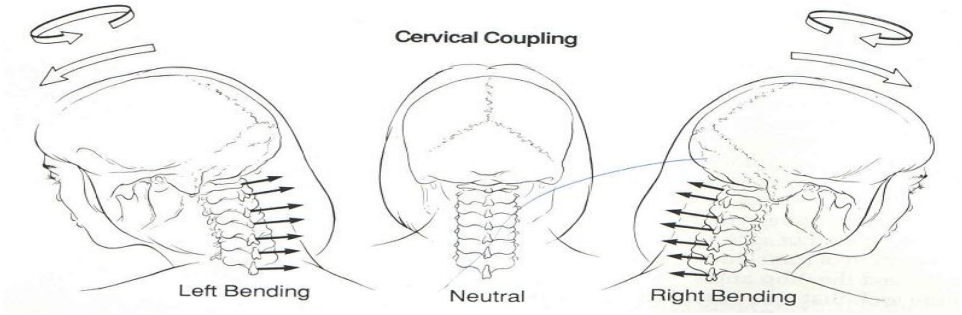


Figure 16: Coupled motion in the cervical spine (White and Panjabi 1990, p.112); Image reproduced with permission from Lippincott

This makes analysis of this motion problematic due to radiographic superimposition of bony structures. Sagittal plane motion is however less susceptible to this problem and for this reason flexion-extension has been more studied in the cervical spine that any other motion (Bogduk and Mercer 2000).

Flexion-extension radiography does not provide real-time dynamic information - such information needs to be extrapolated and calculated from the static images (Figure 7 page 18). Kinetic MRI also suffers from not being able to image continuous motion (McGregor et al. 2001). Radiostereometric analysis (RSA) has been used to provide highly accurate measures of 3D lumbar (Anderst et al. 2008) and cervical (Anderst et al. 2011) inter-vertebral motion. However this technique requires the surgical implantation of tantalum beads into the vertebrae and a large radiation dose which limits the use of this technique to patients undergoing spinal surgery.

Quantitative fluoroscopy (QF), the use of x-rays to produce real-time video images, ameliorates the limitations of these previous methods (Breen et al. 2012). Although cineradiography (precursor to fluoroscopy) of real-time motion has been available for many decades (Fielding 1956; Woesner and Mitts 1972) the analysis of inter-vertebral motion has been mostly qualitative in nature. However, during the last decade progress has been made with quantification of motion variables using QF as higher quality digital imaging systems have become available (Breen et al. 2006; Wong et al. 2006). It is now possible to track lumbar motion variables not only at the end-range of inter-vertebral motion, but continuously throughout a motion (Mellor et al. 2009). Such analysis gives much more information about the quality and sequence of inter-vertebral motion. QF has been found to be accurate and have good repeatability for the lumbar spine (Breen et al. 2006) but has not yet been so studied for the cervical spine, for which it has only recently become available. It is QF that will be employed for the purposes of this thesis.

2.7.7 Inter-vertebral motion kinematic variables from quantitative fluoroscopy

Kinematics concerns the study of motion of rigid bodies, in this case, vertebrae, without regard to the forces involved (White and Panjabi 1990). Kinematic indices used in cadaveric studies have been adapted to the in vivo measurement conditions for analysis with QF. For a number of these indices graphical outputs can be produced as well as numerical data, which allows for visual inspection of the motion parameter as well as statistical analysis. These are further discussed in Part II of this thesis.

Important kinematic indices identified from the literature pertaining to the mechanism of SMT that might be measured with QF include inter-vertebral rotation (hypo-mobility) (Abbott et al. 2006) and IAR (Amevo et al. 1992). While inter-vertebral motion includes both rotation and translation, translation in the cervical spine is very small (White and Panjabi 1990) so it could be difficult to detect changes in this. It is however encompassed by IAR as a parameter of change.

Another parameter that may also be of interest, in terms of differences between people with and without neck pain, is laxity. Laxity is the term given to the increase in the neutral zone as observed in unstable cadaveric motion segments (Panjabi 1992b). The term ‘neutral zone’ refers to that part of the range of motion of a vertebra from the neutral position up to the beginning of some resistance being offered by the joint (White and Panjabi 1990), so measuring this requires flexion and extension to be measured separately from the neutral position (Mellor et al. 2009) (see page 81 for more details regarding the calculation of laxity).

Another parameter that might be explored is motion share, which relates to the contribution each segment makes throughout the motion of a region of the spine. A recent study using QF has identified differences in motion share (proportional inter-vertebral motion pattern variance) between patients with chronic LBP and matched-controls (Mellor et al. 2014). The clinical utility of this observation is uncertain but the findings do provide evidence of the ability to detect mechanical differences between patients and controls with QF.

QF represents an advance over conventional flexion-extension radiography in that kinematic parameters are measured throughout the motion sequence and not just at end-range; thus the true inter-vertebral range of motion (IV-RoM) can be measured which does not necessarily occur segmentally at the end-range of regional spine motion (van Mameren et al. 1990). QF also makes possible the calculation of the average instantaneous axis of rotation (IAR) position across a number of motion-frames, which appears to give more repeatable results than that from end-range radiography (van Mameren et al. 1992). Laxity (attainment rate) can only be measured from continuous motion. Being able to measure both 'true' IV-RoM, IAR and laxity creates the possibility of identifying variables that distinguish patients with neck pain from healthy volunteers, a distinction that has so far eluded previous research efforts.

The approach to QF image acquisition and analysis has been rigorously developed and agreed internationally (Breen et al. 2012). This includes procedures and equipment to reduce the contamination of motion data by, for example, extraneous thoracic motion (see Chapter 3). Therefore it is considered that QF is more repeatable than other IV-RoM measurement methods (An exception to this is RSA; the limitations of this method were discussed on page 54). QF is also associated with half the ionising radiation dose compared to end-range radiography in the cervical spine (0.01mSv *versus* 0.02mSv) (Hart et al. 2010), reducing participants' exposure risk. The development of a QF image acquisition protocol for the cervical spine is described in Chapter 3.

Once differences are found, in order to be able to detect changes in any given parameter in patients with neck pain receiving SMT, changes need to be larger than the MDC to provide confidence that changes are associated with treatment and not simply down to normal intra-subject variation. Finally, any changes will only be of clinical utility if there are correlated with symptomatic and/or functional improvement in patients.

2.8 Conclusion

Neck pain is common and neck pain-related disability is on the increase globally, but identifying the optimum way to manage this problem has been hampered by the inability to accurately diagnose this condition in most cases. Further to that, the mechanisms of commonly applied therapies like spinal manipulative therapy are poorly understood. The availability of quantitative fluoroscopy allows for the first time the ability to measure continuous inter-vertebral motion and therefore test the theory that SMT changes this motion, and that such changes are related to patient-reported outcomes.

To be confident that true changes have taken place in association with SMT requires QF measurements to be accurate and reproducible, and the minimum detectable change in the kinematic parameters of interest need to be known to determine that changes are greater than normal intra-subject variation. These concerns are reflected in the aims, objectives and research questions of this thesis that follow.

2.9 Aims

1. To investigate the accuracy, observer repeatability and intra-subject reproducibility of quantitative fluoroscopy in the measurement of cervical inter-vertebral motion

2. To investigate if any changes in cervical spine inter-vertebral motion in patients with neck pain undergoing spinal manipulation, as measured by quantitative fluoroscopy, are associated with changes in patient-reported outcomes (pain, disability and quality of life)

2.10 Objectives

Primary objective:

1. Determine the relationship between any cervical inter-vertebral kinematic changes as measured by quantitative fluoroscopy, at baseline and after four weeks in patients with neck pain undergoing spinal manipulation, and patient-reported outcomes

Subsidiary objectives:

2. Determine the accuracy and repeatability of quantitative fluoroscopy as a tool for measuring cervical inter-vertebral kinematics
3. Determine any changes in cervical inter-vertebral kinematics as measured by quantitative fluoroscopy in healthy volunteers (intra-subject reproducibility) with no neck pain not undergoing spinal manipulation over a four week period
4. Determine any differences in cervical inter-vertebral kinematics as measured by quantitative fluoroscopy between healthy volunteers with no neck pain not undergoing spinal manipulation and patients with neck pain before they undergo spinal manipulation
5. Determine any differences in cervical inter-vertebral kinematics as measured by quantitative fluoroscopy at baseline and after four weeks in patients with neck pain undergoing spinal manipulation

2.11 Research questions

Q1. What is the accuracy and intra-/inter-observer repeatability of quantitative fluoroscopy in measuring cervical inter-vertebral motion in the sagittal plane during continuous motion?

Q2. Are there differences in cervical inter-vertebral motion between healthy volunteers with no neck pain and patients with neck pain?

Q3. What is the intra-subject variation/reproducibility of cervical inter-vertebral angular range of motion in healthy volunteers with no neck pain between measurement at baseline and four weeks?

Q4. Are there changes in cervical inter-vertebral motion in patients with neck pain after four weeks of spinal manipulation?

Q5. Are any changes in cervical inter-vertebral motion related to short-term patient-reported outcomes?

PART II: Validating the measurement of cervical inter-vertebral motion by quantitative fluoroscopy

"The basis for distinguishing and classifying adjustive [manipulative] procedures should incorporate their measurable characteristics and should not be based solely on therapeutic intention" (Peterson and Bergmann 2011)

Chapter 3. Development of the quantitative fluoroscopy acquisition protocol for measuring cervical spine inter-vertebral motion

3.1 Introduction

Quantitative fluoroscopy (QF) combines fluoroscopy (motion x-rays), using a conventional fluoroscope to image the moving spine, with automated computer-based processing algorithms which track the vertebrae and calculate inter-vertebral kinematic parameters (Breen et al. 2012). QF represents an advance over conventional flexion-extension radiography in that kinematic parameters are measured throughout the motion sequence and not just at end-range; thus the true inter-vertebral range of motion (IV-RoM) can be measured which does not necessarily occur segmentally at the end-range of regional spine motion (van Mameren et al. 1990). QF also makes possible the calculation of the average instantaneous axis of rotation (IAR) position across a number of motion-frames, which appears to give more repeatable results than that from end-range radiography (van Mameren et al. 1992). Finally, QF is associated with half the ionising radiation dose compared to end-range radiography in the cervical spine (0.01mSv *versus* 0.02mSv) (Hart et al. 2010), reducing participants' exposure risk.

QF has been developed independently for the measurement of lumbar spine motion in a number of research centres internationally (Wong et al. 2004; Teyhen et al. 2005; Breen et al. 2006) and a common approach to acquiring and analysing images has been agreed for the lumbar spine (Breen et al. 2012). The QF method developed at the Anglo-European College of Chiropractic (AECC) has been validated for use in the lumbar spine (Breen et al. 2006) and it is that technology that was adopted for the measurement of cervical IV-RoM in this thesis. A protocol did exist for cervical spine image acquisition but had not previously been validated. This study sought therefore to develop the existing QF cervical acquisition protocol for use in the study of patients receiving spinal manipulative therapy and matched healthy volunteers as described in part III of this thesis.

3.2 Methods

3.2.1 Equipment

The QF equipment for image acquisition consisted of a Siemens Arcadis Avantic VC10A digital fluoroscope (CE0123) and a computer-controlled stabilisation and motion-frame manufactured by Atlas Clinical Ltd (declared conformity under MDD93/42/EEC) as shown in Figure 17.

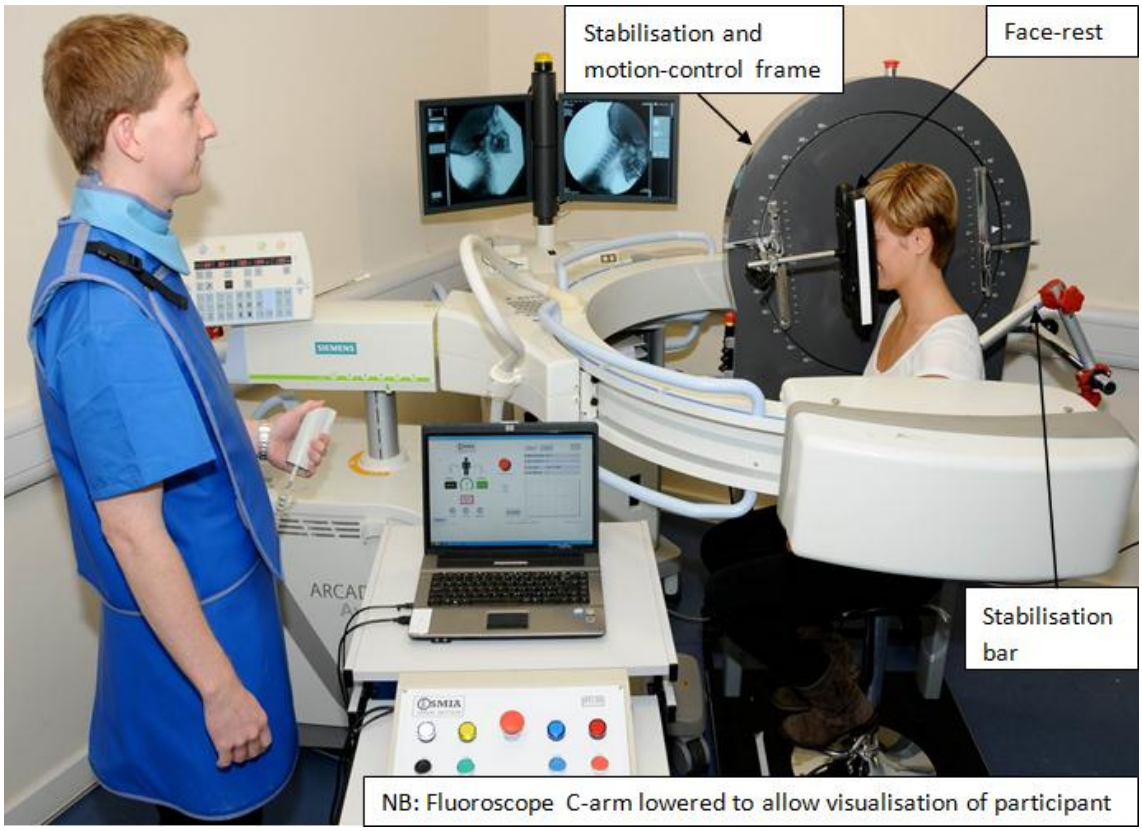


Figure 17: Set-up for cervical spine quantitative fluoroscopy

The motion-frame consisted of a face-rest mounted on a motorised rotating disc attached to a unit that could move vertically up and down (Figure 18). Also attached to the unit were stabilisation bars for limiting the movement of the chest. The computer-controlled motion-frame allowed for the rate and range of the face-rest to be set and thus control the velocity of participants' cervical spine motion. The rate was set at 3° per second[8]. As it moved the angular range of the face-rest was recorded by the computer in real time. As an addition to the existing equipment, measuring tape was positioned on various parts of the motion-frame in order to replicate equipment positioning for follow-up acquisitions.

[8] The rate of motion was based on international consensus concerning the measurement of spine motion with QF (Breen et al. 2012). This is to avoid image blurring which would prevent accurate vertebral tracking and to promote patient comfort.

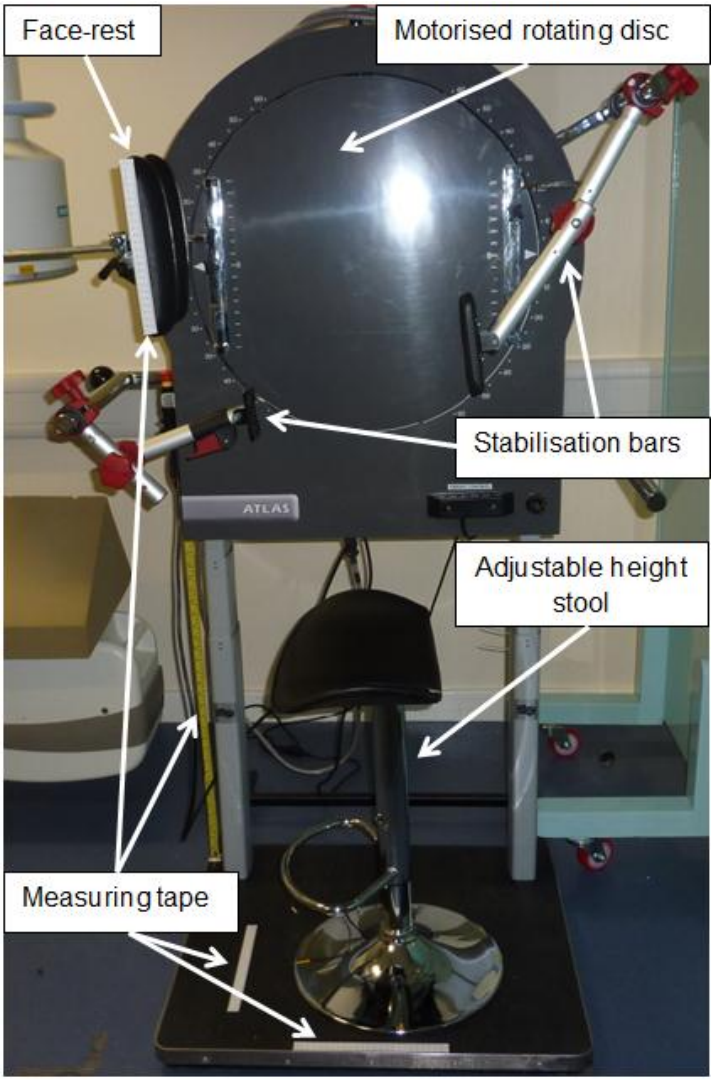


Figure 18: Stabilisation and motion-frame

Participants' cervical spine regional ROM was measured with the CROM (cervical range of motion instrument, Performance Attainment Associates), an instrument worn on the head consisting of three gravity inclinometers (Figure 19). This device was readily available and three systematic reviews of spinal measurement devices have concluded the CROM is a reliable and valid instrument (Jordan 2000; de Koning et al. 2008; Williams et al. 2010). The purpose of this measurement was to avoid injury due to motion beyond the capable or comfortable range as the participant was guided by the face-rest (Hipp and Wharton 2008).

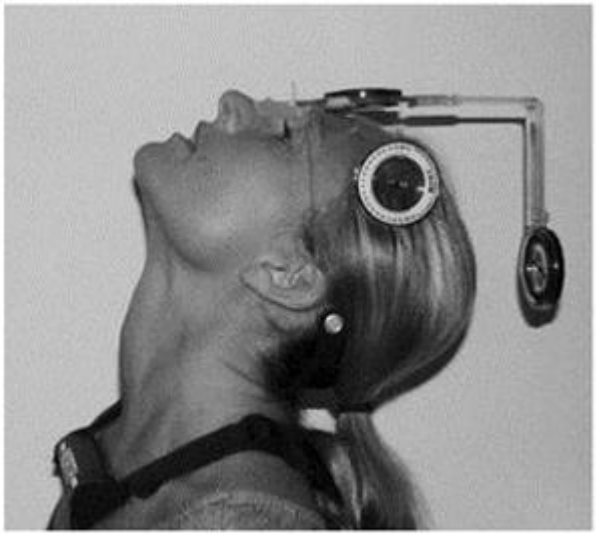


Figure 19: CROM goniometer (Performance Attainment Associates, Roseville, MN) (Reynolds et al. 2009); Image reproduced with permission from Springer Publishing Company

3.2.2 Ethical considerations

The study sample was a subgroup of four healthy participants recruited to the main study (Chapters 6 – 8) and the ethical considerations and approval for this are presented on page 131. In summary, ethical considerations are detailed in participant information sheets (Appendix 11 and Appendix 12) and ethical approval was granted by the National Research Ethics Service Committee South West – Cornwall & Plymouth (11/SW/0072 – Appendix 13).

3.2.3 Procedure

The QF image acquisition procedure was modified from a pre-existing protocol. Both of these are shown in Figure 20 (page 67), and the following describes the modified protocol in more detail. This modified protocol was developed with the kind assistance of four healthy volunteer participants.

• Participant positioning

Reproducible participant positioning is important for obtaining accurate and consistent kinematic data for reliable comparison within and between individuals. Participants were positioned such that they were sitting with the cervical spine in ‘neutral’ (the mid-point between end-range flexion and extension).

This was achieved by sitting the participant with feet flat, hips and knees flexed at roughly 90°, lumbar spine in lordosis (concave), thoracic spine in kyphosis (convex) and cervical spine in lordosis (concave) in what appeared to be neutral to the observer, and what 'felt' neutral to the subject who was looking straight ahead with gaze parallel to the floor. Once seated a lead apron was placed over the participant's lap for gonad protection from ionising radiation.

The C-arm of the fluoroscope was positioned at 90° to participants with the image intensifier approximating a participant's left shoulder (the one furthest from the motion-frame) with the x-ray tube side of the C-arm behind the motion-frame. Positioning the image intensifier close to the patient reduced image magnification, helping to minimise the ionising radiation dose and achieved a sharper image for algorithm tracking of the vertebrae.

Very low dose images (fluoro-grabs) were then acquired to line up the centre of the rotating disc of the motion-frame at the level of the C3/4 inter-vertebral disc. (This is achieved with use of a metal rod suspended behind the rotating disc, the end of which is at the centre of the disc. The rod is removed once correct positioning is achieved).Two bars attached to the motion-frame were then extended to approximate the participant, one against the chest and one against the back around the level of T2 to help maintain correct body position and limit movements to that of the cervical spine only (Figure 18). Participants were instructed to relax their shoulders and position their arms behind their backs with hands together and fingers interlinked to help keep the shoulders drawn down and out of the radiographic field of view.

• **Cervical spine positioning**

In order to position the cervical spine in neutral, participants were instructed to protract then retract the chin as far as possible then to 'feel' for the middle position between these two extremes. A similar approach is used when teaching patients how to place their pelvis and lumbar spine in neutral (Liebenson 1998). The resting angle of the participant's head relative to their chest (~0°), as determined using the CROM goniometer (Figure 19), is documented for reproducing this posture at follow-up. It is only once the cervical spine is positioned in neutral that the face-rest is positioned comfortably against a participant's face.

To avoid facial soft tissues being deformed by the face-rest hence making the positioning more variable, bony contact was made. The face-rest was positioned by first positioning the rotating disc of the motion-frame half the distance of the participant's range in the opposite direction e.g. if a participant could flex 50° the disc was rotated 25° superiorly from horizontal (for extension, it would be rotated 25° inferiorly). From this position the face-rest was comfortably positioned on the forehead (flexion) or maxillae (extension). Participants were instructed to remain still while the face-rest was re-positioned between flexion and extension motion sequences.

• **Measurement of regional cervical spine (neck) range of motion**

Prior to measurement participants were instructed to warm-up with five neck flexion-extension repetitions (Tousignant et al. 2001).[9] The participant's cervical spine range of motion was measured with the CROM once their chest had been immobilised to reduce extraneous motion from the thoracic spine. Instructions were given to flex then extend the neck as far as possible, despite any pain.

[9] Warm-up before QF image acquisition has since been recommended by international consensus (Breen et al. 2012).

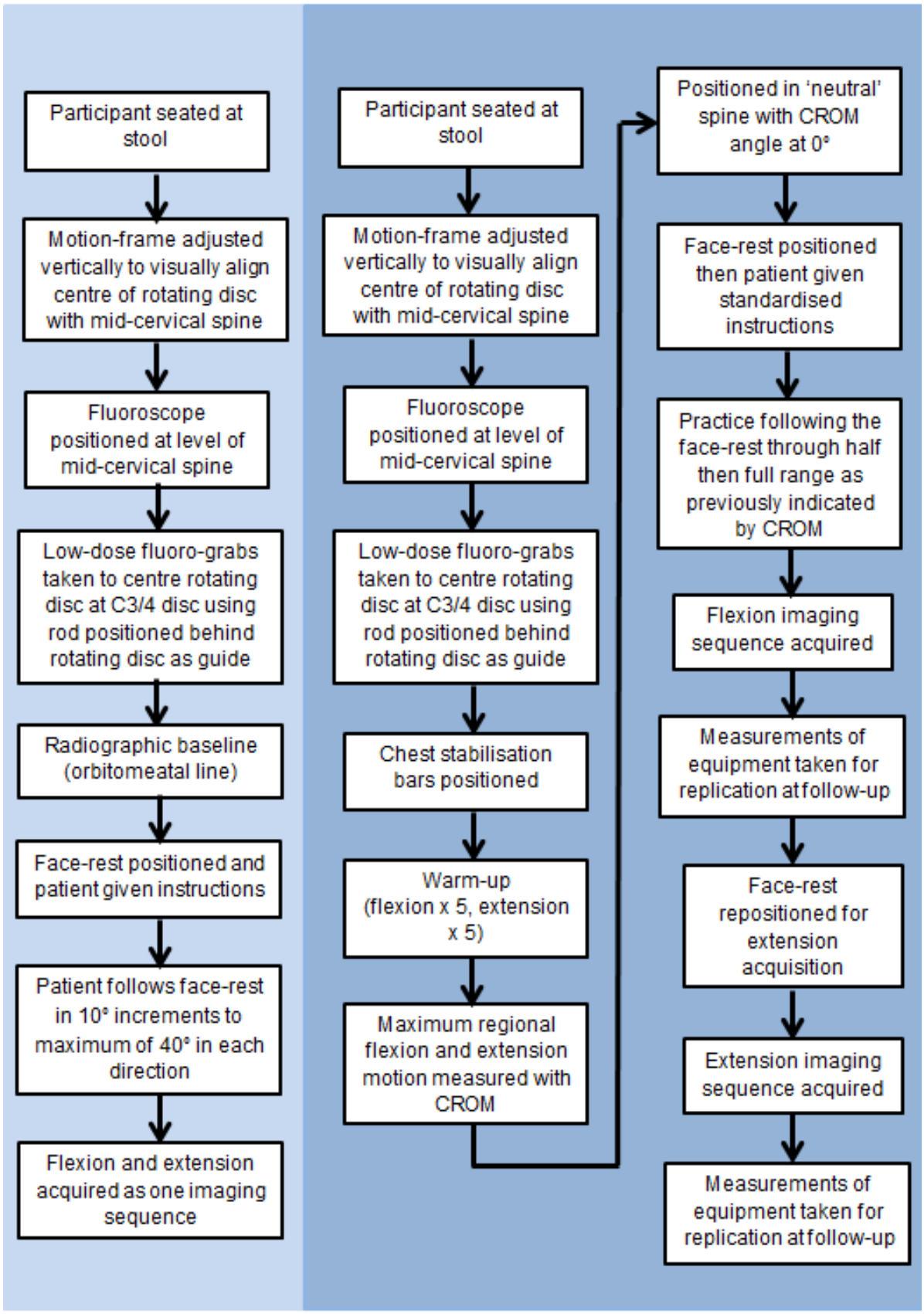


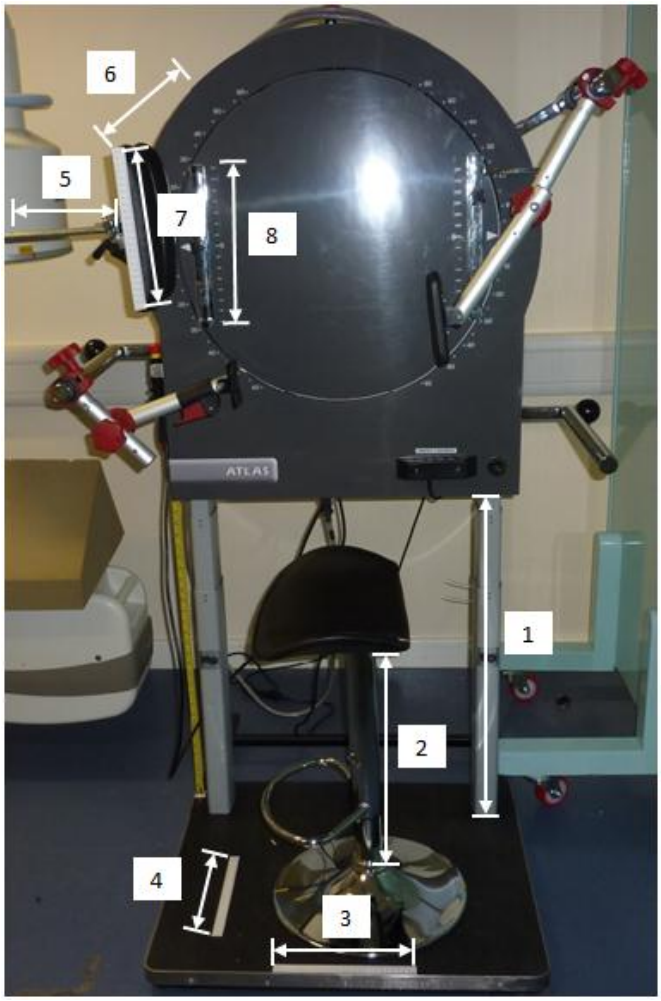
Figure 20: QF image acquisition protocol before and after modification

• Standardised instructions

Participants were instructed to follow the movement of the face-rest and not to tuck in the chin until the end of flexion, and not to lift the chin until the end of extension. This was practiced first during warm-up and with the measurement of regional cervical spine motion, then with practice following the motion of the face-rest. Participants were invited to follow the face-rest through half of the range they were capable of, then the full range. More practice was offered if required until the movements were performed correctly, prior to imaging. Data collection was achieved with the cervical motion-frame and fluoroscope operating simultaneously.

• Replicating positioning at follow-up imaging

To try and ensure that participant positioning was replicated at follow-up, measurements of the various parts of the positioning apparatus were recorded at baseline so that the configuration could be faithfully replicated. The measurements made are indicated in Figure 21.



Key to figure:

1. Height of motion frame
2. Height of stool
3. Position of stool base
4. Position of stool base
5. Horizontal distance of face-rest
6. Distance from motion-frame to face-rest
7. Position of participant's face on face-rest
8. Height of face-rest

Figure 21: Stabilisation and motion-frame with aspects that are measured indicated

3.2.4 Image analysis

• Automated tracking of cervical vertebrae

A QF investigation of the cervical spine produces around 300 images for each motion sequence of flexion and extension. The images are first processed using graphical user interfaces within Matlab (R2007b software, Mathworks Ltd) to enhance the edges of the vertebrae and improve automatic tracking by user-defined algorithmic templates. To analyse data from the fluoroscopic sequences tracking templates (Figure 22), and reference templates (Figure 23), were manually drawn around each individual vertebra in the first image in the sequence. Each template was individually placed five times and the results averaged to reduce operator error and increase repeatability.

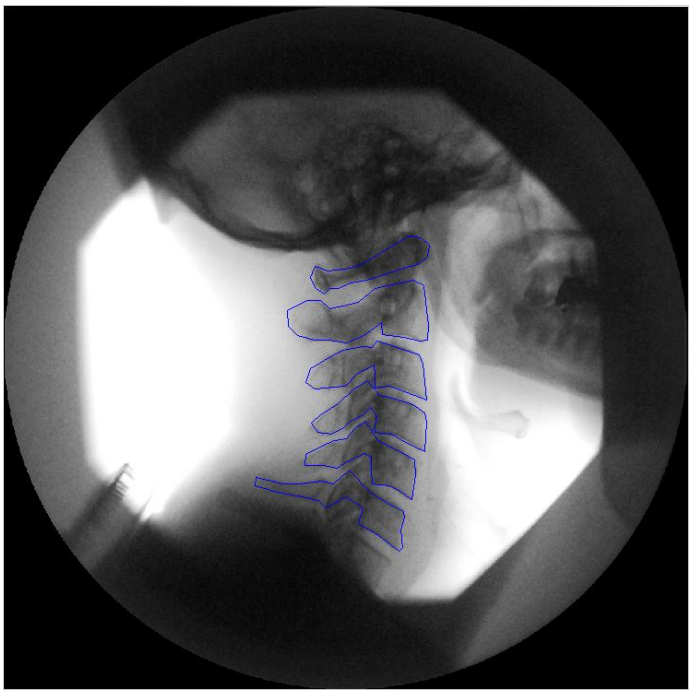


Figure 22: Tracking templates positioned on the first image from a fluoroscopic sequence

The tracking templates were drawn on the cortical margins of each vertebra (Figure 22). These are registered from frame-to-frame automatically throughout the sequence of images using cross-correlations and a rolling average over each two images to reduce noise (Breen et al. 2012). It is from the positions of the tracking templates that angular rotation data are obtained.

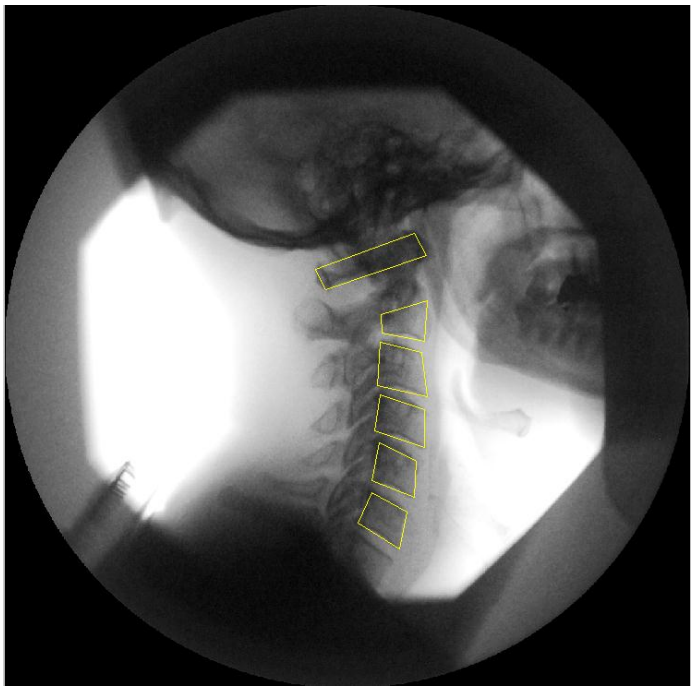


Figure 23: Reference templates positioned on the first image from a fluoroscopic sequence

Reference templates are four point templates which mark the four corners of the vertebral bodies (C3 – 6). Modified shapes are required for the irregular C1 and C2 (Figure 23). These templates are linked to the tracking templates as coordinates in order to verify tracking and to provide data for the calculation of translation, disc height and IAR (Breen et al. 2012).

• Measurement of C1/2 through C5/6 motion

The vertebrae of the upper cervical spine (C1 and C2) and the occipital bone of the skull (C0) are differently shaped from the more regular vertebrae of the middle and lower cervical spine (C2-T1). These differences present a challenge for automated tracking. The tracking algorithms incorporate distortion-compensated Roentgen analysis (Frobin et al. 2002) which is considered to be a precise protocol for registering vertebral positions (Leivseth et al. 2006) and is adopted in other fluoroscopy methods of inter-vertebral measurement (Teyhen et al. 2005; Wu et al. 2007).

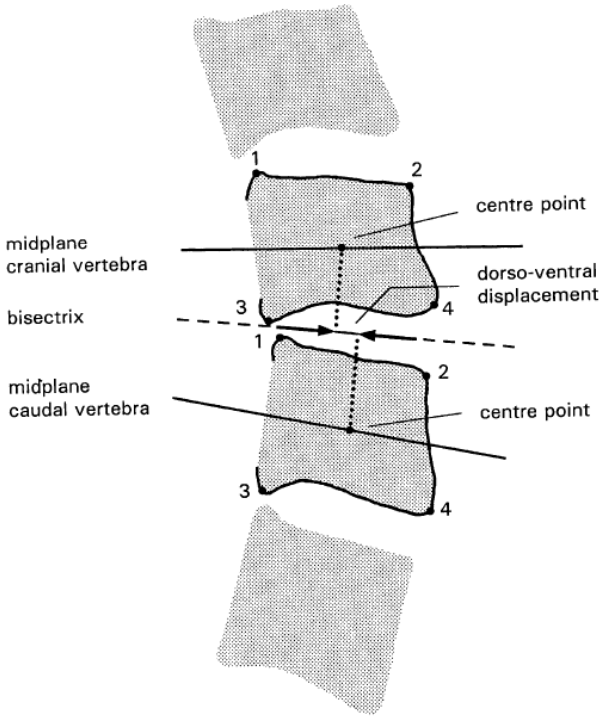


Figure 24: Definition of angle and displacement for motion segments C3/4 – C6/7 (Frobin et al. 2002); Image reproduced with permission from Elsevier

From the four-point tracking templates (Figure 23) are calculated mid-plane lines, as depicted above in Figure 24. The change in angle between pairs of lines allows calculation of the angular range between two adjacent vertebrae, from C3 to C7.

Because of the asymmetrical shape of the vertebral body of C2, it is not possible to consistently identify the same four corners on C2 for the drawing of a template meaning measurements between mid-lines are not repeatable in this case; instead the two inferior corners only, as shown in Figure 25 (corners 3 and 4 of C2) are registered. The remaining sides of the trapezoid reference template (Figure 23) for C2 are superfluous from the standpoint of C1/2 or C2/3 angular range but are useful when visually verifying faithful tracking. The C2/3 angular range is calculated as that between the mid-line of C3 and a line along the inferior border of C2 that joins the two inferior corners of the body of C2 (Frobin et al. 2002).

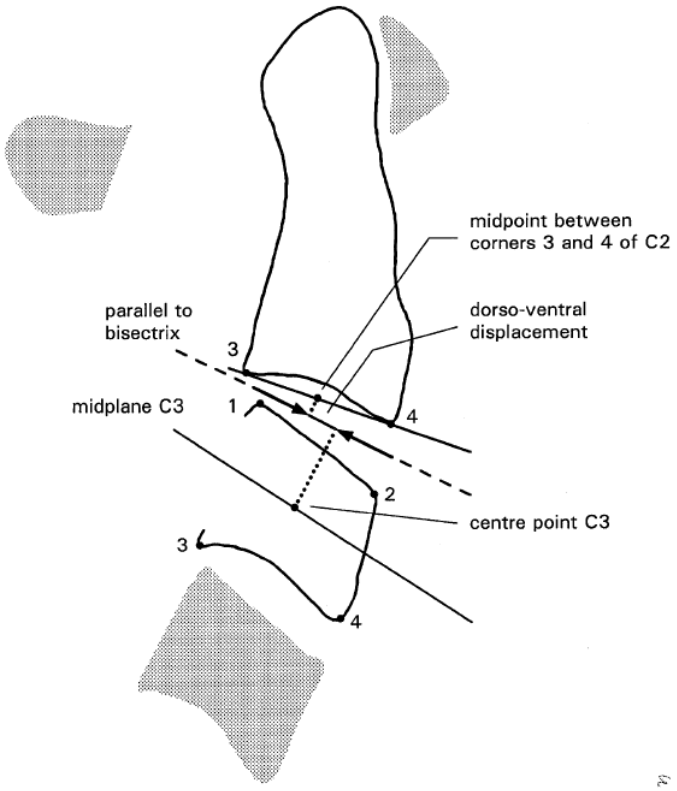


Figure 25: Definition of angle and displacement for segment C2/3 (Frobin et al. 2002); Image reproduced with permission from Elsevier

The mid-point line for C1 is that of a line bisecting the marrow cavities of the anterior and posterior arches (Figure 26). This line is calculated as the mid-line of a rectangular reference template whose four corners are formed at the superior and inferior aspects of the anterior and posterior tubercles (Figure 23). The angular range between C1 and C2 is then calculated as that range exhibited between the mid-point line of C1 and the line through the two inferior corners of C2 (Frobin et al. 2002).

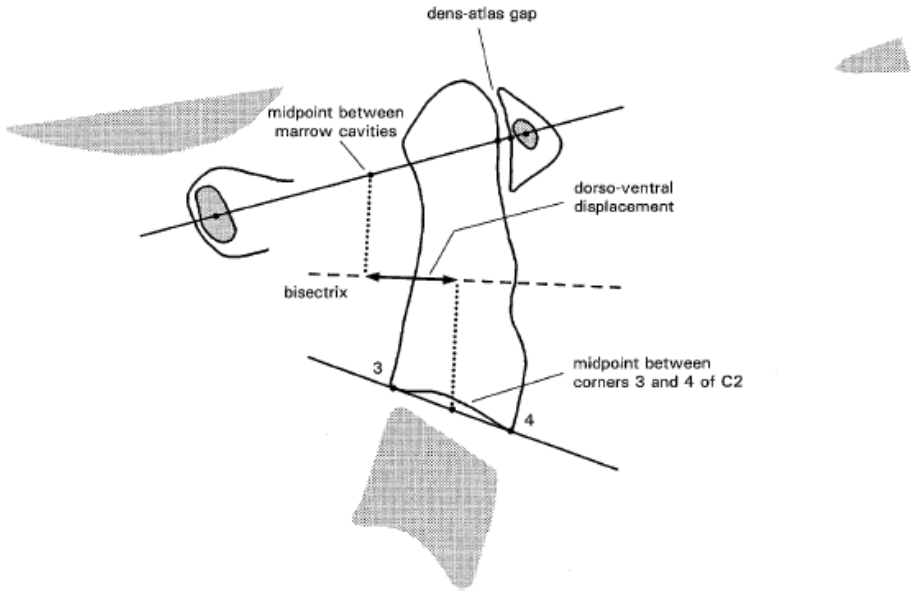


Figure 26: Definition of angle and displacement for segment C1/2
(Frobin et al. 2002); Image reproduced with permission from Elsevier

For C0/1 the range is calculated as the angular displacement between the mid-point line of C1 and the McGregor radiographic line, which is the tangent from the posterior rim of the palatum durum to the contour of the occiput (Figure 27).

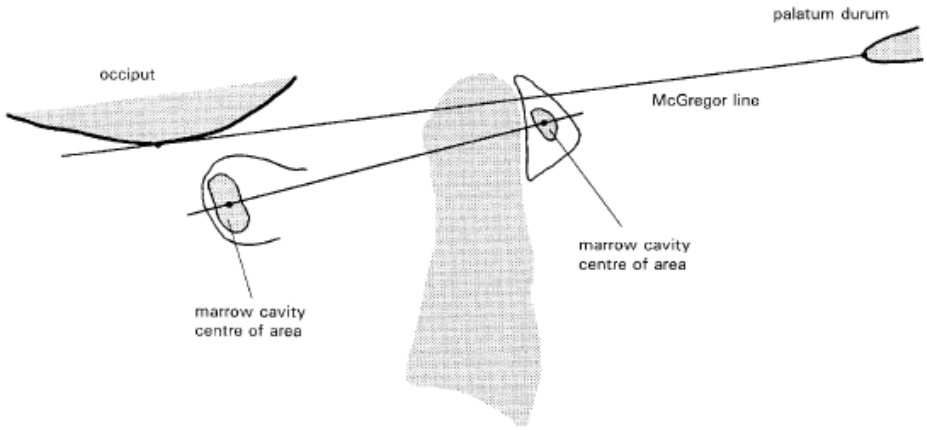


Figure 27: Definition of the angle for the segment C0/1
(Frobin et al. 2002); Image reproduced with permission from Elsevier

• Data quality assurance procedure

The tracking codes include algorithms for frame-to-frame positional registration that automatically calculate the co-ordinates of each vertebral body in each subsequent image and produce a graphical output of *vertebral* rotation (Figure 28).

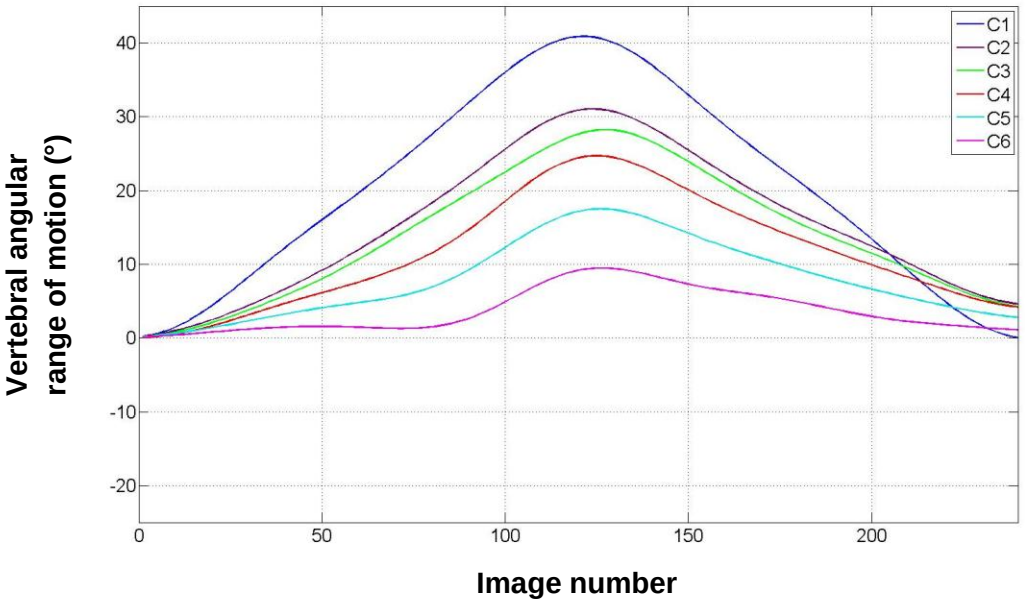


Figure 28: QF graphical output showing individual vertebral (flexion) angular range of motion

Subtracting adjacent vertebral graphs allows the visualisation of *inter-vertebral* rotation over time. Every possible combination of the five individual co-ordinates (from the five templates) results in 25 data points per frame, from which the mean is calculated. Both the mean and 25 data points (scatter) are depicted graphically to ascertain the degree of error in the measurement i.e. agreement between each template (Figure 29).

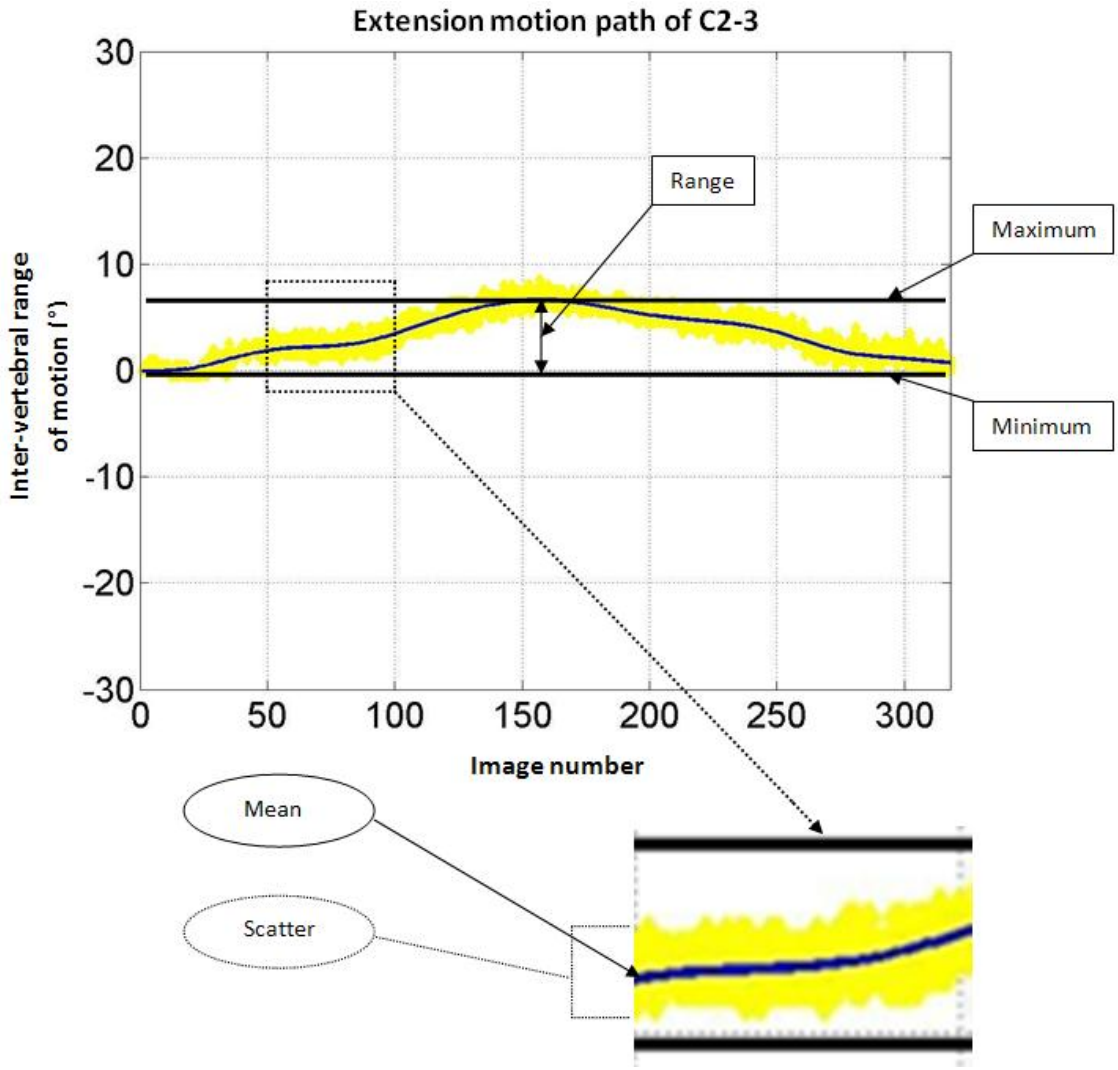


Figure 29: A QF inter-vertebral motion graph for one inter-vertebral level showing maximum angular range limits and scatter

The accuracy of these results is verified by visually checking video playback of the templates (algorithms) tracking the vertebrae through the sequence. If all five individually placed templates do not follow the vertebrae then data for that inter-vertebral level are discarded. The kinematic data is obtained once the quality assurance procedures for checking the veracity of the results are completed. This ability to identify error in the analysis and correct it is considered one of the important advances brought about by computerised methods (Hipp and Wharton 2008).

3.3 Discussion

It was necessary to make changes to the pre-existing QF imaging protocol for the purposes of this thesis and the differences between the two protocols were presented in Figure 20. The reasoning behind these changes, and alterations that were made based on feedback from early participants, are discussed below.

• Positioning and warm-up

Being a mobile structure the positioning of the cervical spine in 'neutral' is challenging but must be defined and standardised, since it is known that head position at 'neutral' influences subsequent cervical motion. If the chin is retracted this causes lower cervical extension and upper cervical flexion, while protraction causes lower cervical flexion and upper cervical extension (Ordway et al. 1999). This initial starting posture subsequently changes the kinematic behaviour of the cervical spine; for example, the extension angle of segmental sagittal rotation at C1-2 is significantly larger if the subject's chin is initially protracted compared to being initially retracted or in a more neutral position (Takasaki et al. 2011). 'Neutral' cervical spine need not be absolutely identical between participants but must be as similar as possible between measuring sessions in the *same participant*.

The orbitomeatal line (radiographic baseline as used in pre-existing protocol), which lines up the outer canthus of the eye and the centre of the external auditory meatus, was found to be inappropriate for positioning as this pre-flexed the cervical spine. The infraorbitomeatal line (a line that connects the infra-orbital margin and the external auditory meatus) was found to be a useful visual guide and setting 0° on the sagittal plane goniometer of the CROM as indicative of 'neutral' was found to be easily repeatable.

Positioning the face-rest in one position over the forehead for flexion and extension was found to compress the neck in those who had a large (>40°) extension range. To avoid this it was found optimal to position the face-rest on a participants' forehead for flexion whereas extension comfort was best when the face-rest was positioned over the maxillae, as previously described. While this change was essential it did necessitate participants remaining still while the face-rest was repositioned thus introducing a potential source of variability regarding the start position between the two motion sequences. It is crucial that participants follow the instructions to avoid extraneous variability (Hipp and Wharton 2008).

Some, but not all, studies of cervical spinal motion ask participants to warm-up or practice the movement prior to measurement (Jordan 2000).A warm-up routine is intended to increase the compliance of the soft tissues in much the same as warm-up prior to exercise of any sort and was introduced into the acquisition protocol to reduce measurement variability. This was also an opportunity to start instructing patients on the movements and meant that guiding patients through 10° increments with the face-rest as with the pre-existing protocol (Figure 20) was no longer required.

• Timing of the CROM measurement

One early participant reported that his neck motion felt reduced after the two stabilisation bars were positioned to limit chest motion, suggesting extraneous thoracic motion when freely bending his neck prior to this. As a result it became the protocol to do the CROM measurement after chest immobilisation and not before.

• Follow-up positioning

At follow-up it is essential that participants are positioned identically as they were for baseline imaging so that any changes in inter-vertebral motion are not simply attributable to changes in positioning (Takasaki et al. 2011). This is especially important for Part III of this thesis in order to be able to associate any changes of inter-vertebral motion in patients to manipulation. For this purpose it is *intra*-subject variation (the stability of measurements *within* an individual) that is paramount rather than *inter*-subject variation (measurements *between* individuals, expected and unavoidable) *per se*. To do this, measurements were made of the positioning apparatus and motion-frame (Figure 21). However, the following two measurements were redundant and not recorded. It was found that the height of the stool, if kept in the lowest position, was adequate for all participants. Secondly, aligning a particular landmark of a participant's face on the face-rest was not precise and it was realised it was not necessary assuming all other measurements and positioning were faithfully repeated.

• Standardising time of day for measurement

Measurements taken in the morning in the same person might be different in the afternoon for reasons other than the measurement instrument (Jordan 2000), hence the standardisation of measurement timing. This is especially important for studies that include follow-up imaging as in Part III of this thesis. The mechanical behaviour of the spine is known to exhibit diurnal variation with regard to the fluid content of the inter-vertebral discs (Adams et al. 1990).

During sleep the loading on the spine is reduced allowing the discs to swell as the water content increases and this absorbed fluid is then expelled during the day when the loading of the spine is increased (Adams et al. 1990). Consequently the height of the discs is greatest in the morning and least at night, which is largely responsible for the gradual loss of human stature observed over the course of a day (Botsford et al. 1994). A change in form is likely to cause a change in function and indeed Adams et al (1987) found that lumbar spine motion measured in 21 asymptomatic subjects using electronic inclinometers increased by an average of 5° in the afternoon compared to the morning measurement (Adams et al. 1987). It is noted, however, that the paper makes no mention of measurement error or whether this was taken into account.

Cervical spine inter-vertebral motion is considered to exhibit diurnal variation (Bogduk and Mercer 2000) although this was concluded from the results of the small sample study by Van Mameren et al (1990) which appears not to have standardised the time of day for repeated measurement (van Mameren et al. 1990). In a study using the CROM goniometer (Figure 19), healthy subjects' regional cervical spine motion was measured twice 48 hours apart at the same 'time period'; in the morning, afternoon or early evening (Audette et al. 2010). The findings from that study suggest that regional cervical spine motion measured during the same time period on different days with the CROM goniometer is reproducible.

• Measurement of sagittal plane motion

Sagittal plane motion is the motion of interest in this study. Flexion-extension motion is commonly studied as one continuous movement, from the extreme of flexion to the extreme of extension and vice-versa (van Mameren et al. 1990) as it was in the pre-existing QF imaging protocol. For calculating overall angular range this approach is appropriate but it does not allow for analysis of flexion and extension motion separately as it is difficult to determine where flexion ends and extension starts (and vice-versa). For this study it was decided to measure flexion and extension separately. This is firstly because it is typical for health professionals who use manipulation to assess these movements separately; therefore ascribing changes in inter-vertebral motion in association with manipulation to either of these movements is therefore more practically relevant. Secondly, this allows for analysis of laxity/attainment rate which requires imaging to begin with the spine in neutral (Mellor et al. 2009; Breen et al. 2012). Finally, this reduces the risk of out-of-plane motion or motion going outwith the radiographic field of view which would preclude tracking of the affected vertebrae.

• Range of voluntary motion

The range of regional cervical spine motion required from participants is that which is maximally achievable at that time by that individual, and so is expected to vary between participants. This is in order to make it more likely that the vertebrae have all rotated through their maximum range which is important in order to more confidently identify inter-vertebral hypo-mobility. The range of flexion-extension allowed by the motion arc of the motion-frame is 120° which is considered sufficient to allow full range of movement for the majority of participants. In a cineradiography study the total sagittal cervical spine range of motion in young asymptomatic adults was on average 118.1° (range 93.8-133.7°) when measured from end-range flexion to end-range extension, or 114.3° (range 97.3-133.0°) when measured from end-range extension to end-range flexion (van Mameren et al. 1990). This range decreases with age (Simpson et al. 2008).

The influence of motor control, Panjabi's neural subsystem of spinal stabilisation (Panjabi 1992a), is controlled for to some extent as the rate of cervical spine motion is itself standardised (by the speed of the face rest) between subjects and measurement sessions. Since the movement is ultimately voluntary however, the influence of the active subsystem of spinal stability (muscles), the passive subsystem (vertebrae, discs, ligaments) and, to a lesser extent, the neural subsystem (motor control) cannot be fully disaggregated (Panjabi 1992a). In other words, if hypo-mobile segments are present this could be as the result of derangement of any combination of these subsystems for example, muscle spasm (active), fibrous facet capsules (passive) or adaptation (motor control). Conceivably all three could be present, but this does not detract from the primary purpose of this research - to identify segmental hypo-mobility and any change in inter-vertebral motion post-manipulation, irrespective of the underlying derangement (see Part III).

• Duration of procedure

With two operators, one to operate the fluoroscope, the other to operate the motion-frame, the process of obtaining images from one participant took on average 45 minutes. At follow-up, since measurements had been made at baseline, this was reduced to around 30 minutes. This amount of time appeared to be acceptable to participants, as was the acquisition procedure in general.

• Streamlining the image analysis procedure

In order to streamline the image analysis procedure, and to identify which components of the cervical morphology contributed the most information towards tracking, different shapes of tracking template were attempted. Templates were drawn to include either anterior (vertebral bodies) posterior (spinous processes) or middle (posterior vertebral body, pedicles and laminae) vertebral architecture. [For C1 templates either encompassed the anterior or posterior arches]. This approach is similar to that used in a different video-fluoroscopic method for tracking cervical vertebrae (Reinartz et al. 2009). In general these templates did not track as consistently (and therefore not time-saving) as templates that included all of the visible vertebral architecture (Figure 22). However such templates are potentially useful for tracking where motion is out-of-plane at some point in the motion sequence. This typically leads to tracking failure at that point when the greyscale contrast between the vertebra and the background changes, but might be remedied by templates drawn to include only components of the vertebrae that maintain their contrast through the remainder of the motion sequence.

This early feasibility work revealed that due to radiographic superimposition of the shoulder complex, C7 was often not sufficiently visible for tracking throughout the motion sequence. So that the inter-vertebral levels from which data are collected is consistent between participants it was decided not to pursue tracking of C7 and therefore of C6/7 motion. Another research group has encountered similar difficulties visualising C7 and likewise did not pursue tracking it (Reinartz et al. 2009). Preparatory work with a computer programmer identified that accurate tracking of C0 was difficult due to poor adherence of the tracking templates. Correcting this would necessitate time and resources not available to the project, so it was no longer attempted to track C0/1.

In the literature review a number of kinematic variables were identified as being of interest regarding the mechanism of SMT (section 2.7.7). The calculation of these by QF is discussed below.

• Angular range, hypo-mobility, paradoxical motion

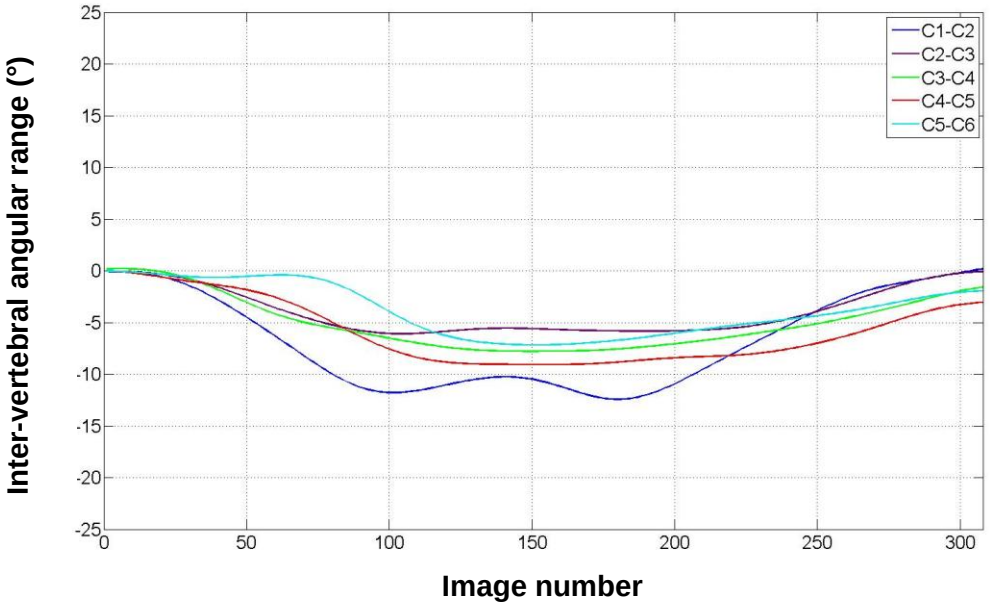


Figure 30: A QF graph of inter-vertebral (flexion) motion

Above is an example of the graphical output for segments C1/2 through C5/6 for one motion sequence, in this case flexion, from one participant (Figure 30). This graph shows that paradoxical motion, as exhibited by C1/2 (dark blue), can be readily visualised. Hypo-mobility may be recognised visually if there is almost no motion at an inter-vertebral level. Alternatively hypo-mobility cut-offs may also be calculated as motion at or below the 2.5th percentile for a given inter-vertebral level as derived from normative cervical inter-vertebral kinematic information such as that obtained from healthy volunteers.

An advantage of obtaining continuous rotational data from QF, as opposed to plain-film flexion-extension studies, is that measurement of inter-vertebral maximum range is possible wherever it is obtained during neck motion. Also, as shown in Figure 31, maximum rotation of a given segment is not always coincident with maximum neck bending nor with the maximum of other inter-vertebral levels.[10] Thus true inter-vertebral range is measured and not that derived from vertebral positions at end-range of neck bending.

[10] As observed in the cineradiography study by van Mameren and colleagues (van Mameren et al. 1990).

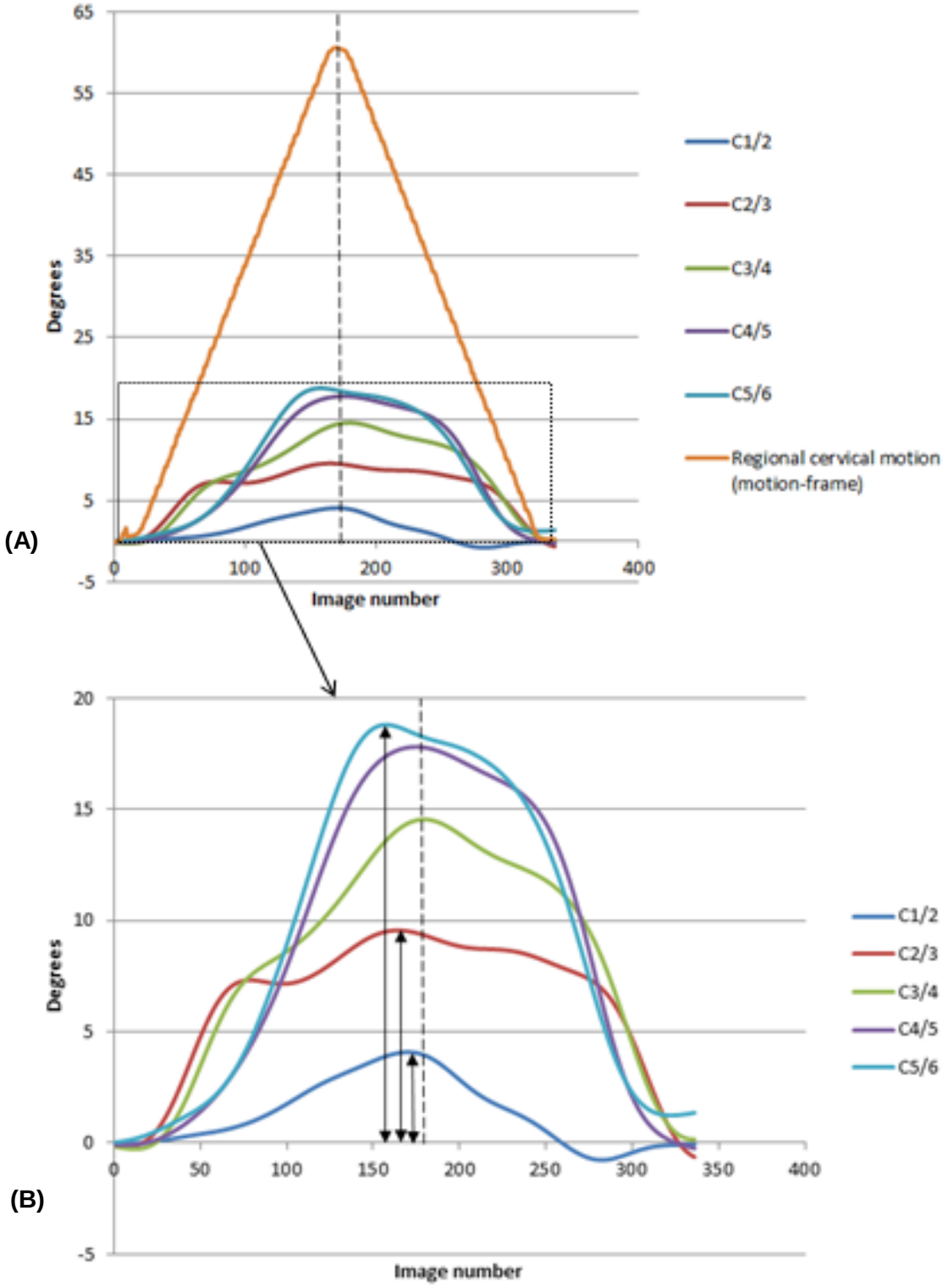


Figure 31: C1/2 through C5/6 inter-vertebral (extension) motion for one participant shown with regional cervical motion (A) and expanded (B) to show maximum IV-RoM is not necessarily coincident with maximum regional motion (dotted line)

• Instantaneous axis of rotation

IAR[11] (see section 2.5.2) positional data can be calculated between any two template positions, but the smaller the inter-vertebral range of motion the greater the measuring error associated with the calculation; conversely the more a motion segment rotates and translates the more data are available for IAR calculation. 7° rotation was the minimum set by Van Mameren and colleagues to minimise error (van Mameren et al. 1992). [Since many cervical segments do not rotate by this minimum amount in flexion or extension, so limiting data collection, ranges below 7° were explored in the observer repeatability studies (see Chapter 5)].

For segments that rotate the minimum required, IAR positions are determined between the first frame of the imaging sequence and the image frame where angular rotation is at its maximum ±0.5°. The inclusion of 0.5° either side of the maximum angular range is included as this is the increment through which the tracking templates rotate when calculating vertebral body position within each image. The average IAR position found in all subsequent frame-pairs is then calculated. Averaging IAR position across a number of frames has been found to be more reproducible than IARs calculated only from the two frames from the extremes of neck flexion and extension bending (van Mameren et al. 1992). IARs locations are expressed as x, y co-ordinate distances (proportion of vertebral body depth) from the posterior inferior corner of the inferior vertebra of a motion segment (Figure 32).

[11] Translation in the cervical spine is very small (White and Panjabi 1990) therefore detecting changes above measurement error was expected to limit its utility as a kinematic parameter of change so translation was not measured in this study. However, IAR incorporates translation.

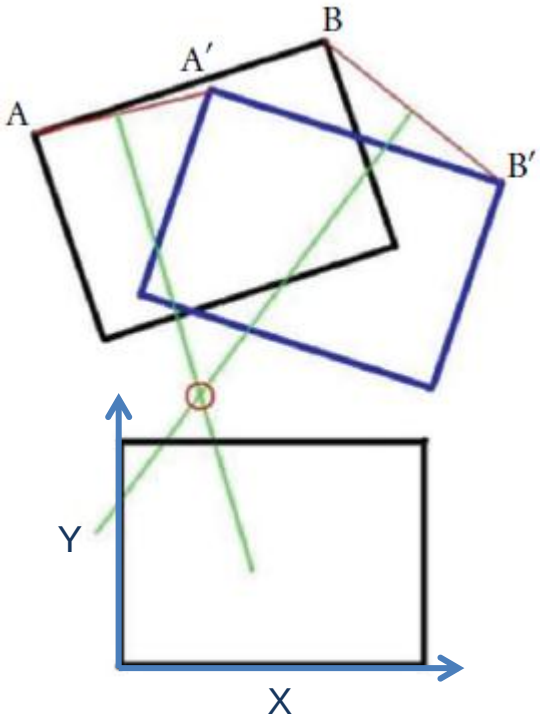


Figure 32: Block diagram illustrating the determination of IAR location

They can be displayed on the fluoroscope imaging sequence (Figure 33), graphically (Figure 34), or numerically.

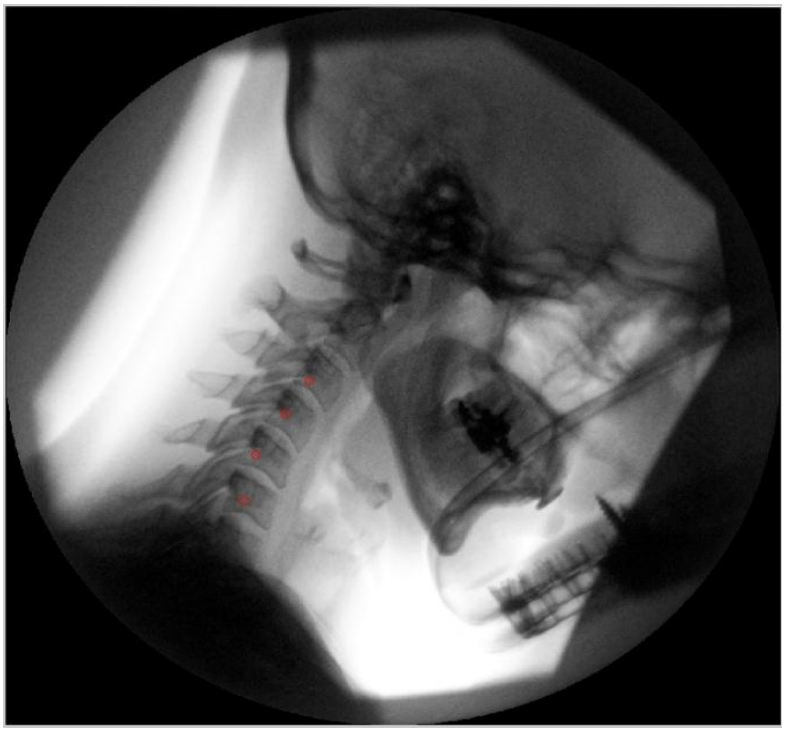


Figure 33: IARs displayed on fluoroscopic image of cervical spine in flexion

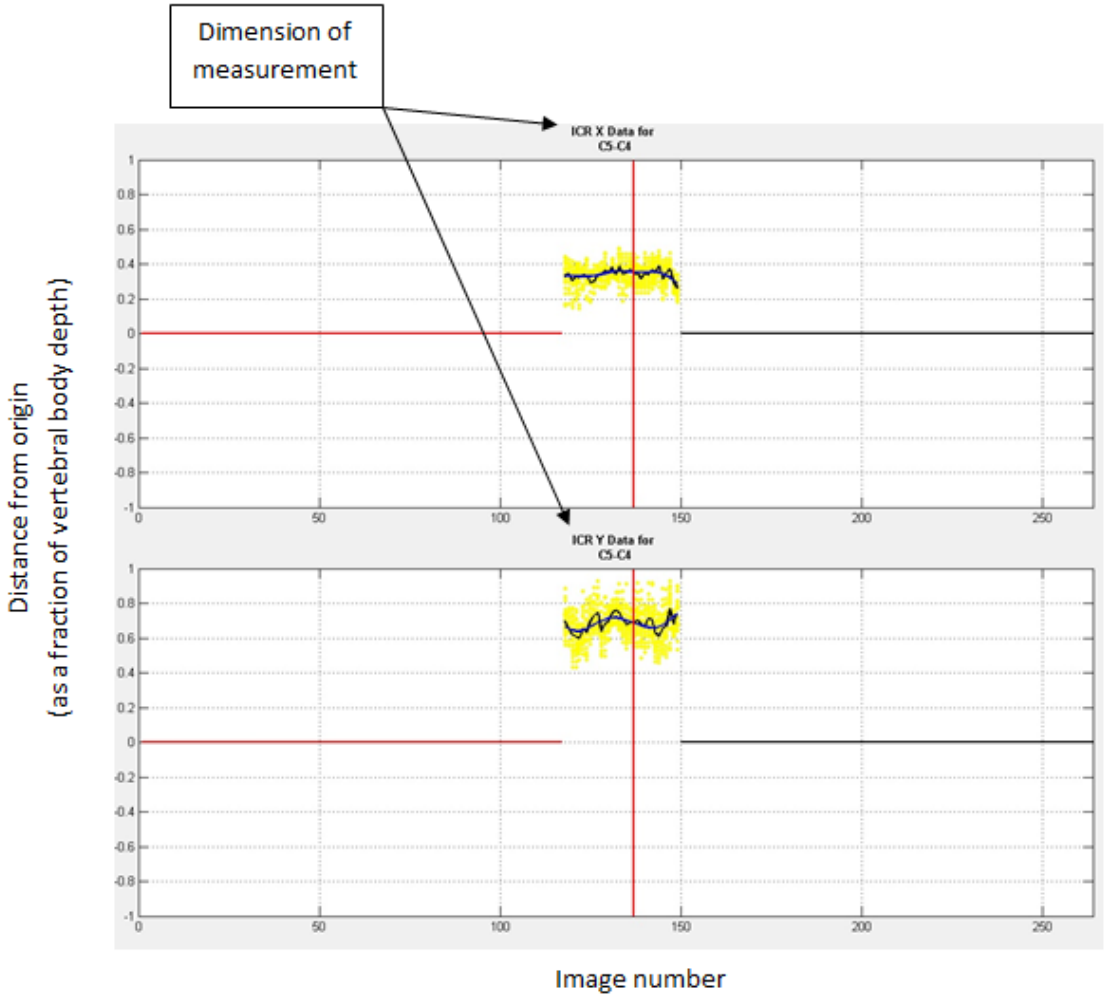


Figure 34: Graphical output of incremental X and Y IAR positions

The units used are vertebral body units (VBU) based on Frobin's method where one VBU is the equivalent of 15mm (Frobin et al. 2002). This helps to compensate for radiographic distortion and varying stature between individuals so that data can be compared between radiographs. To allow comparison of data VBU are multiplied by 15 to give the distance of the IAR from the origin in equivalent millimetres.

• Laxity by Attainment rate

Two methods of quantifying laxity (see section 2.7.7) from QF have been described in the literature. In the first the neutral zone/inter-vertebral motion ratio, which was found to increase with the amount of disc degeneration in *in vitro* studies (Mimura et al. 1994), was adapted to the *in vivo* environment as the proportion of inter-vertebral motion that a segment achieves in the first 10° of trunk bending (Mellor et al. 2009).

This approach was compared with that of the ratio between the slopes of inter-vertebral motion and trunk bending, a method described by Wong et al (2004, 2006) and adapted by Mellor et al (2009) to take account of the fact the ratio is not a linear one (Wong et al. 2004; Wong et al. 2006; Mellor et al. 2009). The ratio of the slopes over the first 10° of trunk bending was found to be the more responsive measure because it was less sensitive to variation caused by small rotational changes. This method was updated to the first 10° of trunk bending after the segment in question had begun to move (Breen et al. 2012) and is the method adopted here and further described in Figure 35. As the equation below describes, laxity is calculated as the ratio of the gradients of the two slopes displayed in Figure 35.

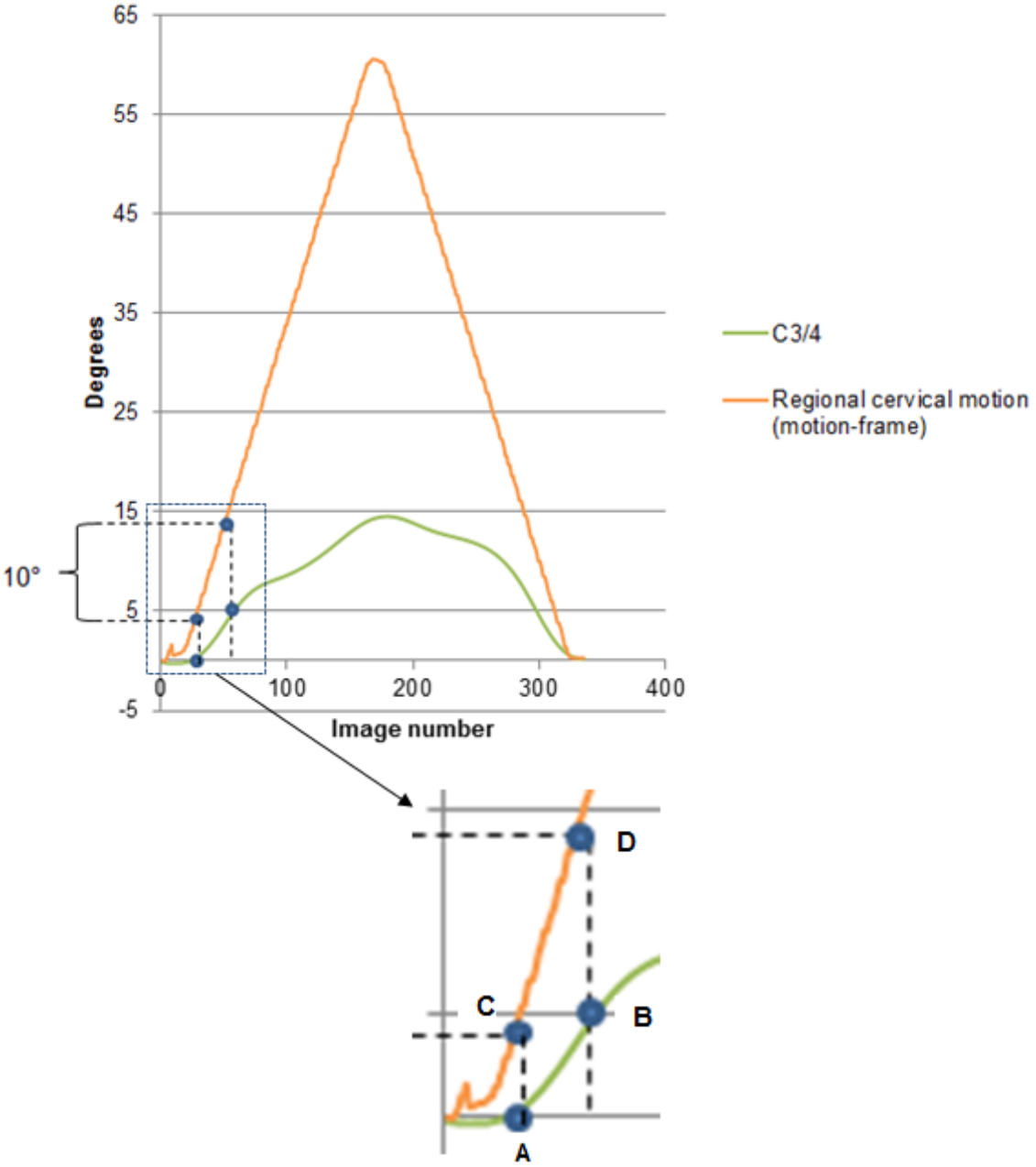
$$Laxity = m_{AB} \div m_{CD}$$

$$where\ m_{AB=\frac{\Delta y_{AB}}{\Delta x_{AB}}}\ ,\ m_{CD=\frac{\Delta y_{CD}}{\Delta x_{CD}}}\ ,and\ \Delta x_{AB} = \Delta x_{CD}$$

$$\rightarrow \frac{\Delta y_{AB}}{\Delta x} \div \frac{\Delta y_{CD}}{\Delta x}$$

$$\rightarrow \frac{\Delta y_{AB}}{\Delta y_{CD}} \times \frac{\cancel{\Delta x}}{\cancel{\Delta x}}$$

$$\rightarrow Laxity = \frac{\Delta y_{AB}}{\Delta y_{CD}}$$



The inter-vertebral segment commences its motion at point A and has moved as far as point B after 10° of corresponding regional cervical motion (points C to D). Laxity is calculated as the ratio of the slopes of the 'best fit' (linear regression) lines that describe the motion of the motion segment (m_{AB}) and neck (m_{CD}) during this 10° of neck bending.[12]

Figure 35: Laxity by attainment rate – C3/4 shown as example

[12] m = gradient of (best fit) line.

3.4 Conclusion

In this chapter a QF image acquisition protocol was described, as informed by the research literature, for the purposes of collecting kinematic data from patients with neck pain receiving SMT and matched healthy volunteers (Part III of this thesis). The new protocol was found to be comfortable and achievable within a reasonable time-frame based on testing with four participants. The best way to analyse the image sequences was identified as were the limits of image analysis meaning kinematic data would be collected from C1/2 to C5/6 only. Finally the kinematic data that may be collected with QF, and as informed by the literature regarding the mechanism of SMT, were presented. The next step was to validate QF in the analysis of cervical IV-RoM and that is the subject of the next chapter.

Chapter 4. Accuracy of QF in the measurement of cervical inter-vertebral flexion and extension motion

4.1 Introduction

The accuracy (please see Glossary for definition, page 284) of a measurement system is determined by comparison with a reference standard (Bossuyt et al. 2003). The accuracy of QF at measuring spinal motion is dependent on operator-placement of templates around the vertebrae on the first in a series of fluoroscopic images and the adherence of these templates to the vertebrae throughout the motion sequence (as described on page 69). The purpose of this chapter is to determine the accuracy of QF in the measurement of cervical inter-vertebral flexion and extension motion, partially addressing Research Question 1 (page 59).

For the determination of accuracy to be valid it is important that the reference standard is representative of the scenario in which the measurement method will be used. In a study assessing a QF method for measuring lumbar inter-vertebral motion a motor-controlled model of a cadaveric L4 vertebra with a piece of fresh pork roll wrapped around to simulate soft tissue degradation was imaged while moving (Wong et al. 2006). However, this was used to calculate the error in measuring the speed of the vertebra, not its' range. The accuracy of inter-vertebral angular position of the L3/4 joint was investigated with the lumbar flexion-extension imaging of five normal subjects. The RMS error between the QF-tracked results and those of a radiologist were calculated (Wong et al. 2006). The RMS was considered to be less than 10% on average, after at least 30 image frames had passed (Wong et al. 2006). This might be useful in making comparisons with the current clinical standard where measurements from x-ray images are commonly made by physicians, but QF is not being compared to a criterion or reference standard here.

Reitman and colleagues conducted a study to validate a fluoroscopic technique for the measurement of cervical inter-vertebral motion (Reitman et al. 2004a). This technique involved automated tracking of vertebral positions at end-range flexion and extension from operator-marked templates on the neutral image. To assess measurement error they imaged two complete human cervical spines that were frozen in ice to simulate the radiographic scatter associated with the soft tissues of the neck. They rotated and translated the spines to represent gross flexion-extension motion while the specimens were imaged in three separate motion trials. It was stated that any inter-vertebral motion reported by the tracking software during these experiments would represent measurement error as there was no actual inter-vertebral motion.

Measurement error was reported as averaging less than 0.5° for 'inter-vertebral rotations' (Reitman et al. 2004a) however, as acknowledged by the authors, out-of-plane motion, which is liable to occur when measuring inter-vertebral motion *in vivo*, especially with continuous motion, was not represented in the validity study. Hence, the error in this technique is likely to be larger when applied to living people.

In living people, dynamic radiostereometric analysis (RSA) can provide precise motion measurements (Selvik 1990). The accuracy of RSA for inter-vertebral motion has been investigated by test-retest examination of a phantom representative of the 'typical marker configuration' used in the RSA assessment of the cervical spine post-fusion surgery (Ryd et al. 2000). The authors did not describe the methods or statistical analysis of this sub-study in any detail, but reported an upper 95% confidence limit of 0.36° for rotation (Ryd et al. 2000). However, RSA is invasive and unsuitable for patients not receiving surgery; alternatively, it has been used as a "gold standard" against which to compare results from non-invasive radiographic methods of inter-vertebral motion measurement.

In one such study, to validate a biplane x-ray technique for measuring 3D *in vivo* cervical inter-vertebral motion, an ovine cadaveric spine (C0 – C5) was imaged while the neck of the specimen was manually manoeuvred into extension and axial rotation (McDonald et al. 2010). Three trials of these motions and three static trials were conducted. The vertebral positions were measured using a mathematical model-based tracking technique which necessitated CT imaging of the specimen. The CT image was reconstructed to generate a 3D bone model, and combined with positional information provided by the biplane x-rays. The results of this technique were compared with that from dynamic RSA tracking of tantalum beads implanted in levels C3 and C4 of the specimen (McDonald et al. 2010). Dynamic accuracy, defined as the RMS error between the two measurement techniques, was 0.61±0.44° for sagittal rotation. While this technique might provide accurate and detailed data, on all planes of motion, it appears to be time and resource intensive. When used *in vivo* a participant receives biplanar radiography as well as a CT exposure which means this technique has a large associated ionising radiation dose (dose not stated) (McDonald et al. 2010). Additionally, gross head/neck motion needs to be measured with a video-based motion capture system. However, some of the findings from the application of this technique to a participant are noteworthy.

When the participant was imaged while moving from a fully flexed position into full neck extension there was associated lateral bending and axial rotation at the three segments they measured (C4/5 to C6/7) that were significantly greater than zero (McDonald et al. 2010). This is relevant to the out-of-plane errors associated with radiography of the spine in living people, which the authors did not take into account in the validation cadaveric study. The authors did not state why the participant's inter-vertebral motion was not measured above C4/5. It is possible that either the model-based tracking system does not work with the varying morphology of the upper cervical spine, or perhaps this area was out-with the radiographic field of view and would therefore require additional imaging, increasing the ionising radiation dose.

As suggested by the findings from McDonald et al (2010) and contended by Anderst et al (2011), it is probably the case that a more reliable indication of measurement accuracy would be obtained under 'real world' *in vivo* (includes biological variability of participant behaviour and characteristics such as muscle and ligaments and body habitus) testing rather than from the more controlled but ultimately simulated *in vitro* (no biological variability) cadaveric model-based experiments (Anderst et al. 2011).

In a study seeking to validate a similar biplane x-ray/CT/mathematical model-based technique for assessing cervical inter-vertebral motion, dynamic RSA was also used as a reference standard, but this time using an *in vivo* methodology. Three subjects had tantalum beads implanted during cervical discectomy and fusion surgery and motion was measured only at the fused and two adjacent levels (Anderst et al. 2011). Biplane x-ray and CT images were collected after surgery and the tantalum beads were tracked in the biplane x-rays images by dynamic RSA. The results were compared with those calculated from a model-based tracking algorithm over seven trials of each method. Precision, defined as the standard deviation of measurement differences across these trials, was 1.3 ± 0.6° or lower in flexion-extension (Anderst et al. 2011). This *in vivo* derived precision is expectedly larger than the *in vitro* precision reported by McDonald et al (2010) of less than ± 0.26° [McDonald et al (2010) calculated precision from static, not dynamic, imaging].

Both the methods of McDonald et al (2010) and Anderst et al (2011), while apparently very accurate, suffer from a high ionising radiation dose. The effective radiation dose for each dynamic flexion-extension motion trial was estimated at 0.16mSv (Anderst et al. 2014), while the dose from a cervical CT scan is reported as 3.0 – 4.36mSv (Anderst et al. 2014).

These previous studies are instructive however in that any *in vitro* study needs to as closely replicate that of the *in vivo* situation as possible as measurement error will almost certainly be larger *in vivo*. Secondly, measurement error needs to take account of the possibility of out-of-plane motion.

Other studies have utilised calibration models to determine the accuracy of spinal motion measurement in the *lumbar* spine from plain film radiography (Triano 1984), bi-planar radiography (Pearcy and Whittle 1982) and QF (Breen et al. 1988; Breen et al. 2006) but these models have allowed only for the accurate determination from fixed angles, not continuous angular range. No previous studies appear to have assessed the accuracy of IAR measurement.

For this present study it was decided to construct a model consisting of a pair of dry human cervical vertebrae (C4-5) joined at the centre of the inter-vertebral disc space by a uni-directional plastic joint mounted on a testing platform and which allowed for continuous sagittal rotation of the superior vertebra (Figure 36). The model did not allow for translation (translation equals zero) but this was not a measurement of interest (see page 78).

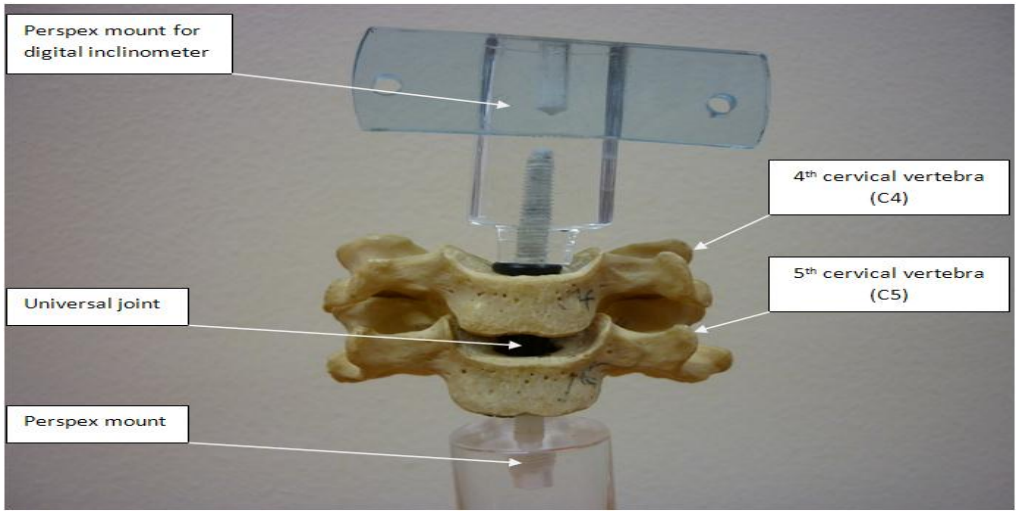


Figure 36: Cervical C4-5 joint model

So as to minimise any influence on image tracking it was important that the universal joint was as radiolucent as possible, hence the choice of acetal which is much less radiopaque than metal [the more radiopaque or radio-dense a material, the more clearly it appears on the image]. While acetal at 1.5g/cm^3 is around 5-6 times denser than typical human cervical vertebra (Weishaupt et al. 2001; Yoganandan et al. 2006a; Yoganandan et al. 2006b) it is nine times less dense than that of the minimum density recommended for visualisation under fluoroscopy (Wang and Weber 2005). In order to observe the instantaneous axis of rotation (the centre of the joint) on the image a small lead ball-bearing was inserted within the joint. A Perspex mount was fixed to the superior vertebra which allowed for the attachment of a digital inclinometer (Penny & Giles STT 280; resolution ± 0.07°) to continuously record angular range reference data during motion.

4.2 Methods

4.2.1 Data collection

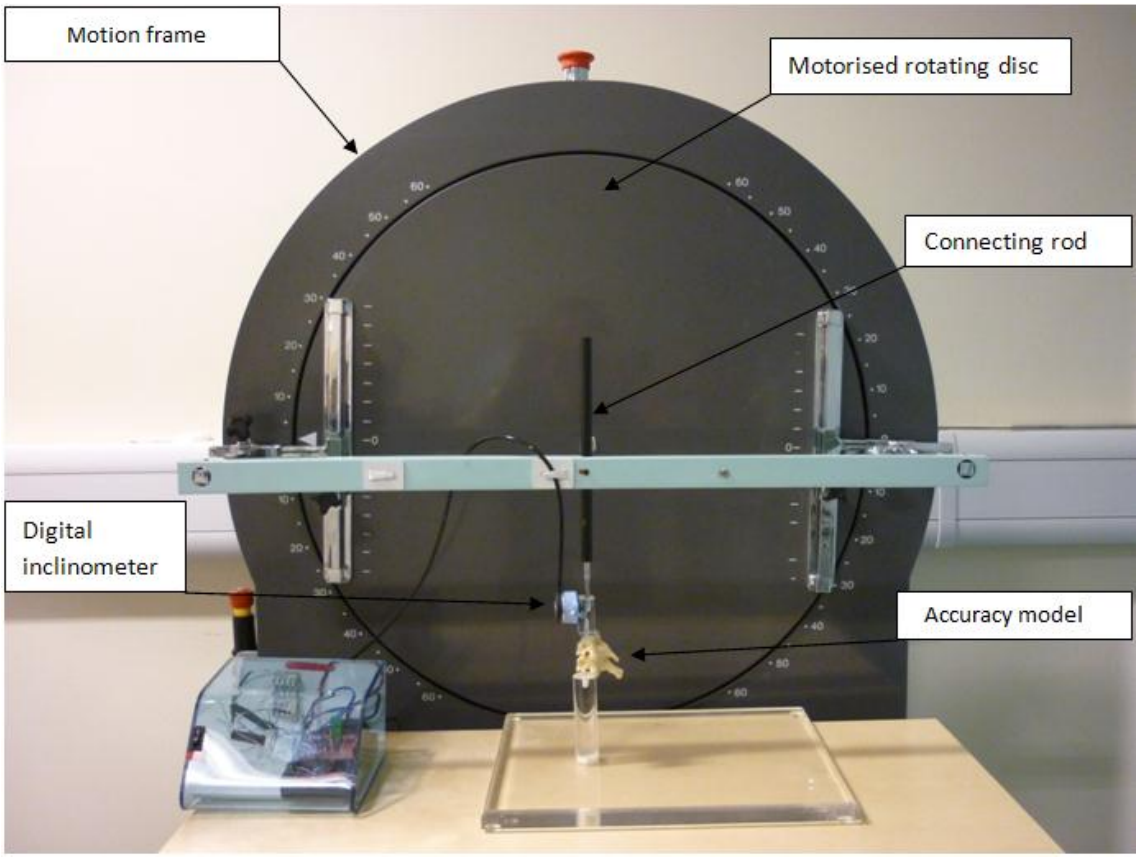


Figure 37: Image acquisition set-up for accuracy study

The model was linked to the rotating disc of the motorised motion frame via a connecting rod and the digital inclinometer was screwed tight to a fixing atop the superior vertebra (Figure 37). The fluoroscope (not shown in image) was aligned at 90° to the model and centred on the universal joint. The computer-controlled rotating disc rotated the superior vertebra, C4, continuously through 20° flexion then 20° extension as a separate sequence while simultaneously being imaged at 15 frames per second. This range is an approximation of the mean in-vivo range of this segment based on existing data (Dvorak et al. 1988; Lind et al. 1989; van Mameren et al. 1990; Frobin et al. 2002). Each sequence was repeated with the fluoroscope axially rotated 10° from the orthogonal alignment to simulate poor positioning of a participant. To replicate the image degrading effects of tissue (for example, muscle) that occur when imaging people, images were taken through a block of animal soft tissue (minced beef).

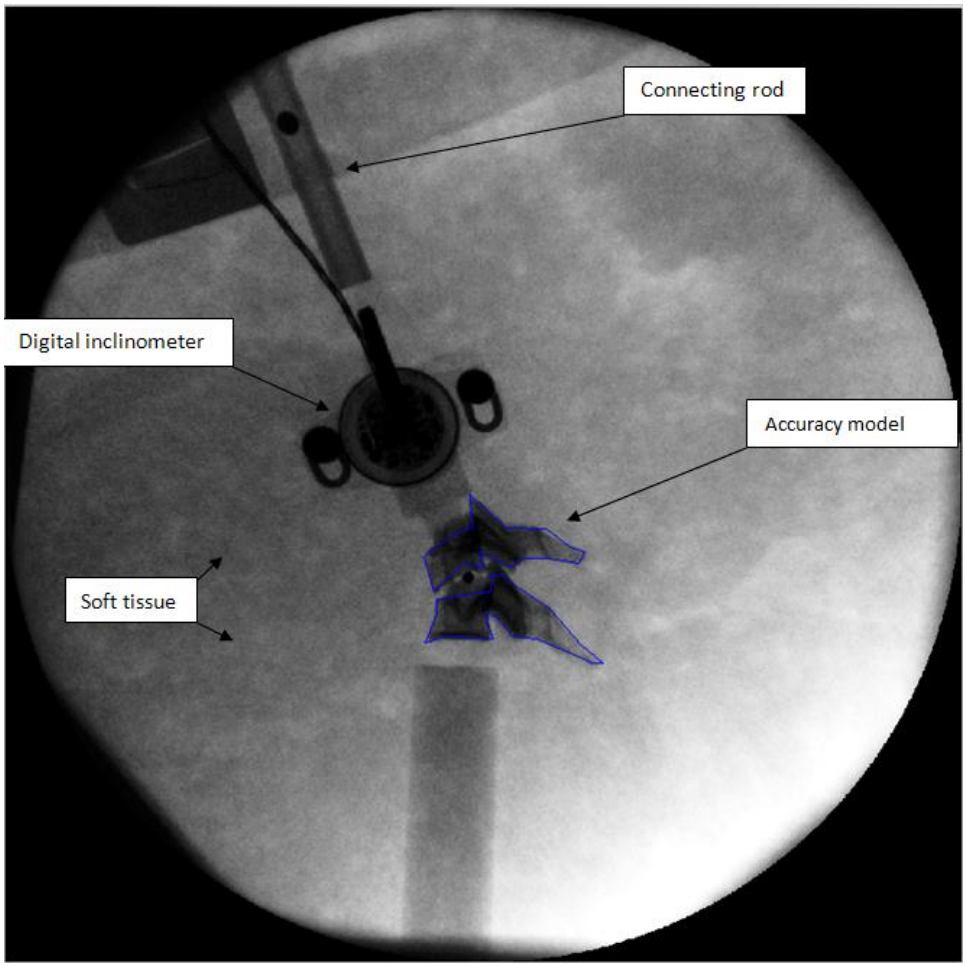


Figure 38: Model as imaged while being rotated by the motorised motion frame via the connecting rod

In Figure 38 can be seen C4 rotating over C5 while being imaged by the fluoroscope. The reference x, y co-ordinates for the instantaneous axis of rotation (lead shot within the universal joint of the calibration model) were identified using Image J (a public domain, Java-based image processing program developed at the National Institute of Health, USA). In order to convert the results of IAR co-ordinates from proportion of vertebral body depth (VBU, the units used in the computer-generated output of results) to equivalent millimetres the anterior-posterior depth of the superior end-plate of the inferior vertebra was measured ten times with electronic callipers (Axminster Instruments Ltd; spatial resolution ± 0.02mm) and averaged to give a mean vertebral body depth of 14.23mm (Figure 39). This measurement is the equivalent of one VBU for this calibration study.

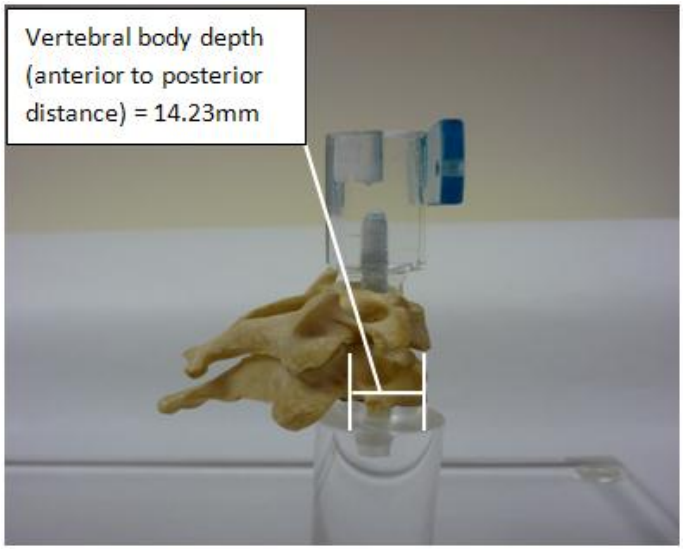


Figure 39: Lateral view of calibration model showing measurement of vertebral body depth (14.23mm = one VBU)

4.2.2 Data analysis

On the first image of each of the four motion sequences (flexion in-plane, flexion 10° out-of-plane, extension in-plane, extension 10° out-of-plane) tracking templates were applied to the two vertebrae of the calibration model, a process previously described (page 69). This process was repeated ten times for each motion sequence giving forty data points for angular range and x, y co-ordinates for IAR locations.

The standard deviation of the differences is representative of accuracy if the true value is known i.e. results are compared to that from a reference standard[13]; if this is not known, it represents the 'precision' of the system (Ryd et al. 2000). Root-mean-square (RMS) differences (standard deviation of the differences) between measured and reference data were calculated for each motion sequence (Bland and Altman 1986). RMS errors were calculated to take account of the errors including both positive and negative values.

[13] This is termed the "trueness" (ISO5725-1 1994) or the "bias" (ASTM 1996) of the measurement method.

4.3 Results

RMS errors for maximum angular rotation and averaged IAR location for both in- and out-of-plane imaging conditions are presented in Table 4. The largest error for angular rotation was 0.50° (out of plane flexion) while for IAR location it was 1.16mm (for X co-ordinate in out of plane flexion).

	Flexion				Extension			
	In plane		Out of plane		In plane		Out of plane	
Rotation RMS error (°)	0.21		0.50		0.34		0.40	
X, Y co-ordinates	X	Y	X	Y	X	Y	X	Y
IAR RMS error (mm)	1.06	0.79	1.16	0.63	0.73	0.98	0.48	0.55
IAR RMS error (VBU)	0.07	0.06	0.08	0.04	0.05	0.07	0.03	0.04

In plane: x-ray beam centred on universal joint, horizontal and orthogonal to model; *Out of plane*: x-ray beam axially rotated by 10° from centre of universal joint; *IAR*, instantaneous axis of rotation location; *VBU*, Vertebral Body Unit (14.23mm)

Table 4: Root-mean-squares of difference between reference and computed inter-vertebral angular ranges and instantaneous axis of rotation locations

4.4 Discussion

• Inter-vertebral angular range

This study combined continuous sagittal motion of a cervical vertebral model with simultaneous measurement with a reference standard (digital inclinometer). Angular range of flexion or extension, in- or out-of-plane, was accurate to less than one degree. The error in this during extension measurement was only marginally increased with out-of-plane imaging, but the doubling of error with out-of-plane flexion emphasises the importance of the correct positioning of participants.

These findings echo those of a model-based study conducted to assess the accuracy of QF in the measurement of *lumbar* inter-vertebral motion[14]. In this lumbar IV-RoM accuracy study two 'calibration' studies were conducted. In the first the calibration model (L3 and L4 human vertebrae linked together by a universal joint) was positioned orthogonally to the image intensifier and imaged with the joint in seven different positions. The seven different joint position angles, from -10° to +20°, were measured by way of protractors fitted to the model and these angles were then compared to those calculated from the images by QF. Imaging was repeated with the model axially rotated 10° out-of-plane to simulate poor positioning. The RMS difference between reference (fitted protractors) and computed (QF) inter-vertebral angles was 0.52° for the orthogonal configuration. As was found in this cervical accuracy study, error doubled (to 1.03°) under the out-of-plane condition (Breen et al. 2006).

For the second calibration study, the two vertebrae of the lumbar model were rigidly fixed, and images were acquired as the model was moved through 80° on a motor-driven motion-table. Any motion measured by QF in this instance was considered error since the true range of motion was zero degrees. A one-way ANOVA was calculated based on five repeat imaging sequences and error ranged from 1-4.5° in flexion-extension (Breen et al. 2006).[15] It was not feasible to do such an experiment with the cervical accuracy model and the upright motion-frame, but it is noted that the true error could be larger than 0.5° (the largest error found in this present study). Nevertheless this represents an improvement on the accuracy of < 1.5° reported from a model-based validation study of biplane radiography (Pearcy and Whittle 1982).

• Instantaneous axis of rotation

In this current study, measurement of IAR location was accurate to around 1mm or less, in the x and y directions, in- or out-of-plane, and the error appears to be marginally affected by out-of-plane imaging although intriguingly, the extension out-of-plane error is less than that of in-plane. It is noted that measurements were made based on 20° flexion and 20° extension motion, both similar to the average total flexion-extension range of the C4/5 segment *in vivo*.

[14] The QF method of lumbar inter-vertebral motion measurement (Breen et al. 2006) from which the QF methodology for cervical inter-vertebral motion described in this thesis was developed.

[15] In both calibration studies animal soft tissue (sausages) were placed around the model to simulate soft tissue image degradation (Breen et al. 2006).

Since measurement error for IAR location calculations is known to be reduced with larger rotations, when these are calculated from separate flexion and extension sequences, which divides the overall range, it is expected that measurement error will be larger (Pearcy and Bogduk 1988; van Mameren et al. 1992).

In contrast to the number of studies seeking to validate techniques for measuring cervical IV-RoM there is an absence of such studies assessing the accuracy of IAR location measurement. There is no 'known' *in vivo* IAR or centre of rotation to serve as a reference standard, necessitating either an *in vitro* experiment or a computational mathematical approach using data acquired *in vivo*. It is believed that at this current time this present study is the only that has sought to calculate accuracy data from an *in vitro* model.

For the investigation of ICR path measurement (centrode), Baillargeon and Anderst (2013) conducted a simulation experiment to replicate *in vivo* cervical motion (Baillargeon and Anderst 2013). Using data from biplane x-rays and CT reconstruction, simulated bone motion data was created and differentially filtered until an analysis configuration was arrived at that could apparently identify the ICR motion path to ±0.8mm in the superior-inferior direction (analogous to y-co-ordinates) and ±1.0mm in the anterior-posterior direction (x-co-ordinates) (Baillargeon and Anderst 2013). These results appear concordant with those of this present study.

4.5 Conclusion

The results of this model-based study suggest QF is sufficiently accurate for use in the main study, for the determination of inter-vertebral angular ranges and IAR locations from cervical spine motion measurement in the sagittal plane. However, true measurement error *in vivo* is expected to be larger than that indicated by this model-based study. While it is not possible to directly assess accuracy *in vivo* (in people not already receiving cervical spine surgery), assessing *repeatability*, which is straightforward to do *in vivo*, is an important component relating to the validity of a measurement method, and this is the topic of the next chapter.

Chapter 5. Intra-observer and inter-observer QF repeatability studies

5.1 Introduction

The repeatability of a measurement method informs the extent to which results are subject to variations in the measurement process, biological variation of subjects, or both (Bland and Altman 1996a). Important sources of error (factors that cause differences between repeat measurements that are not true differences) in the measurement of cervical IV-RoM with a radiographic technique like QF include: the measurement protocol (the extent to which motion variability is minimised), the behaviour of the participants (how faithfully standardised instructions are followed) (Hipp and Wharton 2008), time of day, timing between repeat measurements (Jordan 2000) and the characteristics of the observer(s) (number, background, experience) (Kottner et al. 2011). A number of these potential sources of error are acknowledged in the QF acquisition methodology previously described (Chapter 3).

There is confusion in the literature over the terminology relevant to repeatability studies such as repeatability, reproducibility, reliability, agreement (please see Glossary for definitions of these terms, page 284) (Bartlett and Frost 2008), and further confusion over which statistics to use (Weir 2005) and how to correctly interpret them (Costa-Santos et al. 2011). There has even been discussion in the statistics literature over whether a particular statistic (the intra-class correlation coefficient, ICC) is representative of reliability or agreement (Costa Santos et al. 2011; Kottner and Streiner 2011).

In repeatability studies it is necessary to calculate both agreement and reliability statistics (Weir 2005; de Vet et al. 2006; Bartlett and Frost 2008). If only ICCs (reliability) are calculated, they can be subject to misinterpretation. A large ICC can mask poor trial-trial consistency when between-subject variability is high. Conversely, a low ICC can be found even when trial-trial variability is low if the between-subjects variability is low (Weir 2005). In this case, the homogeneity of the subjects means it will be difficult to differentiate between subjects even though the absolute measurement error might be small. It is necessary therefore to examine measurement error (SEM) in conjunction with the ICC (Weir 2005; de Vet et al. 2006). Unfortunately, repeatability studies in the published literature have not always followed this guidance (de Koning et al. 2008).

Incorrect use of statistics has included the use of the Pearson (or Spearman) correlation coefficient – this is flawed as an indicator of reliability because it cannot

account for systematic observer bias, unlike the ICC which can (Jordan 2000). In other words, where two or more observers have consist differences in their results, perfect correlation (r = 1) might exist in the absence of agreement. Likewise the paired-Student *t* test is an inappropriate indicator of reliability (Jordan 2000). The null hypothesis, that the mean of the difference in each pair of measurements is zero, may not be rejected despite large discrepancies between measurements when there is a fixed bias i.e. the first and second measurements on each pair are equally likely to be the larger, so incorrectly indicating high reliability. Additionally, although a large standard deviation of the measurement differences is indicative of disagreement, the larger this becomes for a given sample size, the smaller the *t* statistic becomes, leading to less likelihood of a significant result (Jordan 2000).

Some repeatability studies have used 95% limits of agreement (often referred to as the Bland-Altman method) to demonstrate the level of agreement between repeated measures with one measurement tool (van Loon et al. 2012; Williams et al. 2012). However, as pointed out by Myles (2007), the original Bland-Altman method (Bland and Altman 1986) was developed for method-comparison; two sets of measurements from two different methods on one occasion. These data are independent, so this approach is not suitable for repeated-measures (dependent) data (Myles 2007). It was suggested that for repeated measures this approach only be used as a 'naïve analysis' because of the simplicity of the method (Myles 2007). It was perhaps for this reason that Williams et al (2012) had little comment about the width of the limits of agreement (LOA) they calculated in their study on regional cervical spine motion measurement. They reported 95% LOA of -42.1 to 59.3° for active ROM, and -50.7 to 56.4° for passive ROM, which imply poor agreement, yet they discussed only the ICCs and the 'substantial' reliability that they represented (Williams et al. 2012).

Even with the use of the correct statistical analysis, a sample size that is too small leads to wide confidence intervals for the chosen statistic (Jordan 2000). Sample size calculations for 'reliability' studies have been suggested which are based on a null hypothesis assumption of the population ICC (Walter et al. 1998). For example, based on a population ICC = 0.8, with an assumed real value of ICC = 0.9, a sample size of 46 or more is required to give a power of > 80% for two repetitions or observers (Walter et al. 1998). This might be a useful guide but is ultimately based on a speculative guess at the population ICC.

Calculating sample size in order to narrow the confidence intervals around a reported ICC is perhaps more worthwhile (Jordan 2000) however, as is often the case, this study sought to do what was achievable over a given time-frame.

Having a small sample size makes it even more important to report confidence intervals so that the reliability implied by the ICCs is properly interpreted. For example, where the lower limit is larger than a previously chosen acceptable limit, or it is within the range of 'substantial' reliability (Shrout 1998), more confidence can be placed in the reliability of the tool (Jordan 2000). In this present study agreement and reliability statistics are calculated to inform the reasonable interpretation of data collected in the main study (Part III), and not necessarily intended to be representative of the repeatability of this QF method in the more general sense; a greater sample size would be required to inform that determination.

An important facet of the repeatable measurement of inter-vertebral motion with QF is correct placement of tracking templates by the operator, as well as identification and correction of errors when motion sequences are reviewed prior to determining the final results. Estimating the measurement error is necessary for the appropriate interpretation of data collected in the main study, with respect particularly to determining changes in kinematic variables. Therefore repeatability studies of the image processing and analysis stage of QF were conducted, addressing Research Question 1 (page 59). [For intra-subject reproducibility, which encompasses all sources of measurement error, see chapter Chapter 7, page 153]. The reporting of these follows published guidelines for the reporting of reliability and agreement studies (Kottner et al. 2011).

5.2 Methods

5.2.1 Data collection

To obtain sufficient data for analysis it was determined that ten participants would be sufficient to provide at least thirty data points for each of the flexion and extension sequences (Chinn 1990). Tracking templates were placed around the vertebral contours of C1 through C6 (page 69) on the first image of each motion sequence by two independent observers, blinded to each other's results, for inter-observer repeatability. Imaging sequences then underwent the quality assurance procedure (page 74) prior to extraction of results for statistical analysis; the process was repeated by one observer six weeks later for intra-observer repeatability.

Both observers, one a chiropractor with one year's clinical experience, the other a 3rd year chiropractic student, received the same image analysis training (this involved instruction from a medical physicist with five years' experience developing the image analysis software, and practice analysing six existing cervical spine imaging sequences). The kinematic parameters included in the repeatability studies were angular range, IAR location and attainment rate/laxity.

While *intra*-observer repeatability was required for the appropriate interpretation of IV-RoM measurements made in the main study (Part III) - since the same observer was doing all the measurements in the main study - inter-observer repeatability was also conducted for completeness and to further validate the repeatability of QF in the cervical spine. [IAR *inter*-observer repeatability was calculated from inter-vertebral levels that rotated at least 5°. Since errors were large, and were expected to increase with 3° as the minimum rotation, the study was not repeated at the smaller rotation value. Inter-observer repeatability for attainment rate was not calculated].

5.2.2 Data analysis

The repeatability of a measurement method needs to be quantified in terms of the agreement and reliability of the measurements (Bartlett and Frost 2008). The standard error of measurement (SEM) is considered a suitable expression of agreement and an appropriate formula is:

$$SEM_{consistency} = SD_{DIFF}/\sqrt{2}$$

where SD_{DIFF} is the standard deviation of the mean differences between two measurements (de Vet et al. 2006). This parameter is useful as it gives the error in the units of measurement. This was calculated using Excel (Microsoft Windows Version 7, 2010). For repeated measurements on a continuous scale the intra-class correlation coefficient (ICC) is the most suitable reliability parameter (de Vet et al. 2006). This parameter relates the measurement error to the variability between persons.

$$ICC_{consistency} = \frac{\sigma_p^2}{\sigma_p^2 + \sigma_{residual}^2}$$

σ_p^2 – represents the variability between persons; $\sigma_{residual}^2$ – represents measurement error and is the interaction between persons and observers (de Vet et al. 2006).

The type of ICC calculated was ICC (3C,1) for intra-observer reliability, as each target or object of measurement is rated by each of the same *k* observers, where *k* = 1, and it is assumed that this is the only observer of interest (Shrout and Fleiss 1979; McGraw and Wong 1996). For inter-observer reliability ICC (2C, 1) was used, as it was assumed a change in the observers would not meaningfully alter the results. In each case single measures is reported as opposed to average measures as, while there was averaging of template positions (page 69), this was an inherent part of the process of the QF method. The results subsequently produced by each *observer* were not averaged.

Generally $ICC_{absolute\ agreement}$ is the better option over $ICC_{consistency}$ as the first is sensitive to proportional and fixed bias, the later only to proportional bias (Weir 2005). However, both ICCs were calculated in this present study for comparison and they hardly varied numerically, and did not vary in their interpretation, suggesting the absence of a fixed bias; so $ICC_{consistency}$ was reported along with $SEM_{consistency}$. These were calculated using SPSS (version 18). Inter-observer repeatability results are presented in appendices and where relevant are referred to in the following text. Inter-observer data are reproduced with permission from an undergraduate project sub-study (Jasperse 2013).

There is controversy on how best to interpret ICC values (Weir 2005) with disagreement evident in their interpretation within and between clinicians and biostatisticians (Costa-Santos et al. 2011). It has even been suggested that proposed categories for ICCs are ultimately arbitrary (Jordan 2000). However, in order to make some determination over the clinical usefulness of a tool a judgement on the ICCs needs to be made; Shrout (1998) provides a useful guide for this purpose and was used to interpret the ICCs in this study (Shrout 1998).

5.2.3 Ethical considerations

Imaging sequences from a subgroup of participants recruited to the main study (Chapters 6 – 8) were utilised in this observer repeatability study and the ethical considerations and approval for this are presented on page 131. In summary, ethical considerations are detailed in participant information sheets (Appendix 11 and Appendix 12) and ethical approval was granted by the National Research Ethics Service Committee South West – Cornwall & Plymouth (11/SW/0072 – Appendix 13).

5.3 Results

5.3.1 Participant demographics

A convenience sample of ten adult participants (the first ten participants recruited for the main study) aged 23 – 50 years, (mean, SD = 38, 9.1), five female, took part in the observer repeatability studies. All participants received a QF assessment of cervical inter-vertebral motion during neck flexion and extension, separately. Five participants were healthy volunteers (no neck pain) and the remaining five were patients with neck pain.

5.3.2 Inter-vertebral tracking failures

Most (97%) inter-vertebral levels (100% in flexion, 94% in extension) were successfully tracked. As Table 5 shows only three levels did not track, one each of C2/3, C3/4 and C5/6, all in extension. 55% (58% flexion, 52% extension) of levels rotated at least 5°, the initial minimum rotation set as a cut-off from which to calculate IAR locations. Since the 5° cut-off would mean IAR calculations not possible for around half the inter-vertebral levels this would limit the use of IAR location as a kinematic parameter of change. Decreasing the cut-off to 3° increased the proportion of levels available for IAR calculation to a more acceptable yield of 72% (78% flexion, 66% extension). Similar proportions were seen in the inter-observer study (Appendix 2).

	No. of inter-vertebral levels successfully tracked twice by one observer		No. of inter-vertebral levels ≥ 5° sagittal rotation		No. of inter-vertebral levels ≥ 3° sagittal rotation	
Inter-vertebral level	Flexion	Extension	Flexion	Extension	Flexion	Extension
C1/2	10	10	8	2	9	3
C2/3	10	9	3	4	6	5
C3/4	10	9	8	6	9	6
C4/5	10	10	5	9	8	10
C5/6	10	9	5	5	7	9
Total	50	47	29	26	39	33
Percentage of total possible levels	100%	94%	58%	52%	78%	66%

50 (5 levels per participant, 10 participants) is the maximum number of possible inter-vertebral rotations measured in each of flexion and extension

Table 5: Number of inter-vertebral levels successfully tracked twice and those measured at equal to or greater than 5° and 3° sagittal rotation (necessary for IAR calculations)

5.3.3 Intra-observer repeatability: inter-vertebral angular range

The standard error of measurement (SEM) and intra-class correlation coefficients (ICC) for inter-vertebral angular range were calculated for each inter-vertebral level and for all levels pooled as shown in Table 6. Disagreement (SEM) varied by level and while consistently larger in extension, overall disagreement was small; the largest disagreement was 1.1° (C1/2 and C5/6 in extension). The lowest ICC was 0.90 (C1/2 extension) indicating substantial reliability for all levels (Shrout 1998). Taking the lower 95% confidence intervals into account reliability remains substantial for all levels save for C1/2 in extension (0.635) and C3/4 in extension (0.711) which would now be considered in the 'moderate' reliability category (Shrout 1998). In summary, these data indicate excellent repeatability (agreement and reliability) of QF measurement of inter-vertebral angular range. Inter-observer repeatability was equally excellent (Appendix 3).

Inter-vertebral level	Standard error of measurement (°)		Intra-class correlation coefficient (95% confidence interval)	
	Flexion	Extension	Flexion	Extension
C1/2	0.8	1.1	0.97 (0.885 to 0.993)	0.90 (0.635 to 0.973)
C2/3	0.3	0.8	0.97 (0.900 to 0.993)	0.95 (0.806 to 0.988)
C3/4	0.5	1.0	0.99 (0.978 to 0.999)	0.92 (0.711 to 0.981)
C4/5	0.6	0.8	0.97 (0.891 to 0.993)	0.97 (0.886 to 0.992)
C5/6	0.5	1.1	0.99 (0.974 to 0.999)	0.97 (0.854 to 0.992)
All levels pooled	0.6	1.0	0.99 (0.973 to 0.993)	0.96 (0.926 to 0.980)

Intra-class correlation coefficient: ICC(3C,1), two-way single measure mixed effects model (consistency)

Table 6: Standard error of measurement and intra-class correlation coefficients for *intra-observer* repeatability: angular range

5.3.4 Intra-observer repeatability: IAR locations (3° minimum sagittal rotation)

In Table 7 are presented the SEMs for each inter-vertebral level except for C1/2 in extension due to migration of tracking templates making the results unreliable for this level. Setting the minimum sagittal rotation to 3° did not adversely affect the size of the measurement error compared with the SEMs calculated from a 5° minimum (Appendix 4). The highest disagreement in the x direction was 2.7mm (C3/4 in extension), in the y direction 2.7mm (C2/3 in flexion), and the level of agreement varied by level and direction; generally, disagreement was greater in extension. With a vertebral body depth of 15mm these data represent substantial measurement errors. Inter-observer disagreement was higher, in flexion, but less in extension (Appendix 5).

Inter-vertebral level	No. of inter-vertebral levels ≥ 3° sagittal rotation		Standard error of measurement (mm)			
			Flexion		Extension	
	Flexion	Extension	X	Y	X	Y
C1/2	9	3	1.7	1.6	-	-
C2/3	6	5	1.5	2.7	1.5	1.1
C3/4	9	6	0.9	1.3	2.7	2.2
C4/5	8	10	1.2	1.6	0.8	2.4
C5/6	7	9	1.1	1.5	1.5	2.4
All levels pooled	39	33	1.3	1.8	1.9	2.2

mm, equivalent millimetres (1 VBU = 15mm)

Table 7: Standard error of measurement for *intra-observer* repeatability: IAR x, y co-ordinate locations (distance in mm from posterior-inferior corner of inferior vertebra)

Table 8 (next page) shows the ICCs calculated for IAR locations by level and pooled. While some of the ICCs might be considered to indicate 'moderate' to 'substantial' reliability (Shrout 1998), the 95% confidence intervals are wide with the lower limits almost exclusively in the 'virtually none [sic]' reliability category (Shrout 1998).

Therefore these data indicate generally poor reliability for measuring IAR location. Similar conclusions may be drawn regarding intra-observer (Appendix 6) and inter-observer (Appendix 7) reliability for IAR locations calculated from a 5° minimum rotation.

Inter-vertebral level	Intra-class correlation coefficient (95% confidence interval)			
	Flexion		Extension	
	X	Y	X	Y
C1/2	0.71 (0.018 to 0.952)	0.72 (0.042 to 0.953)	-	-
C2/3	0.23 (-1.484 to 0.933)	-0.03 (-0.674 to 0.851)	0.78 (-0.233 to 0.975)	0.80 (-0.073 to 0.978)
C3/4	0.61 (-0.008 to 0.904)	0.58 (-0.156 to 0.899)	0.04 (-0.687 to 0.764)	0.82 (0.183 to 0.972)
C4/5	0.58 (-0.112 to 0.901)	0.87 (0.449 to 0.974)	0.82 (0.072 to 0.974)	0.25 (-0.837 to 0.856)
C5/6	0.70 (-0.174 to 0.953)	0.77 (0.134 to 0.962)	0.66 (0.065 to 0.919)	0.90 (0.615 to 0.980)
All levels pooled	0.82 (0.599 to 0.916)	0.95 (0.891 to 0.974)	0.52 (0.162 to 0.757)	0.84 (0.672 to 0.926)

Intra-class correlation coefficient: ICC(3C,1), two-way single measure mixed effects model (consistency)

Table 8: Intra-class correlation coefficients for *intra-observer* repeatability: IAR x, y co-ordinate locations (distance in mm from posterior-inferior corner of inferior vertebra) calculated from levels that rotated at least three degrees

5.3.5 Intra-observer repeatability: laxity/attainment rate

As indicated by the ICCs in Table 9, there was moderate-substantial reliability of the QF measurement of attainment rate. It is noted, however, that some of the 95% confidence intervals are wide with lower limits in the 'fair' or 'slight' reliability category (Shrout 1998). The SEMs appear to indicate acceptable agreement.

Inter-vertebral level	Standard error of measurement		Intra-class correlation coefficient (95% confidence interval)	
	Flexion	Extension	Flexion	Extension
C1/2	0.029	0.014	0.78 (0.327 to 0.939)	0.97 (0.884 to 0.992)
C2/3	0.009	0.022	0.97 (0.900 to 0.994)	0.96 (0.815 to 0.990)
C3/4	0.025	0.027	0.94 (0.786 to 0.985)	0.96 (0.846 to 0.992)
C4/5	0.017	0.036	0.97 (0.865 to 0.991)	0.87 (0.563 to 0.966)
C5/6	0.043	0.026	0.70 (0.161 to 0.915)	0.84 (0.435 to 0.961)
All levels pooled	0.028	0.024	0.89 (0.810 to 0.935)	0.94 (0.890 to 0.964)

Intra-class correlation coefficient: ICC(3C,1), two-way single measure mixed effects model (consistency)

Table 9: Standard error of measurement and intra-class correlation coefficients for *intra-observer* repeatability: laxity/attainment rate

5.4 Discussion

The term 'repeatability' was used in these observer studies as repeat measurements were made on the same subjects under identical conditions (Bartlett and Frost 2008); subjects were imaged once and the imaging sequences analysed twice. From this study design, therefore, variability in measurements can be ascribed only to errors due to the measurement process itself.

• Angular range

For angular range the largest measurement error (SEM) in this study was 1.1° (intra-observer) which compares favourably with previous studies and represents an advance on the current standard of care using plain-film flexion-extension (Deitz et al. 2011). It also compares favourably with other studies measuring inter-vertebral motion.

In assessing the repeatability of a QF method for the measurement of lumbar inter-vertebral motion Teyhen et al (2005) reported SEMs ranging from 0.4 to 0.7°, and ICCs were all above 0.9 (Teyhen et al. 2005). However the methodology used in that study assessed the repeatability of vertebral location between neutral and end-range flexion images, not continuous tracking of the motion between these two extremes, therefore these values are likely to under-represent the repeatability of this QF method in practice. In a QF study that did assess repeatability based on continuous lumbar motion imaging, sequences from four subjects were repeat-analysed. This gave an RMS error of 1.94°, slightly larger than that calculated in this present study (Breen et al. 2006).

Regarding the cervical spine, in a cineradiography study the maximum difference between five repeat measurements (SEM not reported) on the same x-ray film was 2.6° (van Mameren et al. 1990). In calculating the measurement error of a protocol for measuring inter-vertebral motion from plain-film end-range flexion-extension radiographs, Frobin et al (2002) reported intra-observer and inter-observer errors (standard deviations) as 1.90° and 1.98° respectively. For assessing the repeatability of a video-fluoroscopy method in the cervical spine Wu et al (2007) calculated ICCs and the mean absolute difference of measurements repeated two weeks apart in six subjects (Wu et al. 2007). They reported measurement error as 1.6° (intra-observer) and 1.9° (inter-observer). For a bi-plane radiography/CT method of 3D cervical inter-vertebral motion measurement, repeatability of the semi-automated tracking process was assessed by tracking the movement of one spinal segment (C6/7) from one flexion-extension sequence three times (Anderst et al. 2011). Repeatability was calculated as the within-frame standard deviation for each of the six degrees of freedom from the three sets of tracking results and reported as 0.06° (Anderst et al. 2011). This would suggest this method is highly repeatable although it would have been preferable to know the repeatability for each inter-vertebral level and from a number of different subjects since these vary, as found in this present study and others (van Mameren et al. 1990; Amevo et al. 1991b; Teyhen et al. 2005). In any case this method is associated with a high radiation dose, so not suitable for routine use (Anderst et al. 2014).

As reported in other studies (Frobin et al. 2002; Wu et al. 2007) inter-observer error is typically larger than intra-observer (Deitz et al. 2011). Inter-observer errors for angular range in this present study (Appendix 3) were highly comparable or smaller than that of intra-observer error.

This perhaps evidences a practice effect: the two observers were considered to be at a similar level of training whereas the images may have been analysed more competently when done a second time by the first observer. In any case, the disagreement in both scenarios was small and the ICCs were high, suggesting that measurement error of QF for angular range is low and subjects may be distinguished. It is concluded that acceptable intra- and inter-observer repeatability can be achieved for the determination of maximum IV-RoM, both for the follow-ups of participants and comparisons between them (in Part III).

• IAR location

In contrast to the repeatability for angular range, IAR location did not exhibit as good agreement or reliability. The SEMs ranged from 0.84 – 2.67mm (5.6%-17.8% of vertebral body depth) in the X direction and 1.06-2.73mm (7.1%-18.2% of vertebral body depth) in the Y direction which is too large an error from which to detect changes. ICCs ranged from 0.04 (virtually no reliability) to 0.90 (substantial reliability). But even where ICCs were indicative of substantial reliability, the confidence intervals were mostly very wide and included the value of zero, indicating the possibility of no reliability. It has been previously reported, from a plain-film flexion-extension study of the lumbar spine, that errors for IAR location are too large from rotations less than five degrees (Pearcy and Bogduk 1988). In a cineradiography study the smallest acceptable error for IAR location was considered to be that when measured from a minimum rotation of seven degrees (van Mameren et al. 1992). It was hoped that measurement error with this QF method would improve on that of previous methods; however, the findings from this present study are in agreement with these judgements.

Measuring flexion and extension as one continuous sequence would have increased the number of segments that exceeded the minimum range and thus reduced the error for IAR location. However, for the purposes of this present thesis flexion and extension were measured separately in order to also measure laxity/attainment rate, which can only be done from neutral (Mellor et al. 2009). Also, with combined flexion-extension, the risk of out-of-plane motion or even out-of-frame motion is increased, which makes it more difficult for the vertebral movements to be accurately tracked (Hipp and Wharton 2008). Additionally, if combined movement gives a smaller range than what is considered normal, the composite figure will not record which, or whether both, of the two separate movements caused the limitation (Jordan 2000).

It might be that the error could be significantly decreased by calculating it from the stitching together of the flexion-extension sequences; this is possible, but was not considered feasible during the time-frame of this study. Improvements in the image tracking codes may also be possible but is beyond the scope of this thesis.

In a study evaluating the error for calculating IAR location from end-range flexion-extension plain films, errors varied by level and are shown in Table 10 (Amevo et al. 1991b).

		X co-ordinate		Y co-ordinate	
	Inter-vertebral level	Mean(SD)	Range	Mean(SD)	Range
Intra-observer differences (mm)	C2/3	-0.07 (0.47)	-1.0 to 0.5	0.05 (0.42)	-0.6 to 0.5
	C3/4	-0.09 (0.36)	-0.7 to 0.3	-0.01 (0.43)	-0.7 to 0.9
	C4/5	0.03 (0.32)	-0.4 to 0.6	0.22 (0.40)	-0.4 to 0.9
	C5/6	0.05 (0.37)	-1.0 to 0.7	0.20 (0.42)	-0.4 to 0.7
	C6/7	-0.12 (0.40)	-1.1 to 0.3	0.20 (0.42)	-0.6 to 0.6
Inter-observer differences (mm)	C2/3	-0.05 (0.52)	-1.0 to 0.6	0.28 (0.56)	-0.5 to 0.7
	C3/4	-0.06 (0.47)	-0.8 to 0.3	0.38 (0.48)	-1.2 to 1.0
	C4/5	0.05 (0.36)	-0.4 to 0.6	0.44 (0.42)	-0.2 to 1.1
	C5/6	0.05 (0.47)	-1.0 to 0.7	0.39 (0.45)	-0.4 to 1.0
	C6/7	0.08 (0.47)	-0.9 to 0.5	0.40 (0.47)	-0.5 to 1.4

Table 10: Mean (SD) and range of intra- and inter-observer differences in IAR location (X, Y) (Amevo et al. 1991b)

Intra-observer absolute mean differences ranged from 0.03 to 0.12mm (X co-ordinate) and 0.01 to 0.22mm (Y-co-ordinate) but standard deviations were large and much larger than the corresponding mean difference. Ranges were also reported (Table 10) (Amevo et al. 1991b). These data represented an improvement on the errors associated with other plain-film techniques of measuring IAR location (Amevo et al. 1991a). SEM and ICCs were not reported, making comparisons with this present study difficult, but some of the absolute mean differences in this present study were substantially larger than that reported by Amevo et al (1991b).

To determine repeatability in a cineradiography study, one film was marked each day for six days (van Mameren et al. 1992). Like Amevo et al (1991b), this study did not report SEM or ICCs.

Rather they determined the combination of the number of image frames (20 frames) and the minimum angle (7°) between a pair of frames which produced the closest clustering (precision) of the six IARs calculated for each level (van Mameren et al. 1992). They then reported the average distance between each IAR for each level and compared these data to those obtained from the repeat marking of one cineradiographic film over six consecutive days for the calculation of static IARs. From C1/2 through C5/6 precision was improved with the averaged method (static IAR precision was better for C0/1 and equal at C6/7). Considering only C1/2 to C5/6, the mean (SD) distance between each of the six averaged IARs ranged from 0.5mm (0.2) (C4/5) to 1.4mm (0.2) (C1/2). Mean distances were not reported for x-distance and y-distance making comparisons more difficult. A more recent study sought to determine the 'reliability' of a biplane radiography/CT method of measuring ICR location using simulated data; again, no agreement or reliability statistics were reported to make comparisons or judgements (Baillargeon and Anderst 2013).

In a review of the cervical kinematics literature it was concluded from the findings of van Mameren et al (1992) (and Amevo et al 1991b) that IARs can be reliably and consistently calculated within a small margin of technical error, and that it is a stable parameter over time in healthy individuals (Bogduk and Mercer 2000). Despite this being the case, it has apparently not been adopted in routine clinical practice (Hipp and Wharton 2008) suggesting the lack of an obvious utility clinically. Due to the lack of agreement and low reliability found using the methodology in this present study, and it being anticipated that this will make it difficult to detect any changes in IAR location within-subjects, it was decided not to include this kinematic parameter in the main study (Part III). For future studies improved tracking codes and/or stitching of flexion and extension sequences to increase the size of the range from which IARs are calculated might make such calculations possible.

• Attainment rate

Laxity/attainment rate, as defined in this thesis (the ratio between the two gradients of inter-vertebral motion and corresponding first 10° of regional motion – see Figure 35), is a relatively new concept (Breen et al. 2012) and no study has reported the repeatability of such a proxy measurement of the neutral zone *in vivo*. Some comparison might be made, however, with the results from a recent PhD thesis which sought to determine the repeatability of this parameter using the same QF method (that was adapted for use in the cervical spine for this study) in the lumbar spine (Mellor 2014).

In Mellor's (2014) thesis the observer repeatability of attainment rate was calculated for flexion and extension of L2/3, L3/4 and L4/5. The mean intra-observer agreement (SEM) for flexion was 0.008, for extension it was 0.013. The measurement errors in this present study (Table 6) are larger with the mean SEM for flexion, 0.028, for extension, 0.024; they are of an order of magnitude akin to the *inter*-observer agreement reported by Mellor (mean SEM flexion: 0.028; extension: 0.034). In both studies the number of participants was the same (n=10) but with more segments available for analysis in this study (maximum of 50 in each direction versus 30 in the lumbar study) it is not immediately obvious why the measurement errors should be so different.

There is greater similarity when the reliability statistics are compared between the two studies with both reporting ICCs consistently greater than 0.9, indicating 'substantial' reliability (Shrout 1998). Exceptions to this are the ICCs for C1/2 in flexion (0.78) and C5/6 in flexion (0.70) and extension (0.84), more indicative of 'moderate' reliability (Shrout 1998). The importance of attainment rate is in distinguishing patients from healthy volunteers hence this will be a useful kinematic parameter in the main study.

5.5 Conclusion

The kinematic parameter, IAR location, was not found to be sufficiently repeatable to be of use in the main study. Angular range and attainment rate in contrast were found to be highly repeatable and will be included. Additionally the parameters of hypo-mobility and paradoxical motion, both functions of angular range, could be included. In the following, final part of this thesis, the prevalence of these parameters will be explored in patients with neck pain and matched healthy volunteers.

PART III: Clinical studies

"It doesn't surprise me a bit. Neck pain is a mechanical problem, and it makes sense that mechanical treatment works better than a chemical one" – Dr Lee Green, Professor of Family Medicine at the University of Michigan, responding to the results of an RCT comparing spinal manipulation, medication and home exercise for the treatment of neck pain (Chapman-Smith 2012)

General Introduction

Investigation of the effects of spinal manipulative therapy on inter-vertebral function has been hampered by the lack of an objective, reproducible method of inter-vertebral motion measurement. In part II of this thesis, quantitative fluoroscopy was found to be accurate and repeatable for a number of inter-vertebral motion parameters. These parameters were then explored in patients with neck pain and healthy volunteers in three studies (Chapters 6-8) in this third and final part of the thesis.

Part III begins first with an overview of the main study design (three inter-related studies) followed by a description of the recruitment process and ethical approval common to all three studies.

Methods

Main study design

This was a prospective cohort study of patients undergoing spinal manipulative therapy for neck pain, with a parallel cohort of age and sex-matched healthy volunteers. Please see the flowchart (Figure 40) for an overview.

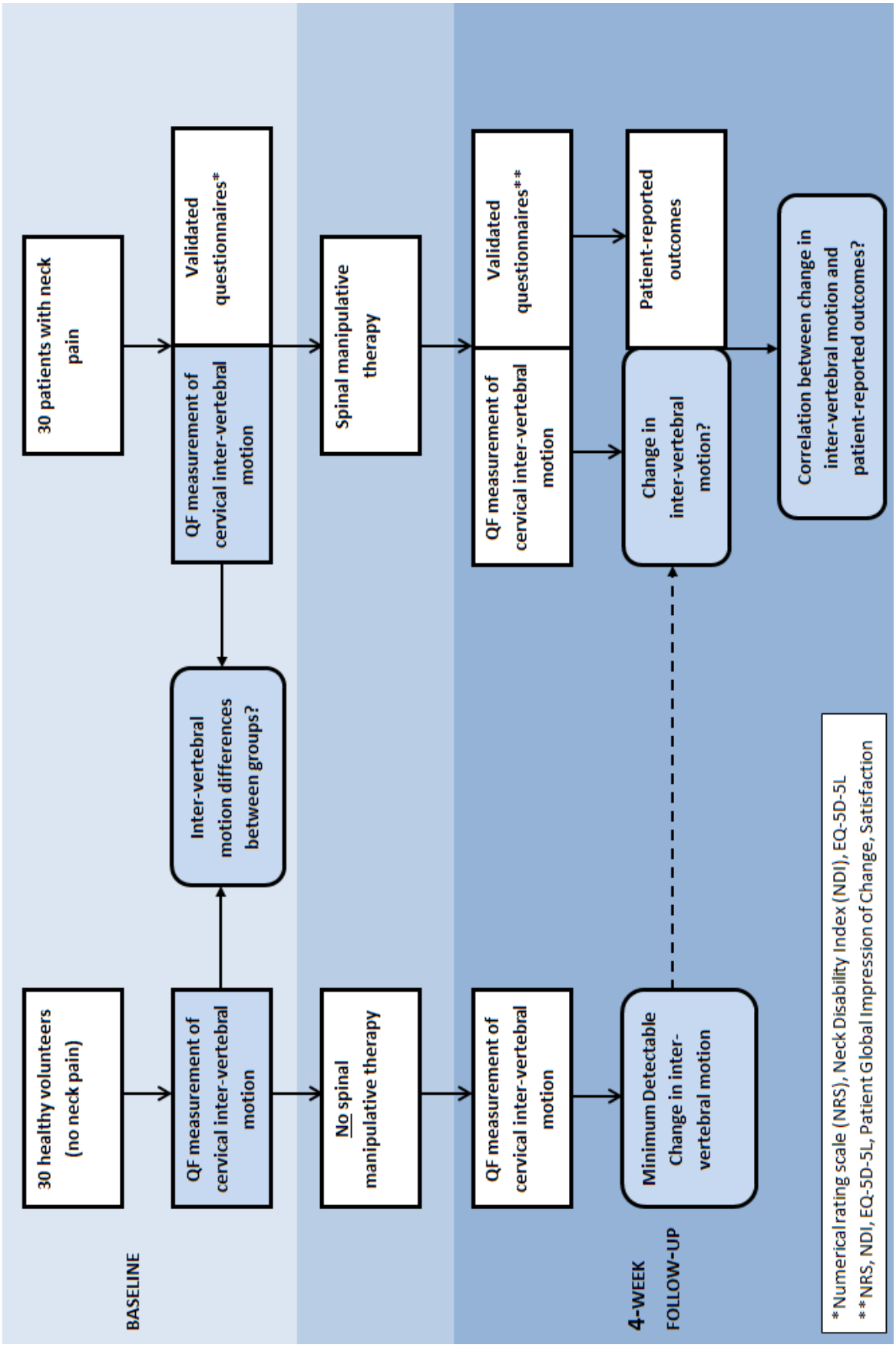


Figure 40: Flowchart of main study

The main study was conceptually divided into three separate but interrelated studies, as outlined below:

(i) Cervical inter-vertebral motion in patients with neck pain and healthy volunteers – a cross sectional study (Chapter 6 pages 132 - 152)

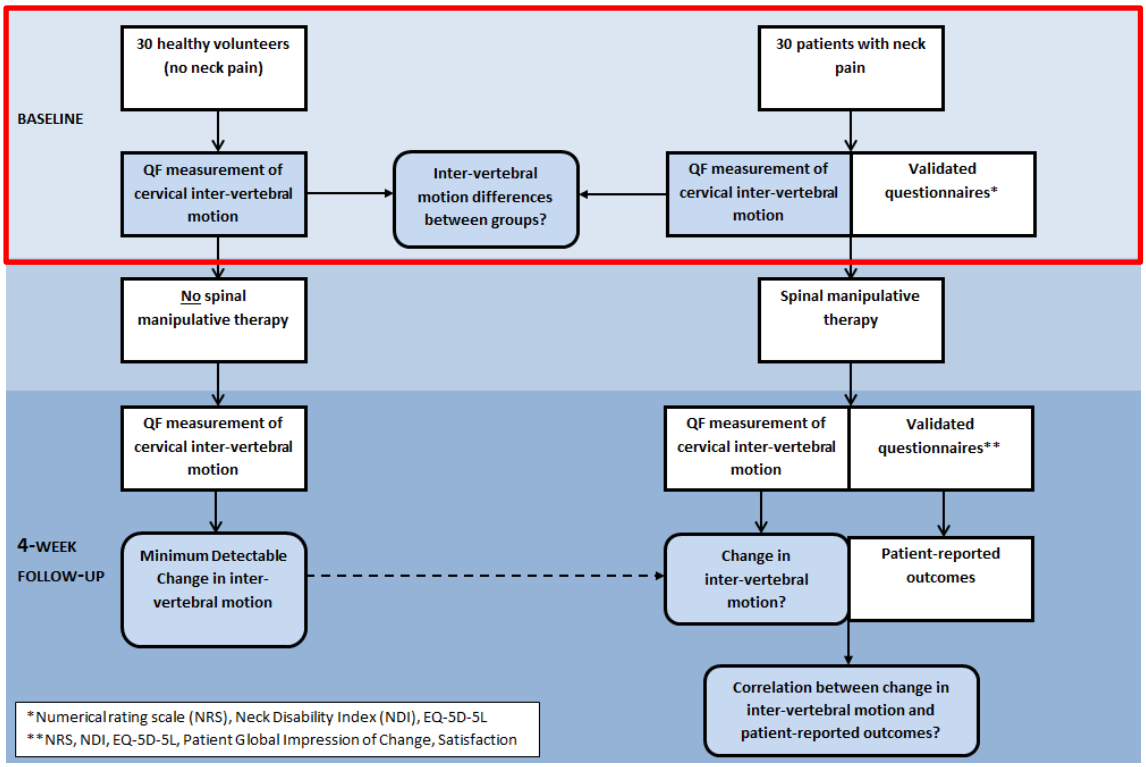


Figure 41: Flowchart of main study with cross sectional study highlighted by red box

The cross-sectional study aimed to identify any inter-vertebral motion differences between groups at baseline thereby indicating potentially important variables regarding inter-vertebral motion changes in patients.

(ii) Intra-subject reproducibility study: Estimating the minimum detectable change of inter-vertebral angular motion from healthy participants (Chapter 7 pages 153 - 161)

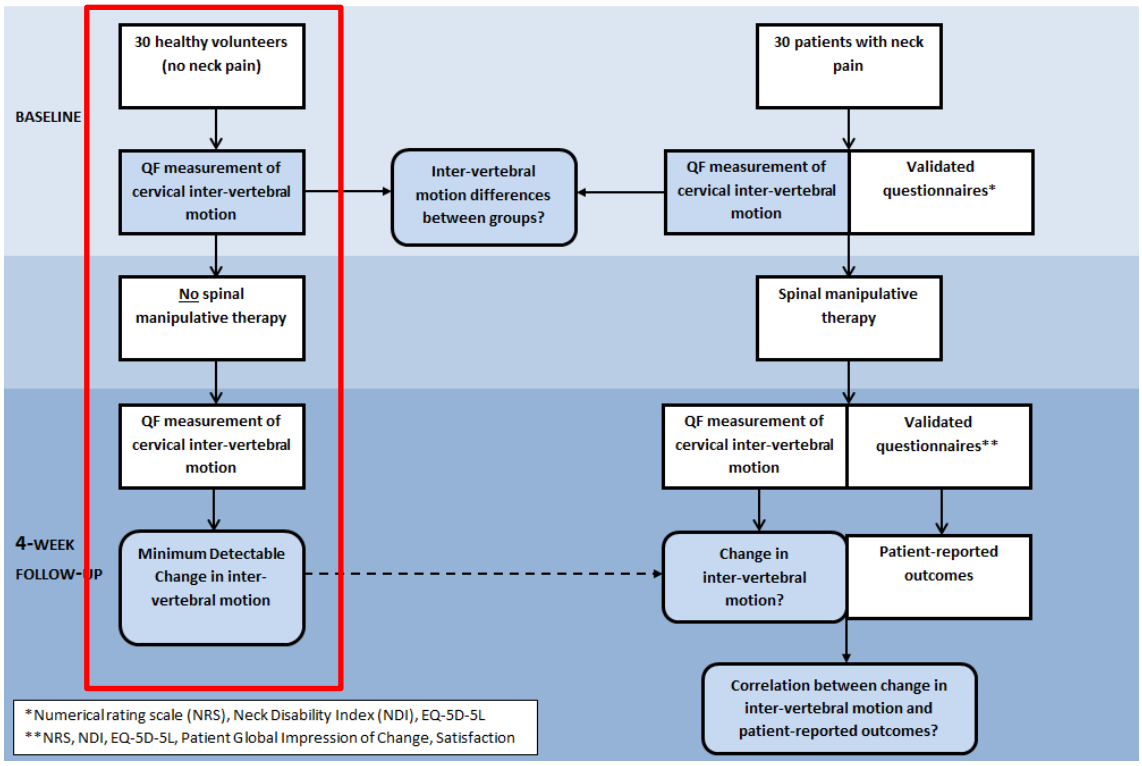


Figure 42: Flowchart of main study with intra-subject reproducibility study highlighted by red box

The intra-subject reproducibility study aimed to identify the magnitude of inter-vertebral angular motion change in healthy volunteers during the four-week study period (minimum detectable change).

(iii) Spinal manipulative therapy for the treatment of neck pain: A prospective cohort study (Chapter 8 pages 162 - 191)

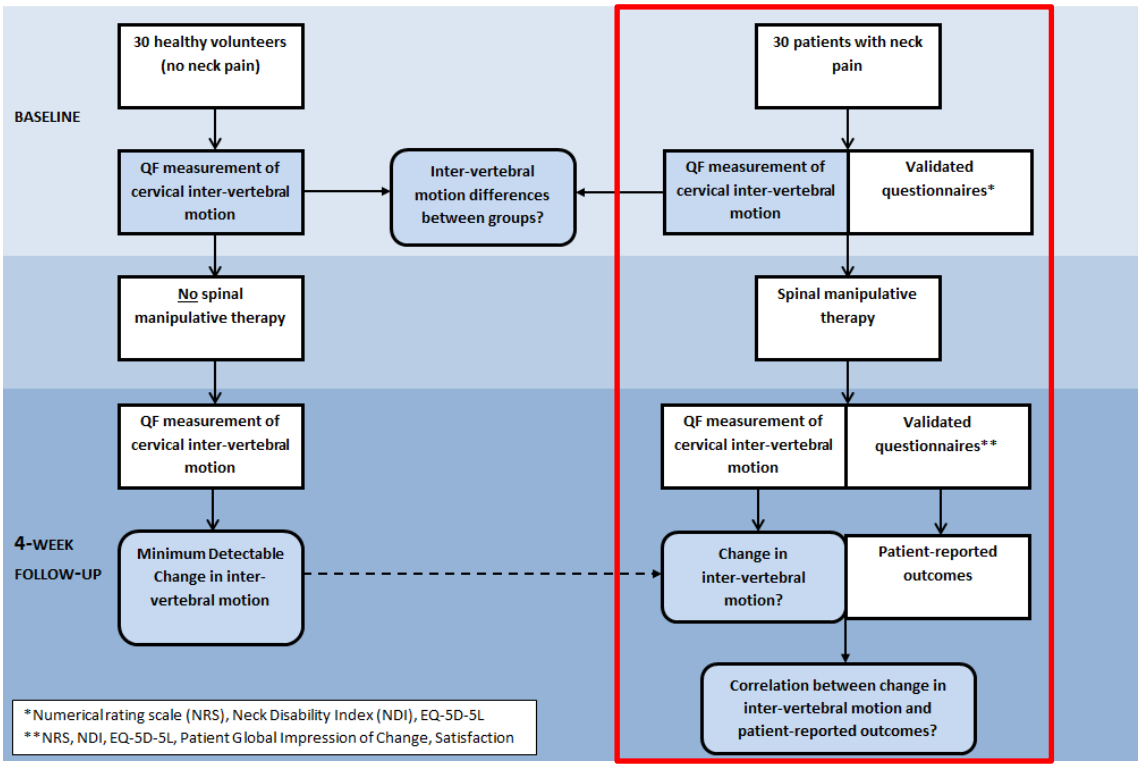


Figure 43: Flowchart of main study with prospective cohort study highlighted by red box

This final study was a prospective cohort of patients with neck pain receiving spinal manipulative therapy. This study aimed firstly, to identify changes in inter-vertebral motion, which were defined as increases in IV-RoM exceeding the minimum detectable change, as identified in sub-study (ii). The second aim of this study was to find out if inter-vertebral motion changes were correlated with changes in patient-reported outcomes.

Participants

A number of sources of bias were anticipated prior to recruitment such as the influence of osteoarthritic changes with age (Simpson et al. 2008), possible gender effects on disability (Cote et al. 2004) and complaint duration on both clinical and biomechanical outcomes. In an attempt to minimise these, the aim was to recruit 36 patients with mechanical neck pain and match them by age and gender to 36 healthy volunteers without neck pain. Anticipating a 20% loss to follow-up this would provide 30 participants in each group. The recruitment of 30 participants to each group was considered feasible considering time and resource constraints. This would also allow adequate opportunity for normal distributions of interval data if present and therefore use of parametric statistical tests which are more sensitive to detecting differences between groups (Field 2009). Based on being able to detect a 3.5° (SD 6.5°) increase in range in patients (the highest threshold for hypo-mobility based on a review of plain-film studies of cervical inter-vertebral motion (Deitz et al. 2011) using the lower 2.5th percentile of rotational range at the 95% significance level) 30 participants would also give an 80% power to detect change in IV-RoM.

While the use of convenience samples is fairly typical in medical research for reasons of practicality, this does limit confidence in generalising findings to the population (Bland 1996). It might also be suggested that if kinematic differences such as in the prevalence of inter-vertebral hypo-mobile segments are not detected in a sample this size then either the sampling procedure is wrong, or it may be that differences are not large enough to be clinically meaningful.

Recruitment

Over an 18 month period (August 2011 – April 2013)[16] participants were recruited based on the eligibility criteria set out in Table 11 (inclusion) and Table 12 (exclusion).

Inclusion criteria	
All participants	Male and female
	Age 18 – 70 years*
	Able and willing to participate
	No large (effective dose greater than 10mSv) radiological investigations or treatments in the past two years
	Capable of giving informed consent
	Not pregnant or likely to be pregnant
	Willing for GP to be informed about participation
Patients	Mechanical neck pain (reproducible by neck movement/provocation tests) and no identifiable aetiology e.g. infection, inflammatory disease (Neck Pain Task Force† Grade I or II)
	Pain located within the area defined by the Neck Pain Task Force†
	Self-reported pain rating 3 or more on 11-point numerical rating scale
	Pain of at least 2 weeks duration**
	No contraindications to spinal manipulative therapy
Healthy volunteers	No activity-limiting neck pain lasting more than 24 hours in the last 12 months
	No current neck pain, dizziness or vertigo (unsteadiness)

† *Neck Pain Task Force*, The Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders (Guzman et al. 2008b)

*****Initially 18-60 years; **initially pain of at least 4 weeks duration (See Exclusions and subsequent amendment to inclusion criteria, page 126)

Table 11: Inclusion criteria for patients and healthy volunteers

[16] Recruitment was suspended for three months during this time period to focus on the MPhil transfer.

Exclusion criteria	
All participants	History of cervical spine surgery
	Poor understanding of English
	Current involvement as a subject in another research study
Patients	Non-mechanical neck pain
	Depression
	Litigation/compensation pending
	Manual therapy already received for this episode of neck pain
	Primary complaint of arm pain
	Traumatic onset of this neck pain episode
	Central sensitisation as assessed by pressure algometry
Healthy volunteers	Cervical/thoracic spine manipulation in week prior to baseline imaging

Table 12: Exclusion criteria for patients and healthy volunteers

Healthy volunteers were recruited from staff and students from AECC and Bournemouth University (School of Health & Social Care). Healthy volunteer participants were identified from a database of interested volunteers collated by the researcher and eligibility was assessed by completion of the healthy volunteer pre-study form (Appendix 8). Participation of one healthy volunteer was delayed by one week due to having recently received spinal manipulation to the cervical spine (practising chiropractic student). Patients with neck pain attending the AECC out-patient teaching clinic were identified at their first visit, and visited by the researcher to discuss their participation in the study; eligibility was confirmed after patients' completion of the patient pre-study form (Appendix 9). Both patients and healthy volunteers had at least 24 hours to make a decision regarding their participation.

Baseline clinical evaluation of patients

The AECC out-patient teaching clinic is predominantly staffed by chiropractic interns in their clinical training year prior to becoming qualified as chiropractors, and the registered chiropractors who supervise them. Patients who participated in this study underwent a standard clinical evaluation by interns used for all new patients.

This included, but was not limited to: a clinical history to establish the nature of the patient's complaint and general health status, and a comprehensive physical examination[17] to evaluate the patient's health status and determine if their neck pain was mechanical in nature.

In primary care, when neck pain is the only symptom, a non-mechanical cause is extremely rare (NHMRC. 2003; Murphy and Hurwitz 2011). Nevertheless, neck pain from a vascular origin, with or without headache, may mimic that of musculoskeletal pain (Taylor and Kerry 2010) and this needs to be ruled out as part of the diagnostic process. Likewise the appropriateness of various treatments that might be offered to the patient (e.g. spinal manipulation) is also an important focus for the diagnostic work-up. It is routine for potential risk factors for VBA stroke to be considered in neck pain patients, including female, age under 45, migraine, genetic predisposition e.g. connective tissue disorder, oral contraceptive use and risk factors associated with atherosclerosis e.g. hypertension and smoking (Rubinstein et al. 2005). It was not part of the routine to perform pre-manipulation testing as such tests are of limited diagnostic utility (Thiel and Rix 2005; Taylor and Kerry 2010; Hutting et al. 2013). Consideration is also given to the unlikely possibility of evolving internal carotid arterial dissection (Taylor and Kerry 2010); in addition to establishing a patient's past medical history, vital signs (pulse and respiratory rate, blood pressure, and temperature), and a neurological examination (cerebellar function and cranial nerve testing) are part of the evaluation carried out on every new patient. A recently proposed International Framework for evaluating risk prior to a manual therapy intervention on the cervical spine emphasised the importance of the history-taking process in detecting those who might be at risk of a vascular event (Rushton et al. 2014).

The clinical evaluation had already been carried out and discussed with the researcher before the researcher approached the patient to discuss their participation in the study. There was the opportunity for the researcher to ask any additional pertinent questions and perform any physical examinations, including pressure algometry (see Central Sensitisation, page 128) to confirm eligibility for the study. All patients were also examined by the chiropractor who was supervising the chiropractic intern; in addition to this, the intern determined the working diagnosis after discussing the case with a senior chiropractor. All stakeholders had the opportunity to make known their opinions regarding the appropriateness of a patient's participation in the study.

[17] In their clinical training year interns are required to perform respiratory, cardiovascular, abdominal and neurological examinations in addition to any orthopaedic and neurological testing focused on the patient's primary complaint.

It was standard practice for treatment not to be initiated until the patient returned for their second visit unless earlier treatment was clinically indicated, therefore treatment was not delayed for study patients needing to return for their first QF assessment prior to treatment commencing. On two occasions otherwise eligible patients were not entered into the study owing to their desire for earlier treatment.

Rationale for inclusion and exclusion criteria

Age-range

The age range was initially restricted to 18 – 60 years due to the prospective healthy volunteer cohort being composed of working-age adults, and spinal manipulation for neck pain has only been adequately studied in the adult population (Gross et al. 2010).

Neck pain – location, category and duration

The location of neck pain was that defined by the Neck Pain Task Force, as shown in Figure 44.

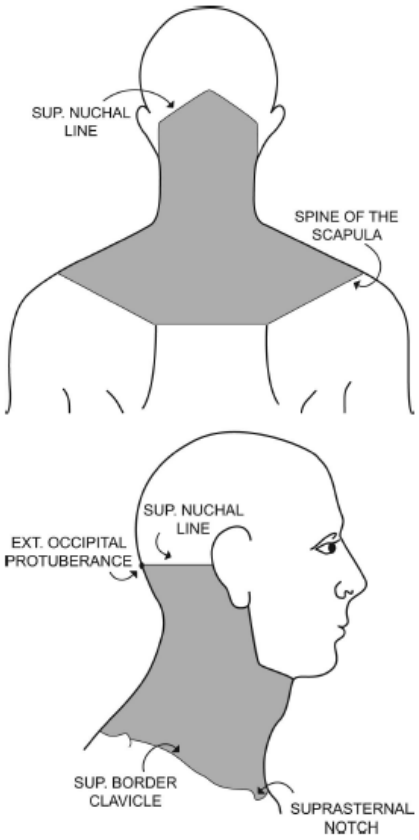


Figure 44: Location of neck pain as defined by the Neck Pain Task Force; image from (Guzman et al. 2008b) with permission from Lippincott Williams & Wilkins

Patients were eligible if they met the Neck Pain Task Force criteria for grade I or II neck pain (Table 13).

Category	Descriptor
Grade I	Neck pain and associated disorders with no signs or symptoms suggestive of major structural pathology* and no or minor interference with activities of daily living.
Grade II	No signs or symptoms of major structural pathology, but major interference with activities of daily living.
Grade III	No signs or symptoms of major structural pathology, but presence of neurologic signs such as decreased deep tendon reflexes, weakness, or sensory deficits.
Grade IV	Signs or symptoms of major structural pathology

*Major structural pathologies include (but are not limited to) fracture, vertebral dislocation, injury to the spinal cord, infection, neoplasm, or systemic disease including the inflammatory arthropathies.

Table 13: Categories of neck pain proposed by the Neck Pain Task Force (Guzman et al. 2008b)

These categories of neck pain include the possibility of radiation of pain to the head, trunk or arms (Guzman et al. 2008b) but patients with arm pain as the main complaint, more likely to be categorised as Grade III, were excluded as this is indicative of cervical radiculopathy (pain from cervical spine nerve roots); it is strongly argued that this has a defined patho-anatomical basis therefore should be regarded as a condition distinct from mechanical/non-specific neck pain (Bogduk 2011). Traumatic neck pain was excluded as spinal manipulative therapy is typically contraindicated, particularly in cases of fracture or dislocation (Peterson and Bergmann 2011). A history of whiplash however, was only exclusionary if this was the reason for the current episode of neck pain.

At least four weeks of neck pain (sub-acute or chronic) was initially designated the minimum duration, as the longer symptoms have been present the more ‘stable’ the condition, (Vernon et al. 2006) so changes in symptoms might be more confidently associated with spinal manipulation rather than only with spontaneous recovery.

An eligible episode of neck pain was defined as an episode which was preceded by one month free of neck pain. This designation was derived from international consensus recommendations regarding the definition of the duration and commencement of an episode of back pain (de Vet et al. 2002; Stanton et al. 2009).

Pain severity

The minimum level of pain was a score of ≥ 3 on an 11-point numerical-rating scale. This is the minimum level of pain from which a 30% change from baseline can be detected and the minimum score change considered clinically meaningful according to international consensus recommendations for LBP research (Ostelo et al. 2008).

Central Sensitisation

Patients who have had pain for a long time may develop central sensitisation, a physiological phenomenon where the central nervous system has become overly sensitive to stimuli and therefore the threshold of stimulus required to evoke pain is reduced (Latremoliere and Woolf 2009). Patients with central sensitisation are best managed with an approach that is beyond the therapy being offered in this study (Nijs and Van Houdenhove 2009). In order therefore to exclude 'central sensitisers' an algometer was used to measure patients' sensitivity to pressure which is a common way of assessing if someone is centrally sensitised in research (Neziri et al. 2011). This was performed by applying pressure to the pulp of the second toe (Figure 45) (or to the low back if patients had problems with their toes) following the methods set out by Neziri et al. (2011) who have published reference values based on age, gender and the location of pressure application. The threshold for ineligibility was pressure-pain provocation at or below the lower reference level (2.5th percentile) for hypersensitivity.

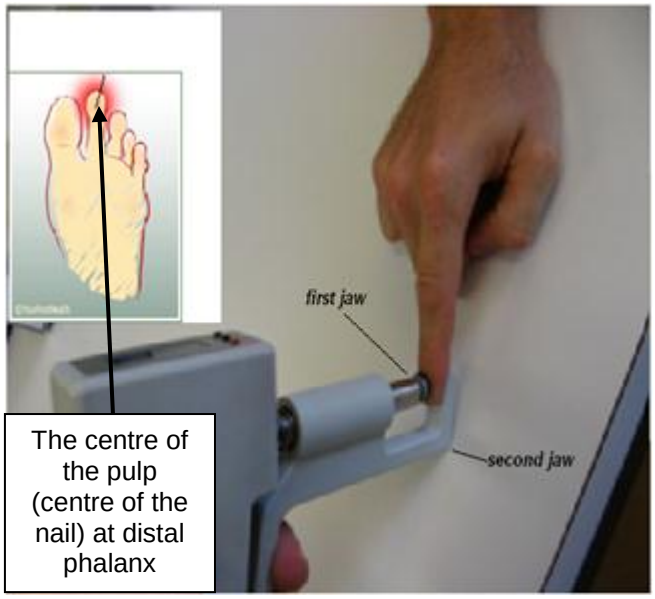


Figure 45: Pressure algometer; image courtesy of Dr A.Y. Neziri

Depression

Poor psychological health is associated with a negative prognosis for recovery from neck pain (Carroll et al. 2008b) and depression is more than twice as likely to be reported by neck and back pain sufferers than those without such pain (Demyttenaere et al. 2007). This represents a risk that patients will report no improvement in pain and disability due to depression and independent of any cervical spine kinematic changes. Therefore patients with a history of diagnosed depression (by a medical doctor) within the previous 12 months (this is the time frame employed by the World Health Organisation World Mental Health Survey Initiative as constituting “major depression”) (Demyttenaere et al. 2007) were excluded. For related reasons patients who had on-going litigation/compensation related to their neck pain were also excluded (Cote et al. 2001; Carroll et al. 2008c).

Disability

Patients typically present to the AECC clinic with neck pain that *anecdotally* causes mild disability. Therefore a minimum level of neck pain-disability as an inclusion criterion, recommended when disability measures are used (Stanton et al. 2009), was considered a potential hindrance to recruitment and therefore not implemented. Healthy volunteers were recruited on the basis of reporting having not had an episode of neck pain lasting 24 hours or more in the previous 12 months (de Vet et al. 2002) and no current dizziness or vertigo, which can be indicative of a cervical spine disorder (Holm et al. 2008).

Exclusions and subsequent amendment to inclusion criteria

In all, 161 patients were considered ineligible for participation (Figure 46). Major reasons for exclusion were: arm pain of a greater intensity than neck pain, a traumatic aetiology, having already received some form of manual therapy for the current episode of neck pain, duration of symptoms, ‘missed’ (patients not visited at their first clinic attendance due to the researcher’s other commitments), depression and age.

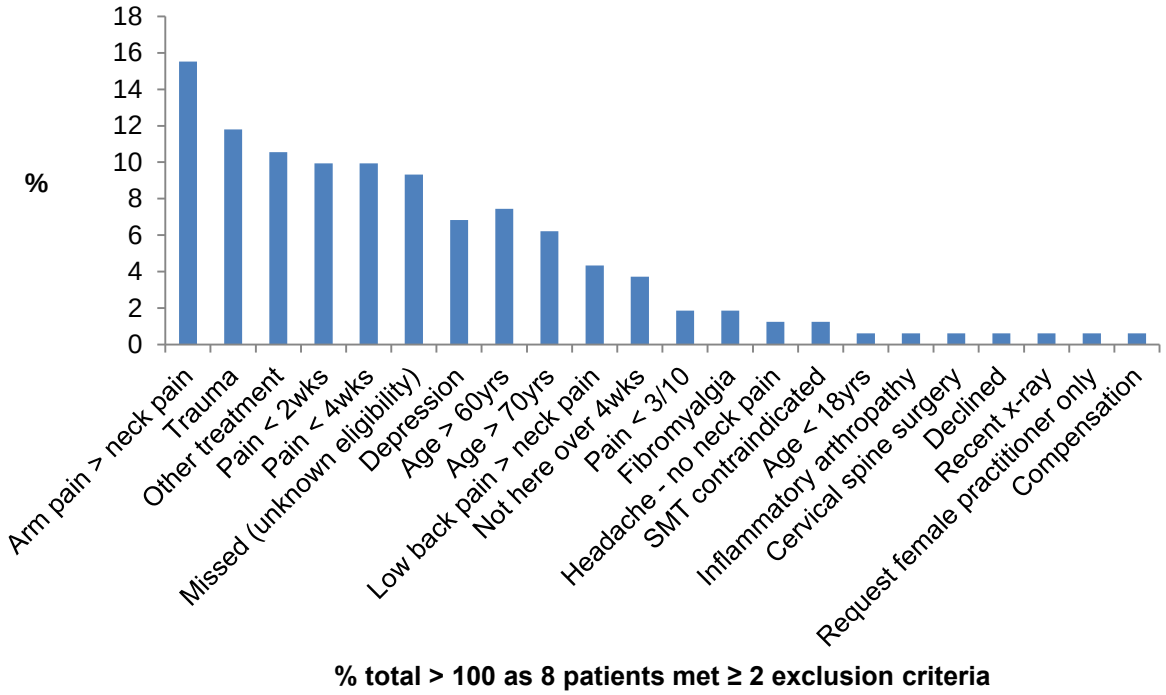


Figure 46: Reasons for patient ineligibility (n=161)

When reviewed at six months the eligible age range and the minimum duration of symptoms were identified as barriers to recruitment that could be modified. As suggested in Figure 46, the exclusion of those over 60 years was identified as a major barrier to recruitment so the upper age-limit was increased to 70 years. It is typical for randomised clinical trials of spinal manipulation for neck pain to include participants aged over 60 (Hoving et al. 2002; Bronfort et al. 2012; Evans et al. 2012; Maiers et al. 2014). While age remained an important reason for excluding patients (Figure 46) this change did allow for the recruitment of three patients over 60. It proved possible to identify suitably aged healthy volunteers for matching despite this increase.

Duration of symptoms was eventually reduced to two weeks to enhance recruitment. This was justified on the basis of evidence that most cases of mechanical neck pain will resolve within two weeks, and for those who have neck pain beyond this time, manual therapy is a rationale treatment choice (Koes 2012). Additionally, two weeks duration is often the minimum eligibility for recruitment into randomised clinical trials (Hoving et al. 2002; Bronfort et al. 2012). While duration continued to be an important reason for excluding patients (Figure 46) this reduction did allow for the recruitment of an additional two patients. Both changes were approved by NRES Cornwall & Plymouth in an amendment to the original study protocol (Notice of Substantial Amendment 2:29/6/12).

Ethical considerations

All participants were informed of study risks and benefits, given the time required to make a decision regarding participation, and informed of their rights to refuse or withdraw at any time without prejudice. Written informed consent (Appendix 10) was obtained from all participants as directed by the Department of Health (DOH 2009) and the General Medical Council (GMC 2008). Ethical considerations and information about the study were included in participant information sheets (Appendix 11 and Appendix 12).

Ethical approval

The RD6 Initial Review of the protocol for this study was approved by the Postgraduate Committee of the School of Health & Social Care, Bournemouth University, and ethical approval was granted by the National Research Ethics Service Committee South West – Cornwall & Plymouth (11/SW/0072 – Appendix 13).

Chapter 6. Cervical inter-vertebral motion in patients with neck pain and healthy volunteers – a cross sectional study

6.1 Introduction

Most cases of neck pain are considered to be 'mechanical' in nature (Binder 2008), based on the clinical finding that pain is made worse by neck movement and/or by provocative orthopaedic testing (Guzman et al. 2008b). It is thus inferred that the source of pain is one or more of the innervated, and therefore potentially pain-producing, structures of the cervical spine (Bogduk 2011). The cause of the pain is another matter (Bogduk 2011). Based on the common finding of reduced regional cervical ROM in patients with neck pain (Hagen et al. 1997; Rudolfsson et al. 2012) it could reasonably be expected to find inter-vertebral motion differences between patients with neck pain, and those without neck pain (Amevo et al. 1992). This study sought to find out if there were differences in cervical IV-RoM (angular range, hypo-mobility, attainment rate, paradoxical motion) between healthy volunteers with no neck pain and patients with neck pain (Research Question 2 page 59).

6.2 Methods

6.2.1 Study design

This was a cross-sectional study of cervical flexion and extension inter-vertebral motion in 30 patients with neck pain and 30 age and sex-matched healthy volunteers to serve as a control group (Figure 41). Details regarding recruitment have been presented previously (see pages 122 - 124).

6.2.2 Data collection

Inter-vertebral motion

Patients and healthy volunteers had QF acquisitions and measurement of cervical inter-vertebral motion following the protocol and procedures detailed previously (Chapter 3). The following inter-vertebral motion data were collected: angular range, hypo-mobility, paradoxical motion (page 81) and attainment rate (page 85). The cut-off for inter-vertebral hypo-mobility was set at the 2.5^{th} percentile from the distribution of healthy volunteer angular range data for each inter-vertebral level (Deitz et al. 2011). In order to avoid differences in IV-RoM being detected simply because of patients not moving through their full range due to pain, they were instructed to move as far as possible, through the pain if necessary, until a physical barrier was felt.

Cervical spine sagittal alignment

To confirm that participants' cervical spines were being correctly positioned in neutral prior to imaging and minimise between-subject variation (see section 3.2.2) the sagittal alignment (lordosis) of the cervical spine was measured using the posterior tangent method (Gore 2001) on the first 'neutral' image of each participant's imaging sequence (Figure 47).

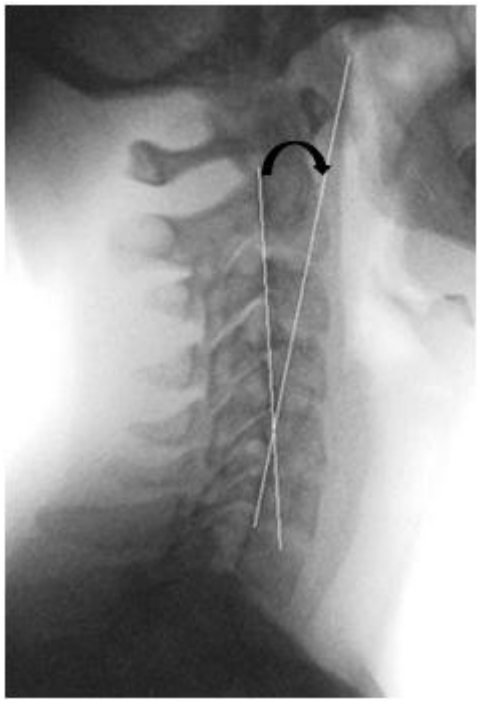


Figure 47: Posterior tangent method of measuring cervical sagittal alignment

This is a simplified version of the method of drawing posterior tangents at each vertebra between C2 and C7, and summing the angles from each of these to give an overall lordosis angle, a method considered more precise than the commonly used Cobb method (Harrison et al. 2000). Since C7 was not fully visualised in eight participants (six patients, two healthy volunteers) measurements were made from C2 to C6 for consistency across all participants.

The measurements were achieved by importing the first image from each participant's motion sequence into' Image J' digital geometric software (a public domain, Java-based image processing program developed at the National Institute of Health, USA - http://imagej.nih.gov/ij/download.html).The image was magnified (75%) to aid precision of line placement and lines were drawn tangentially to the posterior vertebral bodies of C2 and C6 (Figure 47). The Image J protractor tool was used to measure the angle formed by the intersecting lines.

Radiographic anomalies

Images were visually inspected by the researcher to identify any radiographic anomalies, which could act as confounders for IV-RoM differences between groups.

6.2.3 Data analysis

Two observers (the researcher and the first PhD supervisor) independently inspected both groups' motion graphs to visually identify paradoxical rotational motion. Disagreements were resolved by consensus. Discrete data (number of hypo-mobile and paradoxical segments) were analysed for differences in proportions between patients and healthy volunteers with the Fisher's exact test. For continuous data (sagittal alignment, angular range, laxity/attainment rate) normality of the distributions were assessed with the Shapiro-Wilk test. Means for each of the continuous variables from patient and healthy volunteer groups were analysed for differences using the unpaired Student's *t* test. Medians from non-normal distributions were analysed for differences with the Mann-Whitney *U* test. Due to common usage in the literature, data are presented as means and standard deviations. Where data distributions were not normally distributed but Student's *t* test was significant, these were checked with the Mann-Whitney *U* test and results were altered accordingly.

6.3 Results

6.3.1 Baseline characteristics

The baseline characteristics of each group are shown in Table 14 (page 135). One patient's imaging sequence was not available due to a technical error, reducing the patient sample to 29. This patient's data were removed from all analyses, as were the inter-vertebral data from the healthy volunteer matched to this patient. There were no significant differences in age, sex or number of radiographic anomalies between groups at baseline. Sagittal alignment data were normally distributed in each group; the large standard deviations were due to the inclusion of negative (signifying cervical kyphosis) numbers. While sagittal alignment of the cervical spine was on average 4.4° more lordotic in patients, this difference was not statistically significant. Regional cervical spine motion (as measured with the CROM device) was significantly reduced in flexion and extension in patients compared to healthy volunteers'.

Characteristics		Patients (n = 29)	Healthy volunteers (n = 30)	Difference (95% CI)	Significance (p)
Female, n (%)		21 (70.0)	21 (72.4)	-	>0.99‡
Age, years, mean (SD)		39.7 (13.1)	40.9 (13.1)	1 (-5.6 to 8.1)	0.72†
***Cervical radiographic sagittal alignment, degrees, mean (SD)**		9.5 (13.3)	5.1 (13.7)	4.4 (-2.8 to 11.5)	0.23†
Radiographic skeletal variants/congenital anomalies, n (%)		9 (31)	5 (17)	-	0.23‡
Regional cervical spine ROM, degrees, mean (SD)	Flex	49 (6.7)	53 (7.2)	4 (0.1 to 7.5)	0.04†
	Ext	51 (7.2)	56 (6.6)	5 (0.5 to 8.7)	0.03†

SD, standard deviation; ‡, Fisher's exact test; †, (unpaired) t test
*Cervical radiographic sagittal alignment data reproduced with permission from a undergraduate project sub-study (Shilton 2014)

Table 14: Baseline characteristics of patients with neck pain and healthy volunteers

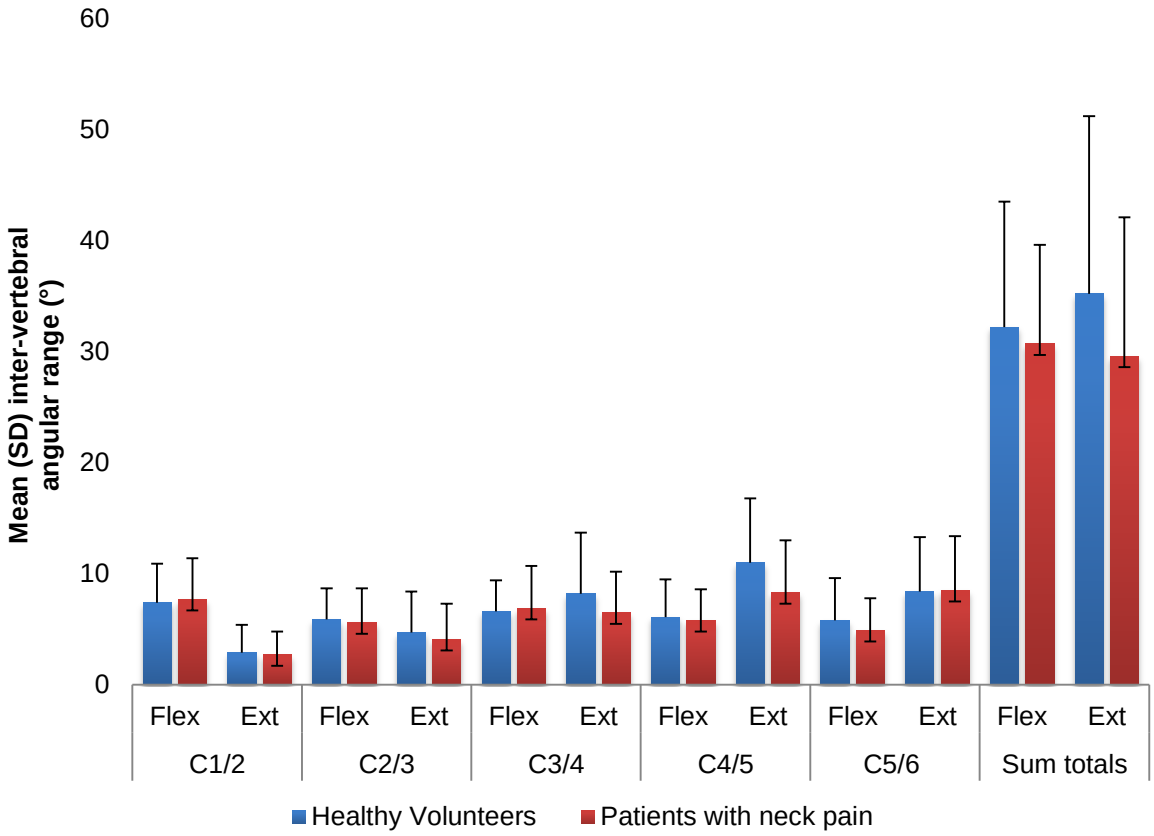
The following radiographic anomalies and anatomical variants were observed in five healthy volunteers: posterior ponticle (n=2), congenital block (n=2, one at C3/4, one at C5/6) and calcification of the anterior longitudinal ligament (n=1).The anomalies in nine patients were: posterior ponticle (n=4), calcification (n =2, one of the nuchal ligament, one of the atlanto-occipital membrane), claw spurs (n=2, one C4-6, the other C5/6) and generalised osteopaenia (n=1).

6.3.2 Inter-vertebral tracking failures

Of the 290 inter-vertebral levels in each group (five levels C1/2 to C5/6 in each of flexion and extension) there were seven tracking failures in the healthy volunteer group and four in the patient group, yielding 283 and 286 inter-vertebral levels respectively for analysis. The levels not tracked in three healthy volunteers were: C1/2 in flexion (n=1 participant), C1/2, C2/3 and C3/4 in flexion (n=1 participant) and C3/4, C4/5 and C5/6 in extension (n=1 participant). Levels not tracked in three patients were: C5/6 in flexion (n=1 patient), C5/6 in extension (n=1 patient), and C5/6 in flexion and extension (n=1 patient).

6.3.3 Angular range

Angular range data were not normally distributed for all inter-vertebral levels. However, for ease of interpretation and comparison with data published in the literature (Bogduk and Mercer 2000; Deitz et al. 2011), the mean (SD) ranges for both groups are shown in Figure 48. Range data from the healthy volunteer group were concordant[18] with data from previous radiographic studies of healthy participants where flexion-extension was measured as one full sequence (Appendix 14) and measured as separate sequences (Appendix 15).



NB: No statistically significant differences

Figure 48: Inter-vertebral flexion and extension angular ranges of patients and healthy volunteers

There were no significant differences in range between groups at any inter-vertebral level in either direction.

[18] With the exception of the mean (SD) of C5/6 which was smaller in this study compared to previously published data. This might be explained by this sample being older, on average.

When ranges were summed from C1/2 through C5/6, the patient group exhibited less overall flexion (mean difference -1.5° (95% CI: -3.9 to 6.9) p = 0.58, unpaired Student's *t* test) and extension (-5.7° (-1.9 to 13.2) p = 0.14, unpaired Student's *t* test), but these differences were not significant.

Angular range data are presented numerically, along with mean differences (95% CI) and p-values, in Appendix 16 (flexion), while medians (IQR) and their differences (95% CI) and p-values (Mann-Whitney *U* test) are presented in Appendix 17 (flexion). These data are presented likewise for extension in Appendix 18 (means) and Appendix 19 (medians). When medians were analysed there were likewise no significant differences.

6.3.4 Proportional range

While most participants in each group exhibited at least 21° summed IV-RoM from C1/2 to C5/6 in each direction, across healthy volunteers this ranged from 14.4° to 55.4° in flexion and 13.0° to 67.9° in extension. In patients summed C1/2 to C5/6 IV-RoM ranged from 12.1° to 49.1° (flexion) and 7.9° to 59.3° (extension). In order to reduce this variability, the within-subject proportional contributions of each inter-vertebral level to the overall segmental motion between C1/2-C5/6 in flexion and extension were calculated. The proportional contribution of each inter-vertebral level in each participant was expressed as follows, in the case of five segments contributing to the overall motion:

$$Contribution\ Cx_1 = \left(\frac{Cx_1}{\sum Cx_{1\ldots}Cx_5}\right) * 100$$

Imaging sequences that did not include data on all five motion segments were excluded, so sample size varied slightly as shown in Table 15 which also shows percentage contributions for each level by group.

Inter-vertebral level	Flexion				Extension			
	Healthy volunteers n=28	Patients n=28	Difference (95%CI)	Sig. (p) †	Healthy volunteers n=29	Patients n=27	Difference (95% CI)	Sig. (p) †
C1/2	23% (10.7%)	24% (11.8%)	-1% (-7.0 to 5.2%)	0.77	10% (8.2%)*	10% (8.3%)*	0% (-5.0 to 3.9%)	0.80
C2/3	19% (7.0%)*	18% (7.6%)	1% (-3.4 to 4.5%)	0.78	13% (6.8%)	13% (7.7%)*	0% (-3.4 to 4.3%)	0.80
C3/4	22% (7.9%)	22% (8.8%)*	0% (-4.3 to 4.8%)	0.91	22% (10.1%)	21% (9.0%)	1% (-4.0 to 6.3%)	0.66
C4/5	19% (6.2%)	19% (7.0%)	0% (-3.3 to 3.9%)	0.88	31% (8.4%)	27% (8.5%)	4% (-1.1 to 8.0%)	0.13
C5/6	17% (9.4%)	18% (10.6%)*	-1% (-5.6 to 5.3%)	0.95	25% (10.2%)	30% (15.1%)	-5% (-11.4 to 2.5%)	0.21
C1/2 - C5/6	100%	100%	-	-	100%	100%	-	-

95% CI, 95% Confidence Interval; p-values are 2-sided; † (unpaired) t test;
* data from a non-normal distribution

Table 15: Mean (SD) percentage contributions of inter-vertebral angular flexion and extension ranges in patients and healthy volunteers

While C4/5 contributed on average proportionally more motion in extension in healthy volunteers (31% in healthy volunteers *versus* 27% patients) with the converse true of C5/6 (25% in healthy volunteers *versus* 30% in patients), differences were not however significant at any level.

6.3.5 Hypo-mobility

The segmental IV-RoM distributions were not normally distributed for all levels and were not all amenable to normalisation by data transformation. It would therefore have been inappropriate to use this data to produce hypo-mobility cut-offs defined as equal to, or less than, the 2.5th percentile. Instead, hypo-mobility thresholds were calculated using existing published cervical segmental rotation data from the four flexion-extension plain-film x-ray studies (Aho et al. 1955; Dvorak et al. 1988; Lind et al. 1989; Frobin et al. 2002) that were found by Deitz et al (2011) to have the most sound methodology and reporting (Deitz et al. 2011). This data is presented in Table 16.

Inter-vertebral level	Aho et al (1955) n=15	Dvorak et al (1988) n = 28	Lind et al (1989) n = 70	Frobin et al (2002) n = 128	Aggregated across sites by Deitz et al (2011) n = 241	Hypo-mobile threshold (Mean – 2*SD)
C1/2	-	-	-	11.3 (4.7)	-	1.9
C2/3	12.0 (5.0)	10.0 (3.0)	10.0 (4.0)	8.2 (3.3)	9.3 (3.8)	1.7
C3/4	15.0 (7.0)	15.0 (3.0)	14.0 (6.0)	14.2 (4.7)	14.3 (5.1)	4.1
C4/5	22.0 (4.0)	19.0 (4.0)	16.0 (6.0)	16.3 (5.3)	16.9 (5.5)	5.8
C5/6	28.0 (4.0)	20.0 (4.0)	15.0 (8.0)	16.6 (6.7)	17.3 (7.4)	2.4

Table 16: Mean (SD) combined flexion-extension ranges and hypo-mobility thresholds from plain-film studies of healthy participants

In these plain-film studies motion was measured as one full motion from end-range flexion to end-range extension while, in this present study, flexion and extension were measured separately from a neutral starting position. Therefore it was necessary to separate the hypo-mobility thresholds into flexion and extension components. The ratio of flexion to extension was calculated for each level from healthy volunteers' IV-RoM data in this present study. These ratios, except for the C1/2 ratios, were averaged with flexion-extension ratios calculated from the data from another fluoroscopy study that similarly measured these motions separately in healthy participants (Wu et al. 2010). The resulting flexion-extension ratios are shown in Table 17.

Level	This study n = 30		Wu et al (2010) n = 48		Aggregate* of the two studies n = 78	
	Number of levels	Flexion : extension ratio	Number of levels	Flexion : extension ratio	Combined number of levels	Mean Flexion : extension ratio
C1/2	28	0.72 : 0.28	-	-	-	-
C2/3	29	0.56 : 0.44	48	0.42 : 0.60	77	0.49 : 0.51
C3/4	28	0.45 : 0.55	48	0.44 : 0.60	76	0.44 : 0.56
C4/5	29	0.36 : 0.64	48	0.45 : 0.60	77	0.40 : 0.60
C5/6	29	0.41 : 0.59	48	0.51 : 0.50	77	0.46 : 0.54

NB. C1/2 not measured by Wu et al (2010). In the absence of reporting the contrary it is assumed that all levels C2/3 to C5/6 were successfully measured by Wu et al (2010). *Ratios of two studies averaged.

Table 17: Cervical inter-vertebral sagittal rotation ratio of flexion to extension

Hypo-mobility thresholds were then calculated for each level and direction by multiplying the hypo-mobility thresholds reported by Dietz et al (2011) by the respective flexion-extension ratios. The hypo-mobility threshold for C1/2 was calculated using data from the only study that measured this level (Frobin et al. 2002). The hypo-mobility threshold calculated for C1/2 in extension was 0.5°, which was below the intra-observer measurement precision of 1.1° previously calculated for that level (Table 6 page 107), so, in this case only, the measurement error was adopted as the hypo-mobility threshold. All hypo-mobility thresholds are shown below in Table 18.

Inter-vertebral level	Hypo-mobility thresholds (°) (Mean – 2*SD)	
	Flexion	Extension
C1/2	1.3	1.1*
C2/3	0.8	0.9
C3/4	1.8	2.3
C4/5	2.3	3.5
C5/6	1.1	1.3

*Equivalent to measurement error for C1/2 in extension

Table 18: Inter-vertebral hypo-mobility thresholds for cervical flexion and extension

Based on these hypo-mobility thresholds, there was no significant difference in the number of participants in each group who exhibited hypo-mobility at one or more inter-vertebral level and in either direction (16 (55%) healthy volunteers *versus* 14 (48%) patients, two-sided p = 0.80, Fisher's exact test). In both groups hypo-mobility was more common in extension (Appendix 20). Considering inter-vertebral levels, there was no significant difference in the number of levels exhibiting hypo-mobility between the groups, as shown in Table 19.

Inter-vertebral level	Number of levels*		Hypo-mobile levels (Mean – 2*SD)		Sig. (p) ‡
	HV	Pt	HV	Pt	
C1/2	56	58	9	7	-
C2/3	57	58	2	3	-
C3/4	56	58	4	6	-
C4/5	57	58	4	7	-
C5/6	57	54	3	2	-
Totals	283	287	22/283 (7.8%)	25/287 (8.7%)	0.76

HV, healthy volunteer group (n=29); *Pt*, patient group (n=29); *Sig.*, significance; *p-value*, two-sided; ‡, Fisher's exact test; * see section 6.3.2 'Inter-vertebral tracking failures'

Table 19: The prevalence of inter-vertebral hypo-mobility in patients and healthy volunteers

6.3.6 Laxity/Attainment rate

As Table 20 shows there were no significant between-group differences in attainment rate[19] at any inter-vertebral level or direction except for C1/2 in flexion, which had a larger laxity index in the healthy volunteer group.

Inter-vertebral level	Flexion laxity indices				Extension laxity indices			
	HV	Pt	Difference (95% CI)	Sig. (p)	HV	Pt	Difference (95% CI)	Sig. (p)
C1/2	0.160 (0.1361)	0.092 (0.0933)	0.068 (0.0066 to 0.1300)	0.03*	0.061 (0.0631)	0.082 (0.0908)	-0.021 (-0.0615 to 0.0198)	0.31
C2/3	0.129 (0.0586)	0.118 (0.0762)	0.011 (-0.0253 to 0.0462)	0.56	0.122 (0.0887)	0.100 (0.0793)	0.022 (-0.0221 to 0.0657)	0.32
C3/4	0.164 (0.1120)	0.137 (0.0788)	0.027 (-0.0246 to 0.0773)	0.30	0.209 (0.1740)	0.155 (0.1466)	0.054 (-0.0306 to 0.1387)	0.21
C4/5	0.140 (0.0714)	0.127 (0.0894)	0.013 (-0.0292 to 0.0550)	0.54	0.161 (0.0898)	0.127 (0.1549)	0.034 (-0.0320 to 0.1012)	0.30
C5/6	0.106 (0.0876)	0.092 (0.0828)	0.014 (-0.0307 to 0.0578)	0.54	0.117 (0.0977)	0.091 (0.1198)	0.026 (-0.0320 to 0.0849)	0.37

HV, healthy volunteer group (n=29); *Pt*, patient group (n=29); *Sig.*, significance; *p-value*, two-sided, Fisher's exact test

Key to interpretation of laxity indices: > 1 = the segment is moving faster than the face-rest; 1 = the segment and face-rest are moving at the same speed in the same direction; < 1 = the segment is moving more slowly than the face-rest; 0 = the segment is not moving while the face-rest moves; between 0 and -1 = the segment is moving more slowly and in the opposite direction to the face-rest; -1 = the segment is moving at the same speed and in the opposite direction to the face-rest; < -1 = the segment is moving faster and in the opposite direction to the face-rest

Table 20: Mean (SD) inter-vertebral laxity/attainment rate in patients and healthy volunteers

[19] Attainment rate is the ratio of the two gradients of inter-vertebral motion and corresponding first 10° of cervical regional motion (measured from the movement of the face-rest) – see Figure 35.

Inter-vertebral level	Upper reference limit for laxity		Number of levels above upper reference limit			
			Healthy volunteers		Patients	
	Flexion	Extension	Flexion	Extension	Flexion	Extension
C1/2	0.249	0.112	7	8	3	10
C2/3	0.185	0.182	7	8	4	3
C3/4	0.220	0.236	8	7	5	3
C4/5	0.183	0.189	8	7	6	6
C5/6	0.150	0.182	8	8	6	5
Total	-	-	38	38	24	27

Upper reference limit = the upper quartile of the data distribution for that segment in the healthy volunteer group

Table 21: Upper reference limits (URL) and the number of inter-vertebral levels in each group that exceeded the URL for laxity/attainment rate

Since not all laxity data were normally distributed, upper reference limits (URL) were calculated as the upper quartile and the URLs for each level are shown in Table 21. Also in Table 21 are the number of inter-vertebral levels in each group that exceeded the URL, revealing there were less lax segments by this criterion in the patient group than in healthy volunteers.

6.3.7 Paradoxical motion

There was no significant difference in the number of participants in each group who exhibited paradoxical motion (16 healthy volunteers *versus* 13 patients, two-sided p = 0.60, Fisher's Exact test) at one or more inter-vertebral level. Similarly, there were no significant differences when considered in terms of inter-vertebral levels (Table 22). Paradoxical motion was most common at C1/2 in both groups and occurred in both flexion and/or extension at all levels (Appendix 20).

Inter-vertebral level	Paradoxical levels		Significance
	HV	Pt	
C1/2	11	6	-
C2/3	2	1	-
C3/4	5	2	-
C4/5	3	5	-
C5/6	4	3	-
Total	25/283 (8.8%)	17/287 (6.0%)	p = 0.20

Table 22: The prevalence of inter-vertebral paradoxical rotation in patients and healthy volunteers

6.4 Discussion

• Regional versus inter-vertebral motion

Most studies investigating cervical ROM have used external measurement methods which measure movement of the head, not inter-vertebral motion (Bogduk and Mercer 2000). Few studies have investigated inter-vertebral motion in neck pain patients and made comparisons with asymptomatic volunteers. In a small study lateral cervical radiographs were taken in five positions from full flexion to full extension (Dimnet et al. 1982). The sample size was too small (six neck pain patients and six unmatched asymptomatic subjects) to draw any definitive conclusions however the two cases of neck pain with no radiographic morphological findings to aid diagnosis had changes in inter-vertebral function compared to the six normal cases (Dimnet et al. 1982). This suggests that inter-vertebral motion changes may have been important in those two cases while not in the remaining neck pain cases.

In a larger study, flexion-extension radiographs (two views) were obtained of 109 consecutive patients of mean age 33.8yrs (SD 8.6yrs) with chronic (≥ 6 months) disabling neck pain (Amevo et al. 1992). The only kinematic parameter reported was IAR location. In that study 46% of patients had at least one abnormally located IAR, or 72% if IARs that were measured outside the normal biological distribution but within the margins for technical error were included (Amevo et al. 1992). However, these findings need to be interpreted with some caution since the asymptomatic group was smaller (n=46), from a separately reported study (Amevo et al. 1991c) and was not matched to the symptomatic group which could give rise to important confounders for inter-vertebral motion differences.

If the neck pain group were older a higher prevalence of age-related degenerative findings would be expected which are associated with decreased IV-RoM (Simpson et al. 2008). IV-RoM in the cervical spine is, on average, larger in females (Frobin et al. 2002); therefore a gender imbalance could also account for IV-RoM differences independent of symptoms. In addition, nine of the 109 patients had previously received anterior cervical fusion surgery to one or more inter-vertebral levels and were not excluded from the study.

While Amevo et al (1992) did not calculate IARs for the fused levels, it could be expected that fused levels were causing adjacent levels to move differently (Anderst et al. 2014) and possibly accelerate adjacent degenerative changes (Lee et al. 2012), thereby introducing another potential confounder for IAR differences between the groups. The authors did posit an interesting speculation - that the reduced regional cervical ROM often seen in patients with neck pain might be correlated with the presence of abnormal IARs, for example, due to muscle spasm (Amevo et al. 1992); it could also be due to pain-related behaviour.

This present study did find that regional cervical ROM was significantly less in the patient group. However, although inter-vertebral motion was also typically reduced in the patient group, particularly in extension, these differences were not significant. This may have been a result of the sample size being too small. Other possible reasons for this discrepancy are that C0/1, C6/7 and C7/T1 levels were not measured and it is possible that undetected but significant differences existed at these levels. Additionally, while stabilisation was utilised to minimise movement of the thorax, it was not possible to completely eliminate the contribution of the thoracic spine to neck bending. In the absence of thorax stabilisation the thoracic spine, as measured with an externally placed electromagnetic device, has been shown to contribute as much as 30% towards overall neck flexion and extension motion (Tsang et al. 2013). Therefore it is possible that important differences in unmeasured thoracic spine motion could have existed between groups.

Between-group differences may have existed in the ratio of upper cervical to lower cervical spine motion. Using a skin-mounted electromagnetic device, Rudolfsson et al. (2012) found that patients with neck pain had less extension in the upper cervical spine and generally less flexion in the lower cervical spine compared to healthy controls.

The ratio of upper to lower cervical spine motion was also altered in the neck pain group such that the lower cervical spine contributed less to overall sagittal motion compared to controls[20] (Rudolfsson et al. 2012). Finally, only sagittal plane motion was measured in this present study and differences might have existed in other planes.

• Whiplash-associated disorders versus mechanical neck pain

It might be that inter-vertebral motion differences are more marked with whiplash-associated neck disorder (WAD) than mechanical neck pain. In a study on cervical rotational and translational IV-RoM (from C3/4 to C5/6 only) measured from flexion-extension radiographs, results were compared between two groups of women: one group with chronic WAD (n=34) and one with grade I-II mechanical neck pain (n=35) (Kristjansson et al. 2003). The results of the chronic WAD group were also compared to a normative database (Frobin et al. 2002).

Significantly more women in the chronic WAD group were observed to have increased motion at C3/4 and C4/5 than in the mechanical neck pain group and all three levels were increased compared to the normal database (Kristjansson et al. 2003). The authors surmised that the lower cervical hyper-mobility might have been the result of the whiplash injury.

• Absolute and proportional range analysis

Detecting differences in angular range between groups is confounded by between-subject variability (van Mameren et al. 1990). Despite the detailed and controlled acquisition procedure employed in this present study, considerable angular range variability between-subjects remained. Attempts were made to statistically control for this by calculating within-subject proportional IV-RoM.

Differences in proportional IV-RoM between the neck pain and healthy volunteer groups were similarly not significant at any inter-vertebral level or in any direction. It was not possible to compare healthy volunteer percentage contribution data with previous studies as percentage contributions published in the cervical kinematics literature were calculated from C2/3 to C6/7, so were not directly comparable (Puglisi et al. 2004; Puglisi et al. 2007; Wu et al. 2010); no such data has been published for patients with mechanical neck pain.

[20] In a case study of a patient with neck pain reported by Dimnet and colleagues, reduced inter-vertebral motion was observed in the lower cervical spine (C3/4 – C6/7) compared to the upper spine (Dimnet et al. 1982).

• The relevance of adjacent segment studies

In a study utilising bi-planar radiography with CT reconstruction, six patients with single level anterior arthrodesis and 18 asymptomatic controls had their cervical IV-RoM compared (Anderst et al. 2013). While total C2-C7 IV-RoM was significantly less in the patient group this was primarily due to the arthrodesis level ($p<0.001$) and no differences were found in C2-C7 flexion-extension end-range percentage contribution between patients and controls (Anderst et al. 2013). These findings are similar to those of Kolstad et al (2007) who found no differences in the rotation and translation ranges of segments adjacent to fused cervical levels as measured from end-range flexion-extension plain x-ray films in 46 patients, in comparison to normal reference data (Kolstad et al. 2007).

However, Anderst (2013a) proceeded to interpolate C2 flexion-extension motion relative to C7 to obtain C2-C7 motion at 1% increments of the total cervical IV-RoM for each participant. Segmental flexion-extension rotation was then interpolated to obtain relative flexion-extension at each inter-vertebral level for every 1% increment of C2-C7 motion. Using this approach to interpreting the motion data, the contributions from the two levels adjacent to the C5/6 arthrodesis level (C4/5 and C6/7) were found to be significantly increased compared to controls (Anderst et al. 2013). The contribution for C4/5 was significantly increased from 30-95% of the total C2-C7 range while C6/7 was significantly increased over the whole flexion-extension range. While this patient population is not comparable to the non-specific neck pain cohort of this present study, the findings from Anderst et al (2013a) and Kolstad et al (2007) further suggest that differences are unlikely to be found comparing only end-range measurements.

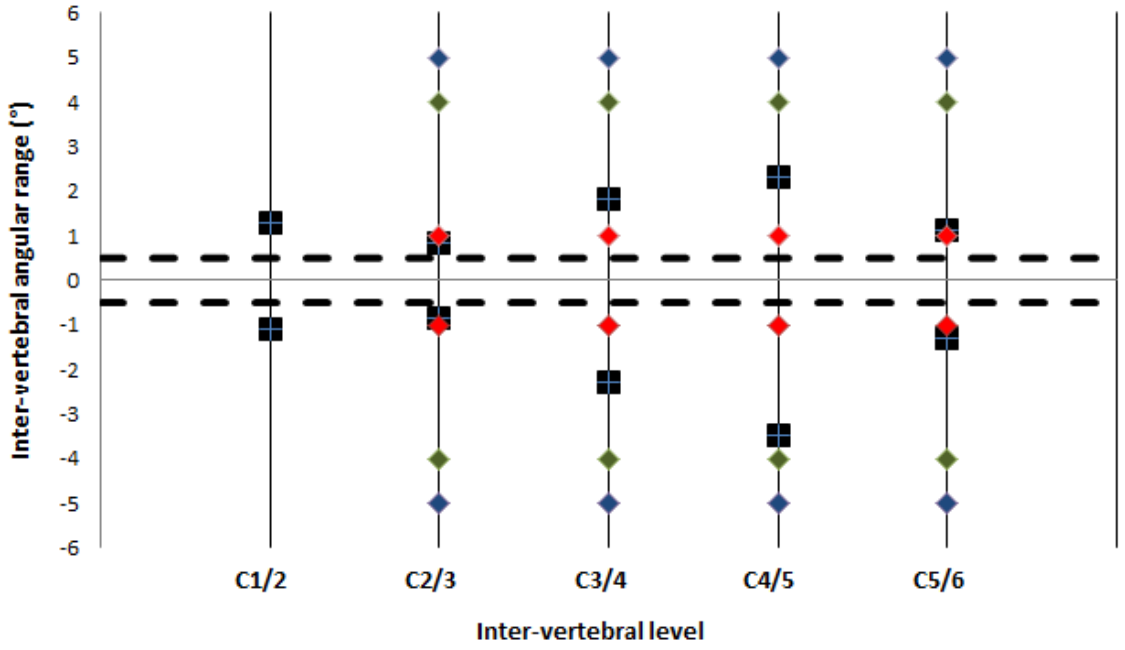
• Muscle activity and loading as confounders

The findings of Anderst et al (2013a) accord with those from a QF study of continuous recumbent passive IV-RoM in the lumbar spine, where proportional motion patterns in the coronal and sagittal planes were found to be more varied across the full motion sequence in patients with chronic LBP than in healthy controls (Mellor et al. 2014).

While the data from Anderst et al (2013a) could have been contaminated by muscle activity during active cervical motion, the findings of Mellor et al (2014), using passive and unloaded motion with minimal muscle activity (Mellor et al. 2009), lend further support to the advantages of analysing IV-RoM patterns continuously.

• Hypo-mobility cut-offs

The definition of hypo-mobility, at or below the 2.5th percentile, includes zero movement. For illustrative purposes, the hypo-mobility thresholds used in this study are displayed below in Figure 48 with three cut-offs (for C2/3 through C5/6) at which a surgically fused spinal segment might be considered immobile, as proposed in the literature.[21] The black dotted line indicates the minimum rotation (0.5°) of the tracking templates, therefore no movement can be measured below this.



Key to figure: Minimum rotation of tracking templates (± 0.5°)

Hypo-mobility thresholds (+ve denotes flexion, -ve denotes extension)

Pseudarthrosis cut off (1°); Pseudarthrosis cut off (4°); Pseudarthrosis cut off (5°)

Figure 49: Flexion (+ve) and extension (-ve) hypo-mobility thresholds displayed with pseudarthrosis cut-offs

It can be seen from Figure 48 that the pseudarthrosis cut-offs of 5° (blue diamonds) or 4° (green diamonds) are larger than all the calculated hypo-mobility thresholds (black squares).

[21] The pseudarthrosis cut-off of 5° is used by the Food & Drug Administration to evaluate the success of spinal fusion surgery due to the measurement error of plain-film flexion-extension x-rays (Deitz et al. 2011). It has been proposed that this cut-off be reduced to 4° or even 1° due to the measurement error being reportedly reduced when using a computer-aided technique of measurement from plain-film flexion-extension x-rays (Hipp et al. 2005).

Therefore, these cut-offs are susceptible to false-positives i.e. are likely to classify a proportion of normally moving segments as hypo-mobile. The pseudarthrosis cut-off of 1° (red diamonds) is less than the majority of calculated hypo-mobility thresholds therefore is susceptible to false-negatives i.e. is likely to result in a proportion of hypo-mobile segments being classed as within normal range.

Lending additional validity to the hypo-mobile thresholds derived in this study, the two congenitally fused inter-vertebral levels present in two healthy volunteers were correctly identified as hypo-mobile in both flexion and extension. These immobile levels were subsequently excluded when the prevalence of hypo-mobility between groups was analysed. Motion segments adjacent to congenital block vertebrae have been shown to have rotational and translational motion within normal limits (Leivseth et al. 2005). The two healthy volunteers with congenital block vertebrae both exhibited normal regional and summed C1/2 to C5/6 IV-RoM ranges, and were therefore included in the other IV-RoM analyses.

In this present study there were no significant differences in the number of participants who had at least one hypo-mobile level or in the number of hypo-mobile levels between groups. Using a similar statistical approach to classifying IV-RoM as hypo-mobile or not, Abbott et al (2006) calculated reference levels for hypo-mobility[22] (mean – 2SD) for lumbar IV-RoM measured from flexion-extension radiographs taken of 30 asymptomatic volunteers (Abbott et al. 2006). When applied to lumbar IV-RoM data from the flexion-extension radiographs of 123 consecutive patients with recurrent or chronic LBP, 27/468 lumbar segments (5.8%), present in 19.6% of the patients, were classed as rotationally hypo-mobile.

The clinical importance of this is uncertain, as while the authors state that 'segmental mobility disorders [sic]' were found in 'significantly greater numbers in patients', data on the prevalence of hypo- (or hyper-) mobility in the asymptomatic sample were not published for comparison. While this present study classed 25/287 (8.7%) of cervical segments present in 48% of neck pain patients as hypo-mobile, this was not significantly different to the 7.8% prevalence of hypo-mobile segments (55% of healthy volunteers) in the age and gender-matched healthy volunteer group. In addition, as acknowledged by the authors, Abbott et al.'s asymptomatic group was small and had a higher proportion of females than the LBP group, lending a risk of bias to the study's findings (Abbott et al. 2006).

[22] The terminology used by Abbott et al (2006) was 'lumbar segmental rigidity' (mean-2SD) and 'lumbar segmental instability' (mean+2SD), which are analogous to the terms hypo-mobility and hyper-mobility respectively, as adopted in this thesis.

When hypo-mobility was calculated based on the proportional contribution of each segment to total lumbar motion, in an attempt to reduce between-subject variability, the proportion of hypo-mobile segments was increased to 28% (Abbott et al. 2006).

It was not possible to calculate hypo-mobility cut-offs based on proportional within-subject IV-RoM and replicate the approach of Abbott et al (2006) as the within-subject data were not all normally distributed. It is possible that these proportional hypo-mobility cut-offs would be more discriminating between patients and healthy controls. However, this present study's findings still bring into question the importance of segmental hypo-mobility as a cause or contributory factor in neck pain, at least in the sagittal plane.

Attainment rate, calculated in the first 10° of regional spinal motion as a surrogate for the measurement of laxity in the neutral zone, was developed from a passive recumbent acquisition QF protocol for measuring lumbar IV-RoM (Breen et al. 2012). In the passive lumbar protocol, QF is performed with the participant lying on a motorised passive motion table and during movement of the table participants' paraspinal muscle activity as measured by surface electromyography (sEMG) is minimal (Mellor et al. 2009), thereby reducing an important confounder. During active weight-bearing motion however, paraspinal muscle activity would be expected to be different between subjects and even within-subjects if measurements are repeated, and must therefore be considered a confounder when measuring attainment rate.

In this present study, participants were seated upright and the motion-frame (Figure 18) served only as a reference for participants to actively follow, therefore the influence of paraspinal muscle activity was present. Despite this limitation, the only significant difference in attainment rate was for C1/2 in flexion where patients exhibited on average, lower attainment rates. It is not immediately clear why this should be so. C1/2 hypo-mobility, which could accompany reduced attainment rate, was not more prevalent in patients (Appendix 20) and there was no significant difference in angular range between groups at this level (Appendix 16). This difference in attainment rate could perhaps be due to the possibility of differences in resting cervical extensor activity, in which higher resting muscle tone might inhibit the initial segmental movement.

In a different study investigating the flexion-relaxation phenomenon in patients with chronic neck pain and controls, surface EMG activity of the cervical erector spinae was measured while participants remained still for four seconds (Maroufi et al. 2013). Resting activity was found to be significantly greater in the patient group, and remained higher throughout the flexion-extension motion (Maroufi et al. 2013).

Therefore, it may not be that a true difference in the size of the C1/2 neutral zone was detected in this present study, but rather perhaps an indication of altered upper cervical muscle activity in the patients.

Based on upper reference levels for attainment rate calculated from the healthy volunteer group, the patient group exhibited less lax segments than the healthy volunteers, suggesting more segmental stiffness in the neutral zone in patients. This again could have been related to higher resting cervical muscle tone, but this was not measured.

• Paradoxical motion

Paradoxical (reversed) motion is known to commonly occur as part of the normal motion of the atlas flexing or extending over the axis (Bogduk and Mercer 2000). C1/2 is where paradoxical motion was most commonly measured in this present study (Table 22). While reversal of motion has also been previously detected by cineradiography at C5/6 during flexion (van Mameren et al. 1990), this present study found, in addition to C1/2, at least one of each inter-vertebral level in each direction from C2/3 to C5/6 that exhibited paradoxical motion (Appendix 20). QF is possibly more sensitive at identifying such motion due to its ability to measure continuous flexion-extension sequences. Paradoxical motion in the mid-lower cervical spine is probably related to the influence of sagittal alignment or cervical lordosis on segmental loading (Anderst et al. 2014). While there were no significant differences in neutral position between groups, there was considerable variability of this within each group (Table 14). The probable correlation between neutral cervical spine sagittal alignment and paradoxical motion was not explored and is fertile ground for future work.

• Limitations

The researcher was not blinded as to whether an individual's data was from a patient with neck pain or a healthy volunteer which could have biased the interpretation of inter-vertebral motion graphs. However, the lack of differences between the groups suggests this was not a confounding factor. Secondly, the inputting of data into the database was not checked by a second observer, so there was the possibility of data entry errors.

6.5 Conclusion

There were no significant differences found in the kinematics of cervical spine sagittal motion between patients with neck pain and healthy controls in terms of angular range, hypo-mobility or paradoxical motion. The implication of these findings is that, at least in the sagittal plane, these kinematic variables may not be important regarding the presence of neck pain. Since lax segments were less prevalent in the patient group, suggesting more segmental stiffness in the neutral zone, the effects of SMT on this would be worth exploring. However, change in laxity/attainment rate was not considered a primary outcome of interest and pursuing this was not feasible within the time constraints of this thesis.

According to the literature it might be that IAR location measurement is more discriminating of patients and healthy controls, but repeatability studies of the QF method used in this present study suggested it was not possible to measure this reliably; therefore, IAR location was not measured. For future work to maximise the chances of detecting kinematic differences between groups, should they exist, all possible steps need to be taken to reduce the biological variability of inter-vertebral motion and improve the reliability of IAR measurement. This includes following a standardised acquisition protocol to reduce between-subject and within-subject (for repeated measures) variability such as that used in this study. Inter-subject variability can be further reduced by analysing data in terms of proportional motion. Finally, continuous motion data as acquired by QF appears to be more promising for discriminating between patients and controls than the use of end-range flexion-extension data which, up until now, has dominated most of the work in the cervical kinematics field.

Chapter 7. Intra-subject reproducibility study: Estimating the minimum detectable change of inter-vertebral angular motion from healthy participants

7.1 Introduction

Reproducibility refers to the variation in repeat measurements made on the same subject under changing conditions (ISO5725-1 1994); cervical IV-RoM is known to exhibit variation between measurement sessions in healthy subjects (van Mameren et al. 1990). Intra-subject reproducibility in this study encompasses those sources of variation (error) as detailed in the observer repeatability chapter (Chapter 5) pertaining to the QF measurement method. Of particular importance is the potential for error that exists during the acquisition procedure, for example, through the positioning and behaviour of participants, and the flexibility of a participant's neck at baseline versus four weeks later. This study sought to determine how much IV-RoM varied between measurement sessions in the healthy volunteer group, and to determine the minimum detectable change (MDC) in segmental angular range over the four-week study period (Research Question 3, page 59). In addition, the prevalence of hypo-mobile and paradoxical segments was quantified.

7.2 Methods

7.2.1 Study design

This was an intra-subject reproducibility study of cervical flexion and extension inter-vertebral motion in healthy participants measured twice over four weeks with QF (Figure 42).

7.2.2 Participants and data collection

Thirty healthy volunteers, recruited as previously described (see page 122), received QF measurements of their cervical flexion and extension IV-RoM from C1/2 to C5/6 at baseline and four-week follow-up using standardised image acquisition and analysis protocols (see Chapter 3). Cervical sagittal alignment (lordosis) was measured also (see section 6.2.2 page 127). Inter-vertebral angular range data were extracted from the analysed motion sequences in order to calculate the MDC in this measurement over the four-week study period. The presence of hypo-mobile segments was detected using previously derived hypo-mobility cut-offs (section 6.3.5) while paradoxical motion was identified visually from the motion graphs (Figure 30).

7.2.3 Data analysis

The data were analysed using StatsDirect (StatsDirect Ltd. StatsDirect statistical software. http://www.statsdirect.com. England: StatsDirect Ltd. 2008). The distributions of the differences between repeated-measures were checked for normality using the Shapiro Wilk test. The paired Student's *t* test was used to confirm if mean differences between baseline and follow-up were significantly different. In each case Kendall's tau rank correlation coefficient was used to check that the standard deviation was unrelated to the size of the measurement in order to allow parametric comparison (Bland and Altman 1996a). Repeatability coefficients were then calculated for each inter-vertebral level using the following formula (Bland and Altman 1996a):

$$\text{Repeatability coefficient (MDC)} = 2.77s_w$$

where s_w is the within-subject standard deviation. The repeatability coefficient estimates the magnitude of within-subject motion change that can be expected 95% of the time (Bland and Altman 1996a); this is the minimum detectable change (MDC).

7.3 Results

7.3.1 Participant characteristics

Thirty healthy volunteers, of whom 21 were female, aged 19 – 67 years (mean 40.9, SD 13.1), participated in the intra-subject reproducibility study. As shown in Table 23, while cervical sagittal alignment was on average 2.4° more lordotic at follow-up, differences were almost, but not quite, significant. There was also no significant difference in regional flexion or extension cervical spine ROM at follow-up.

Measurement		Baseline	Follow-up	Difference (95% CI)	Significance (p) †
***Cervical radiographic sagittal alignment, degrees, mean (SD)**		5.1 (13.7)	7.6 (12.8)	+2.4 (-0.1 to 5.0)	0.06
Regional cervical spine ROM, degrees, mean (SD)	Flex	53 (7.2)	54 (6.6)	-0.1 (-1.3 to 1.1)	0.91
	Ext	56 (6.6)	56 (7.1)	0.3 (-0.4 to 0.9)	0.42

†, (paired) Student's *t* test; *Cervical radiographic sagittal alignment data reproduced with permission from an undergraduate project sub-study (Shilton 2014)

Table 23: Mean (SD) cervical radiographic sagittal alignment and regional ROM at baseline and follow-up in healthy participants

7.3.2 Angular range differences

Eight of 300 inter-vertebral levels (2.7%) were not successfully tracked at baseline and/or follow-up. Levels not tracked in three participants were: C1/2 in flexion (n=1), C1/2, C2/3 and C3/4 in flexion (n=1) and C2/3, C3/4, C4/5 and C5/6 in extension (n=1). The mean difference in angular range measurements between baseline and follow-up was not significantly different for any motion segment in either flexion or extension (Appendix 21 and Appendix 22). However, as indicated by Figure 50 (flexion) and Figure 51 (extension), while most of the data points are grouped close to zero a degree of intra-subject variation was present.

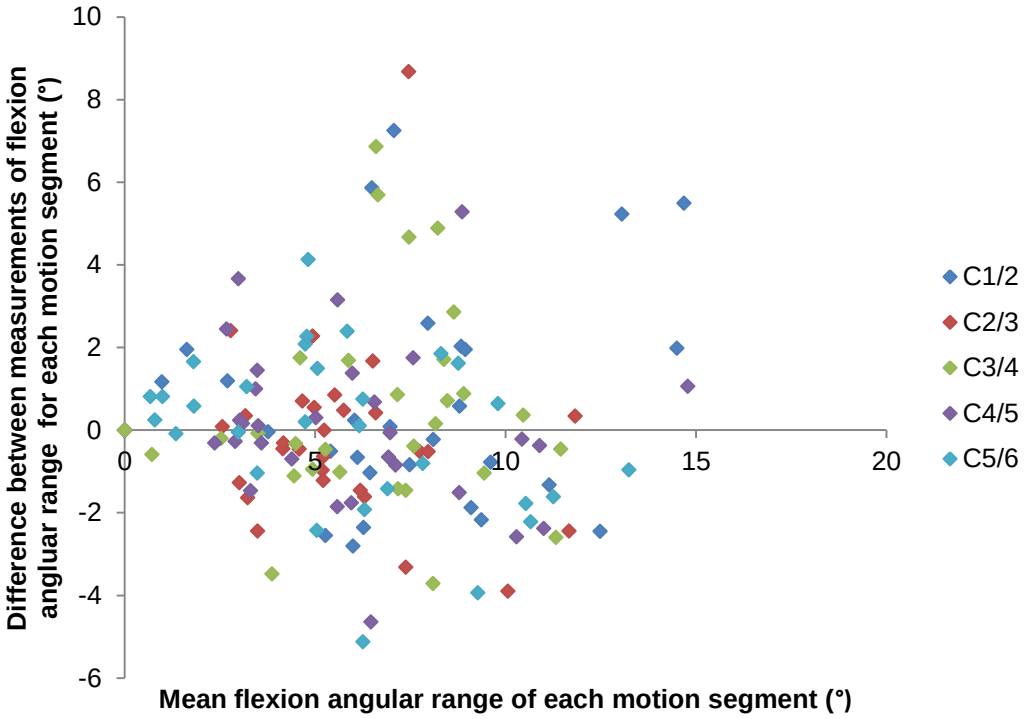


Figure 50: Difference against mean flexion angular range of each motion segment in healthy volunteer group (n = 146 segments)

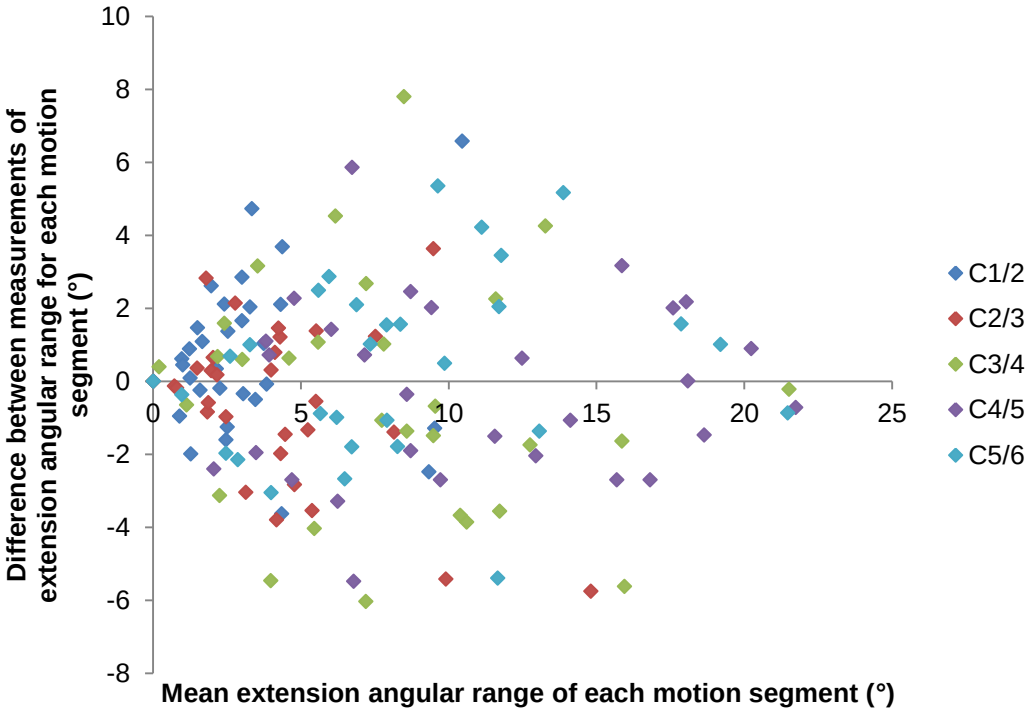


Figure 51: Difference against mean extension angular range of each motion segment in healthy volunteer group (n = 146 segments)

The repeat-measurement differences were normally distributed except for C1/2, C2/3 and C3/4 in flexion. Exploration of the data with Bland-Altman plots (not shown) (Bland and Altman 1986) revealed a number of measurement differences which were out-with the 95% limits of agreement (eight segments in four participants). The distributions became normal once these 'outliers' were removed.[23]

On two occasions Kendall's tau was statistically significant (C1/2 and C2/3 in extension), indicating that the within-subject standard deviation was not independent of the size of the measurement (Bland and Altman 1996b), albeit the correlations were modest (for C1/2: $\tau = 0.34$, $p = 0.008$; for C2/3: $\tau = 0.48$, $p = 0.0003$; see Appendix 23). Transformation of the data did not alter the dependence, so the untransformed data were used in the MDC calculations. The MDCs for each motion segment are displayed in Table 24; they were consistently larger in extension, and range from 3.03° (C2/3 in flexion) to 6.35° (C3/4 in extension).

[23] All data from one participant were removed since all measurement differences were much larger than zero, suggesting either the set-up was incorrect and/or the participant chose to flex differently at follow-up. C1/2 and C2/3 data were removed for one participant, and C1/2 data were removed for two further participants.

Inter-vertebral level	No. of intervertebral levels available for calculation †		MDC (°)	
	Flexion	Extension	Flexion	Extension
C1/2	25	30	3.82	4.36*
C2/3	28	29	3.03	4.5*
C3/4	27	29	3.90	6.35
C4/5	29	29	3.38	4.71
C5/6	29	29	3.41	4.95
Total	138	146	-	-

*Kendall's tau, $p < 0.05$; †, segments available for calculation in flexion reduced by the removal of 'outliers' – see previous page for details

Table 24: MDC for each inter-vertebral level and direction

7.3.3 Differences in the prevalence of hypo-mobility and paradoxical motion

Table 25 shows the number of hypo-mobile and paradoxical segments at baseline and follow-up.

Inter-vertebral level	Number of levels	Hypo-mobile		Sig. (p) †	Paradoxical		Sig. (p) †
		Baseline	Follow-up		Baseline	Follow-up	
C1/2	56	9	2	-	11	11	-
C2/3	57	2	2	-	2	0	-
C3/4	56	4	3	-	5	1	-
C4/5	57	4	4	-	3	0	-
C5/6	57	3	1	-	4	0	-
Totals	283	22/283 (7.8%)	12/283 (4.2%)	0.08	25/283 (8.8%)	12/283 (4.2%)	0.03

Sig, significance; *p*, two-sided p-value; †, Fisher's Exact test

Table 25: The difference in prevalence of hypo-mobile and paradoxical segments at follow-up in healthy participants

While the number of hypo-mobile segments was nearly halved at follow-up, this difference did not reach statistical significance. Of the 12 hypo-mobile segments at follow-up, only four had remained hypo-mobile from baseline, and eight levels were classed as hypo-mobile at follow-up which had been normal at baseline. Conversely, the halving of paradoxical segments was statistically significant. However, of the 12 paradoxical levels at follow-up while eight remained from baseline, four were new. The prevalence of hypo-mobile and paradoxical motion segments in flexion and extension is shown in Appendix 24.

7.4 Discussion

The MDCs calculated in this study estimate the magnitude of IV-RoM change expected 95% of the time when measured twice, four weeks apart, in healthy participants. They incorporate the measurement error associated with QF as well as normal biological variation in cervical sagittal IV-RoM. In order to confidently identify IV-RoM changes in patients receiving treatment, any changes need to be in excess of this normal biological variation.

• Comparison with previous work

This is possibly the first study to have calculated the MDC for cervical flexion and extension IV-RoM as no studies of the MDC for cervical IV-RoM measurement from plain film flexion-extension x-rays or kinetic MRI could be found in the published literature. Radiographic studies evaluating IV-RoM after an intervention (Kolstad et al. 2007), or looking for changes due to spinal anomalies (Leivseth et al. 2005), have compared motion against previously derived normative values rather than assessing the magnitude of intra-subject change from baseline.

In a cadaveric study 12 cervical spine specimens were subjected to increasingly severe soft tissue damage and IV-RoM was measured with a computer-based plain-film technique in four different flexion-extension positions (Hwang et al. 2008). Even at the most severe level of damage to ligaments and disc, segmental rotation and translation were found to remain within normal limits, based on normative data from a previous study of healthy participants (Reitman et al. 2004b). The centre of rotation, also measured, was apparently more abnormally located in response to the anatomical changes, although measurements were only made at one motion segment (Hwang et al. 2008).

A number of studies have calculated the MDC for regional cervical motion using various types of external measurement devices (Appendix 1), and consistently the MDC is large. Even when measurements are repeated immediately (with the CROM), differences can be 25% (flexion) and 16% (extension) of the respective mean measurements (Dunleavy and Goldberg 2013).

The MDC is lower, however, when repeat-measurements are made by the same observer versus two or more observers (Appendix 1). For example, the MDC calculated from inter-observer repeat-measurements using the Cybex Electronic Digital Inclinometer-320 was deemed so large (greater than 10%) by the authors of one study they did not report it (Hoving et al. 2005). The MDC also appears to be lower in healthy volunteers than in patients with neck pain, suggesting that neck movements may be more consistent in the absence of pain (Fletcher and Bandy 2008). However, in another study where measurements were repeated up to 14 days later, important confounders such as changes in pain levels and treatments received by the patient group between measurements were not accounted for (Shahidi et al. 2012).

• Importance of participant positioning

While such external devices do not measure cervical IV-RoM, it is instructive to note that in one study the MDC was lowered by instructing the participants to sit in an upright ‘correct’ posture instead of them choosing how to sit (Dunleavy and Goldberg 2013). This reinforces the importance of standardised participant positioning.

An important aspect of positioning is to ensure that the sagittal alignment (lordosis) of participants’ cervical spines is identical at each measurement session. When measuring cervical IV-RoM Anderst et al (2014) found in a cross-sectional study that a significant proportion of inter-subject variability in cervical kinematics could be explained by the disc height and static orientation of each motion segment at neutral (Anderst et al. 2014). This would also be a confounder for intra-subject variability in a repeat-measures study. In the present study the cervical sagittal alignment was on average 2.4° more lordotic at follow-up, a difference that approached statistical significance (Table 23). Therefore, in at least in some of the participants, sagittal alignment might have been sufficiently different to have contributed to the intra-subject variation (MDC) in IV-RoM (Table 24).

• Clinical usefulness

The MDC was highest for C3/4 and, in extension, was more than 1° greater than the next largest segmental MDC. No data entry errors or 'outliers' were found that would readily explain this, and the measurement error found in the repeatability study was not larger for this segment (Table 6). The size of the MDCs in this study indicate that the detection of true angular inter-vertebral motion change is challenging, especially in extension, and risks being too large to be clinically meaningful for the evaluation of patients with neck pain. Ultimately, the usefulness of these MDCs will not be known until they are applied in a patient population.

The prevalence of both hypo-mobile and paradoxical segments was also subject to considerable intra-subject variation. Only four out of 22 hypo-mobile segments remained so at follow-up, with eight new hypo-mobile segments detected. Only eight out of 25 paradoxical segments remained so at follow-up, with four new paradoxical levels detected. Hypo-mobility is commonly considered to be an indication for spinal manipulation (Evans 2002); paradoxical motion has also been considered an indication for the therapy (Schafer and Faye 1989). However, due to the changing nature of these motion features in healthy participants receiving no treatment, assessing patients for changes in hypo-mobility or paradoxical motion in response to manipulation may not be possible or even clinically meaningful.

• Future work

There is scope for future work with a larger sample size. Data from this study may be used to estimate this and so provide normally distributed repeat-measurement differences for all inter-vertebral levels. It is important, however, that modifiable sources of measurement error be kept to a minimum and the present acquisition protocol could be further refined to achieve this. Close attention is required to the set-up of participants prior to image acquisition and observation of their movement behaviour, to identify and if possible prevent any avoidable confounders of measurement differences. Kinematic parameters other than those explored in this study should also be considered; for example, IAR location or phase-lag (the order in which segments move) for their relevance to segmental loading and their MDCs determined.

Some caution is warranted regarding the interpretation of the MDC values in this study. For the purposes of calculation it was assumed that the distribution of the measurement differences was normal. This condition was not met in the case of the three most superior motion segments in flexion and eight 'outliers' were removed to normalise the distributions.

This will have reduced the within-subject standard deviation and hence, the ‘true’ MDC for C1/2, C2/3 and C3/4 in flexion could be larger than those presented in Table 24. Despite this, the MDCs for these levels are of a very similar order of magnitude to C4/5 and C5/6 in flexion.

A second condition that was not met in two cases (C1/2 and C2/3 in extension) was that the within-subject standard deviation was not independent of the mean. Logarithmic transformation is recommended to achieve this independence (Bland and Altman 1996b) however neither this nor any other commonly used transformation (Bland and Altman 1996c) was successful. These were necessary compromises in order to calculate the MDC. Without an estimate of the MDC a study to detect changes in patients receiving treatment would not be possible.

7.5 Conclusion

This chapter showed that IV-RoM, while reliably measureable with QF, is subject to a high degree of intra-subject variability over four weeks. Furthermore, hypo-mobile and paradoxically moving segments occur, resolve, and reoccur elsewhere over this interval. This means that IV-RoM is not a stable measure of cervical kinematics across time, making the detection of differences in response to therapy difficult unless this variability can be reduced by improved acquisition protocols or by identifying and controlling for covariants. Sagittal alignment appears to be important in this. Other kinematic parameters, as discussed, may be of greater importance in future work with this technology.

Chapter 8. Spinal manipulative therapy for the treatment of neck pain: A prospective cohort study

8.1 Introduction

Spinal manipulative therapy is predicated on the idea that inter-vertebral motion can be changed, and that such changes can produce clinical improvement. However, investigation of this proposed mechanism has been hampered by the lack of an objective, reproducible method of inter-vertebral motion measurement (Dimnet et al. 1982). Having established the MDC in cervical IV-RoM in the intra-subject reproducibility study (Chapter 7), this study sought to observe if inter-vertebral motion, as measured by QF, changes in patients after spinal manipulative therapy (Research Question 4, page 59), and if changes are linked to patient-reported improvement (Research Question 5, page 59). In addition, the level of agreement between hypo-mobility identified by palpation and measured by QF was explored.

8.2 Methods

8.2.1 Study design

This was a prospective cohort study of 30 patients with neck pain attending a chiropractic out-patient teaching clinic for spinal manipulative therapy (Figure 43). The participants (page 122), inclusion and exclusion criteria (Table 11 and Table 12), and recruitment strategy (page 124), have been previously described. In summary, patients had mechanical neck pain of at least two weeks duration with intensity rated at least 3/10.

8.2.2 Treatment protocol

The treatment options available to patients were restricted to HVLA spinal manipulation of the cervical spine, myofascial trigger point therapy and light massage delivered over eight treatment sessions, twice per week for four weeks. These treatments are typical of manual therapy practice for neck pain (Leaver et al. 2010). The treatment frequency was not dissimilar to that found in randomised trials of manipulation for back (UK BEAM 2004) or neck pain (Bronfort et al. 2012); these studies were designed to detect, if present, differences between baseline and follow-up patient-reported outcomes. Collection of data at four-weeks is fairly typical of randomised trials (Hurwitz et al. 2002; UK BEAM 2004; Bronfort et al. 2012; Evans et al. 2012) suggesting that any significant change in patient outcomes can be expected to be detected at this time.

If IV-RoM changes are related to patient-reported outcomes then this treatment regimen over four weeks should be sufficient to detect this relationship also.

To reduce variation in the type of manipulation only high-velocity low-amplitude (HVLA) or "thrust" manipulation was permitted (Peterson and Bergmann 2011). This avoided having to sub-group based on manipulative technique in the data analysis, which would have reduced statistical power. In order to ensure the competent delivery of manipulation this was performed only by chiropractors with at least five years postgraduate experience[24]. Chiropractors were instructed to palpate the patient's cervical spine and deliver manipulation where clinically indicated (segmental pain provocation/motion restriction). If not clinically indicated then it was permissible to deliver no manipulation at that visit. Patients were required to receive at least one HVLA manipulation during the study.

Other therapies - included and not included

The two soft tissue therapies (trigger point and light massage) were included so that patients who had muscular pain may get relief. These were delivered by chiropractic interns in their clinical training year. The inclusion of soft tissue therapy has been used in randomised trials of spinal manipulation for back pain (Hawk et al. 2002; Harvey et al. 2003) and neck pain (Bronfort et al. 2012; Evans et al. 2012). Commonly used treatment modalities for neck pain other than spinal manipulation that have been demonstrated to increase neck range of motion and therefore perhaps change inter-vertebral motion, were not offered. These include a neck strengthening programme (Highland et al. 1992), muscle stretching administered at home (McCarthy et al. 1997) and by the practitioner (Burns and Wells 2006), and rhythmic joint mobilisation (McNair et al. 2007).

There is evidence of trigger point therapy increasing neck range of motion, but changes are small (Hou et al. 2002) and therefore these were not expected to affect inter-vertebral hypo-mobility. Patients were required to attend each treatment session and the intern/chiropractor retained the right to treat based on clinical findings within the limitations just described. Chiropractors were able to give usual advice such as avoidance of aggravating activities, and ice/hot-packs or analgesia could be offered as rescue remedies if required. Patients were requested not to seek concurrent alternative care.

[24] Level of experience of manipulators in trials varies and includes: not reported (Hurwitz et al. 2002), 2 years (UK BEAM 2004; Leaver et al. 2010) and, commonly, 5 years (Hawk et al. 2002; Bronfort et al. 2012; Maiers et al. 2014).

Chiropractors/interns were asked to document the treatments that were administered at each treatment visit, as well as patient's use of analgesia or cold/hot packs (Appendix 25). A form was placed in participating patient's files to remind the clinicians of included and excluded therapies (Appendix 26).

Limiting of treatment options

While patients' treatment options were deliberately restricted so as to more confidently associate any changes in inter-vertebral motion with spinal manipulation, this was not expected to negatively affect patients' recovery. Patients were only included if they were deemed suitable for manipulation as spinal manipulation alone has been shown to be effective for the short-term relief of neck pain (Miller et al. 2010). They were, however, informed that results are typically better when combined with exercise (Vincent et al. 2013). Patients were not charged for their treatment, though, they were reminded at the time of recruitment that any treatment required beyond the four week study period would be subject to the usual charging policy of the out-patient clinic.

8.2.3 Data collection

Inter-vertebral motion

Patients had QF acquisitions and measurement of cervical inter-vertebral motion at baseline and four-week follow-up following the protocol and procedures detailed previously (Chapter 3). The following inter-vertebral motion variables were measured: angular range, hypo-mobility, paradoxical motion (page 80) and attainment rate (baseline only, page 85). Additionally, palpation findings of segmental hypo-mobility were recorded at baseline by chiropractic interns.

Patient-reported outcome measures

The effect of patients' neck pain on their ability to work was documented in the patient file as per the clinic's procedures. Study questionnaires were administered to patients at baseline (Appendix 27) and four-week follow-up (Appendix 28) and consisted of the following:

(1) *Pain* – 11-point (0-10) Numerical Rating Scale (NRS)

The commonly used methods of rating pain intensity include visual analogue scales and verbal rating scales as well as numerical rating scales (NRS). All are considered reliable and valid, and no one scale consistently demonstrates greater responsiveness in detecting improvements associated with pain treatment (Jensen and Karoly 2001). However, NRS scales are often preferred by patients.

They are more likely to be completed, are easy to understand for the patient, and for the researcher to record (Dworkin et al. 2005). When patients first attend the AECC clinic they are asked to complete the Bournemouth Questionnaire (Bolton and Breen 1999), the first question of which is an NRS measure of pain intensity and it is this score that determined eligibility for entry to this study.

(2) *Neck specific function* – Neck Disability Index (Vernon and Mior 1991)

There are numerous neck function or disability measures that have been employed by neck pain outcomes studies (Gross et al. 2009). In their systematic review of neck function outcome measures Pietrobon et al (2002) found five scales considered to be reliable, valid and responsive to change (Pietrobon et al. 2002). They found the Neck Disability Index, the Copenhagen Neck Functional Disability Scale and the Northwick Park Scale to have similar psychometric properties, concluding that the Neck Disability Index was marginally superior as it had been most extensively revalidated (Pietrobon et al. 2002). A more recent systematic review of the Neck Disability Index itself found it still to be the most commonly used measure of neck function and concluded it had sufficient support and usefulness to retain its status (MacDermid et al. 2009b).

A minor modification to the wording of the instructions of how to complete the Neck Disability Index was made, with the authorisation of the developer, H. Vernon (personal communication, November 4, 2011). The time frame for answering the questions was changed from “today” to “...over the last few days...” placing this in the same time frame as the NRS from the Bournemouth Questionnaire utilised at AECC clinic. This was in recognition of the fluctuating nature of neck (musculoskeletal) pain which may be present one day but hardly discernible the next (Deyo et al. 1998). There is precedent for such a modification with the Oswestry Disability Index which is used to measure back pain disability, from which the Neck Disability Index was developed.

The original version stipulated no time frame (Fairbank et al. 1980), the second version stipulates “today” (Baker et al. 1989) while the North American Spine Society version has “past week” as the time frame (Daltroy 1996).

A qualitative study has helped to elucidate how patients might interpret time frames in questionnaires measuring musculoskeletal pain (Ong et al. 2006). For the ten patients with musculoskeletal pain interviewed it was typical not to stick to the time frame stipulated when different questionnaires with different time frames were contained within the one survey (Ong et al. 2006). The researchers could not conclude whether this was due to error switching between time frames, but patients did emphasise the fluctuating nature of their pain.

Pain can vary by intensity or duration, for instance, and patients wanted to be able to convey this lived experience of pain and avoided time frames if they felt constrained by this. Therefore it was common to average out pain over a number of days to take account of “good” and “bad” days (Ong et al. 2006). The Neck Disability Index is now translated into many languages. Perhaps as an acknowledgement of this characteristic of musculoskeletal pain neither Spanish (Kovacs et al. 2008), Greek (Trouli et al. 2008), Korean (Lee et al. 2006) or Polish (Misterska et al. 2011) versions [recent translations readily available online] stipulate a time frame.

(3) *Generic health status* – EuroQol EQ-5D (Euroqol-Group 1990)

The European Quality of Life (EQ-5D) is a widely utilised (Rabin and de Charro 2001), short to administer, generic quality of life measure intended to complement other questionnaires such as those that are condition-specific. The responsiveness to change of the EQ-5D-3L has been criticised as it is susceptible to ceiling effects (McDowell 2006). A new five-level version, EQ-5D-5L, has been developed to try and avoid these ceiling effects (Herdman et al. 2011) and has been shown to perform well when compared to the originally validated version (Luo et al. 2013). The new version was adopted in this current study.

(4) *Participant ratings of improvement* – Patient’s Global Impression of Change (PGIC)

The collection of participants’ ratings of improvement has been recommended for chronic pain clinical trials (Turk et al. 2003) and a PGIC is a recommended measure for this (Dworkin et al. 2005). The PGIC selected is an 11-point numerical rating global improvement/deterioration scale (Farrar et al. 2001; Bolton 2004). The wording of the PGIC scale is taken from the scale used in a prospective cohort study of back pain outcomes (Breen et al. 2011).

(5) *Patient satisfaction*

While not strictly an outcome measure (Haldeman 2012), finding out the extent to which patients in the study were satisfied can provide a simple indication of patients’ impressions of the conduct of the study. There are a number of patient satisfaction measures and no single method is clearly preferred (Bombardier 2000). In the interest of brevity, a global measure where one question is asked regarding overall satisfaction was selected and the wording is as recommended in a review of these measures (Hudak and Wright 2000).

8.2.4 Data analysis

The normality of data distributions was assessed with the Shapiro-Wilk test. Continuous data (IV-RoM) were analysed for differences with the paired Student's *t* test or the Wilcoxon test where data was not normally distributed. Dichotomous data (hypo-mobility, paradoxical motion) were analysed for differences with the Fisher's Exact test. The level of agreement between palpation and measured hypo-mobility was assessed by Cohen's un-weighted Kappa coefficient (Sim and Wright 2005). EQ-5D-5L Index values using the UK algorithm were calculated using the EQ-5D-5L Index Value Calculator Version 1.0 (Available online: http://www.euroqol.org/about-eq-5d/valuation-of-eq-5d/eq-5d-5l-value-sets.html). Changes in pain, disability and quality of life were assessed by the Wilcoxon signed rank test. Correlations between baseline severity and cervical IV-RoM and between changes in patient-reported outcomes and cervical IV-RoM were made with the Spearman's correlation coefficient. Where appropriate, comparisons were made with previously analysed IV-RoM healthy volunteer data (Chapter 7).

8.3 Results

8.3.1 Baseline characteristics

The baseline characteristics of the patient cohort are shown in Table 26. 70% of the cohort were female, mean (SD) age was 40 (13.1), and the median duration of symptoms was 12 months. On average baseline severity was 5/10 for pain, 13/50 for disability, and 75/100 for quality of life. For regional cervical motion and radiographic features please see Table 14 (page 135).

The majority of patients (60%) complained of musculoskeletal pain at body sites in addition to the neck. Most often pain was reported at two additional sites, most commonly LBP and/or headache but, in all cases, neck pain was the most severe symptom and the reason for seeking care.[25] Three patients had a prior history of whiplash, which they associated with the start of their history of episodic neck pain, but whiplash was not temporally associated with the current episode of pain.[26] Most patients (90%) attended all eight treatment sessions, 3 patients attended seven.

[25] Symptoms in addition to neck pain: LBP (n=1); LBP + headache (n=5); LBP + knee pain (n=1); LBP + knee + temporomandibular joint pain (n=1); LBP + shoulder pain (n=2); headache (n=4); headache + upper back pain (n=1); shoulder pain (n=1); shoulder + upper back pain (n=1); elbow pain (n=1).

[26] The road traffic collisions occurred at three, 15 and 20 years prior to the respective patients attending the chiropractic out-patient clinic. Due to these long histories it was considered that spinal manipulation to the cervical spine was not contraindicated.

Patient characteristics * (n=30)	
Female, n (%)	21 (70.0)
Age, years	40 (13.1)
Duration of symptoms, months - median (interquartile range)	12 (2-36)
Pain sites other than neck, n (%)	18 (60)
Pain pressure threshold, kPa	475 (160.4)
NRS/10	5 (1.5)
NDI/50	13 (6.7)
EQ-5D-5L VAS/100	75 (15.5)
EQ-5D-5L Index/-0.59 to 1.0	0.744 (0.099)

*mean(SD) unless otherwise stated; *kPa*, kilopascals; *NRS*, Numerical Rating Scale for pain; *NDI*, Neck Disability Index; *EQ-5D-5L*, Euroquol; *VAS*, Visual Analogue Scale

Table 26: Baseline patient demographic and clinical characteristics

8.3.2 Treatments received

Table 27 presents the treatments received by patients over the four-week study period. All patients received HVLA manipulation to the cervical spine and this was delivered at a mean rate of 1.3 manipulations per patient visit (range 0 - 4). On average each patient received 10.7 manipulations over the study period. Trigger point therapy and light massage were delivered less frequently, on average at 5/8 (63%) treatment visits.

	Number (%) of patients who received intervention	Mean (SD) over four-weeks
Cervical HVLA manipulation	30 (100)	10.7 (3.5)
Trigger point therapy	27 (90)	5.3 (2.3)
Light massage	27 (90)	5.4 (2.4)
Cold/hot pack*	7 (23)	1.2 (3.4)
Medication*	18 (60)	3.3 (5.2)

*Self-administered; *HVLA*, high-velocity low-amplitude

Table 27: Frequency of treatments received by patients over four-week study period

Cold/hot packs and medication were self-administered by patients at a mean frequency of 1.2 and 3.3 days per week respectively. Data was not collected on the type, dose or within-day frequency of medication use.

8.3.3 Adverse events

Adverse event	n (%)
Temporary increase in symptoms	19 (63.3)
Headache*	4 (13.3)
Events self-resolved within: 24 hours	15 (65.2)
Events self-resolved within: 96 hours	23 (100)
Received treatment outwith study protocol	2 (6.7)

*Two patients reporting headache also included in the number of those with temporary increase in symptoms

Table 28: Adverse events documented during four-week treatment period

Twenty-one (70%) of the 30 patients had a documented adverse event during the four-week study period. This rate is at the upper end of mild-moderate adverse events rates reported in a systematic review of adverse events in manual therapy (pooled proportion estimate of incidence of minor or moderate adverse events calculated was ~41% (95% CI 17-68%) (Carnes et al. 2010a). Adverse events consisted of a temporary increase in symptoms (19/21 or 91% of cases) which for one included exacerbation of arm pain/numbness (Carlesso et al. 2010), and/or headache (4/21 or 19% of cases), all occurring within 48 hours of treatment.

One adverse event might be classed as 'major,' with the patient reporting "horrific" neck pain/headache two hours post-treatment.[27] All events self-resolved and the majority (68%) within 24 hours, consistent with the literature (Carnes et al. 2010a); 100% were self-resolved within four days. In two cases, due to the response to treatment, it was deemed most appropriate to offer treatment outside the study protocol. In both cases this included manipulation to the thoracic spine at two treatment visits, and one of the patients also received cervical spine traction and stretching techniques to the neck musculature at one treatment visit. These two patients were kept within the study.

[27] As defined by modified Delphi consensus on adverse events in manual therapy, 'Minor': short term and mild intensity; 'Moderate': medium to long term; moderate intensity; 'Major': medium to long term; moderate or severe intensity (Carnes et al. 2010b).

8.3.4 Severity of symptoms and baseline cervical inter-vertebral angular motion

There were four tracking failures of C5/6 motion in three patients at baseline (Appendix 29). Due to a technical error it was not possible to retrieve one patient's IV-RoM data so this patient was removed from any further analysis. This patient was one of the two who received some treatment outwith the study protocol (section 8.3.3). Pain, disability and quality of life scores at baseline were not correlated with angular range, the presence of hypo-mobility or paradoxical motion (Table 29). The number of inter-vertebral levels exhibiting laxity however, was negatively correlated (lower side p=0.02) with baseline pain; however, it was not correlated with any other baseline score.

Baseline measure	**IV-RoM versus baseline scores ‡ (n=29 patients)**									
	Flexion range	Sig. (p)	Extension range	Sig. (p)	Hypo-mobility	Sig. (p)	Paradoxical motion	Sig. (p)	Laxity	Sig. (p)
NRS	-0.08 (-0.432 to 0.297)	0.69	-0.15 (-0.491 to 0.228)	0.43	0.23 (-0.152 to 0.548)	0.24	-0.07 (-0.422 to 0.308)	0.73	-0.40 (-0.667 to -0.036)	0.03
NDI	0.26 (-0.114 to 0.575)	0.17	0.08 (-0.299 to 0.430)	0.69	-0.13 (-0.473 to 0.249)	0.50	-0.09 (-0.441 to 0.287)	0.64	0.18 (-0.199 to 0.513)	0.35
EQ-5D-VAS	0.11 (-0.268 to 0.457)	0.57	0.21 (-0.167 to 0.537)	0.27	-0.11 (-0.454 to 0.271)	0.58	-0.08 (-0.435 to 0.294)	0.67	0.16 (-0.220 to 0.497)	0.41
EQ-5D-Index	0.02 (-0.350 to 0.383)	0.92	0.003 (-0.364 to 0.369)	0.99	-0.16 (-0.495 to 0.222)	0.41	-0.12 (-0.463 to 0.261)	0.54	0.01 (-0.357 to 0.376)	0.95

‡, Spearman's rank correlation coefficient (95% confidence interval); *Sig*, significance; *p*, two sided p-value; *Laxity*, the number of inter-vertebral levels in each patient exhibiting attainment rates (over the corresponding 10° of regional cervical spine motion) above the upper quartile calculated from healthy volunteers

Table 29: The relationship between severity of symptoms and baseline cervical inter-vertebral angular motion

As with inter-vertebral motion, regional cervical ROM as measured with the CROM device was likewise not correlated with pain at baseline in flexion (Rho = 0.15 (95%CI: -0.233 to 0.487), two-sided p = 0.45) or extension (Rho = 0.11 (95%CI: -0.270 to 0.456), two-sided p = 0.58).

8.3.5 Agreement between measured and palpated hypo-mobility

The number of hypo-mobile segments identified by palpation and confirmed by QF measurement are shown in Table 30. Agreement was poor and statistically significant only for C1/2 and C4/5 in extension.

	Inter-vertebral level	Identified hypo-mobile	Confirmed hypo-mobile*	% confirmed	Kappa (95%CI)	Sig. (p)
Flex	C1/2	18	1	6	0.04 (-0.063 to 0.148)	0.21
	C2/3	20	0	0	-0.07 (-0.161 to 0.021)	0.94
	C3/4	9	0	0	-0.18 (-0.477 to 0.110)	0.89
	C4/5	13	2	15	0.17 (-0.034 to 0.369)	0.05
	C5/6†	13	1	8	0.01 (-0.192 to 0.214)	0.46
	Pooled	73	4	5	-0.02 (-0.094 to 0.063)	0.65
Ext	C1/2	18	6	33	0.28 (0.024 to 0.526)	0.02
	C2/3	20	0	0	-0.14 (-0.272 to -0.015)	0.99
	C3/4	9	1	11	0.01 (-0.280 to 0.307)	0.46
	C4/5	13	4	31	0.26 (-0.033 to 0.554)	0.04
	Pooled	60	11	18	0.08 (-0.022 to 0.181)	0.06

*Number of hypo-mobile levels identified on palpation and confirmed by measurement as movement ≤ the hypo-mobility threshold; †, flexion only – no hypo-mobility detected by QF in extension

Table 30: Hypo-mobile levels identified by palpation (C1-C6) and confirmed by measurement in flexion (n=141 segments) or extension (n=116 segments)

Table 31 (next page) shows the number of hypo-mobile segments identified by palpation and those identified by QF measurement when the threshold for hypo-mobility was raised to 5°. The Kappa values indicate no agreement between these.[28]

[28] The hypo-mobility cut-offs calculated previously (section 6.3.5 page 134) are likely to be too small to be detected by palpation. Due to the reported inaccuracy of spinal palpation (Robinson et al. 2009), adjacent segments were included.

Inter-vertebral level	Identified hypo-mobile	Confirmed hypo-mobile*	% confirmed	Kappa (95%CI)	Sig. (p)
C2/3	20	6	30	0.00	0.50
C3/4	9	2	22	0.06 (-0.064 to 0.193)	0.16
C4/5	13	6	46	0.04 (-0.160 to 0.248)	0.34
Pooled	42	14	33	0.06 (-0.032 to 0.158)	0.10

*Number of hypo-mobile levels identified on palpation and confirmed by measurement as movement of <5° in flexion or extension at the identified or adjacent segment

Table 31: Hypo-mobile levels (<5°) identified by palpation (C2-C5) and confirmed by measurement (n=87 segments)

The sensitivity and specificity values for identifying hypo-mobile segments (<5°) with palpation are shown in Table 32. These suggest that palpation of hypo-mobility is only moderately sensitive and specific at C4/5 in extension.

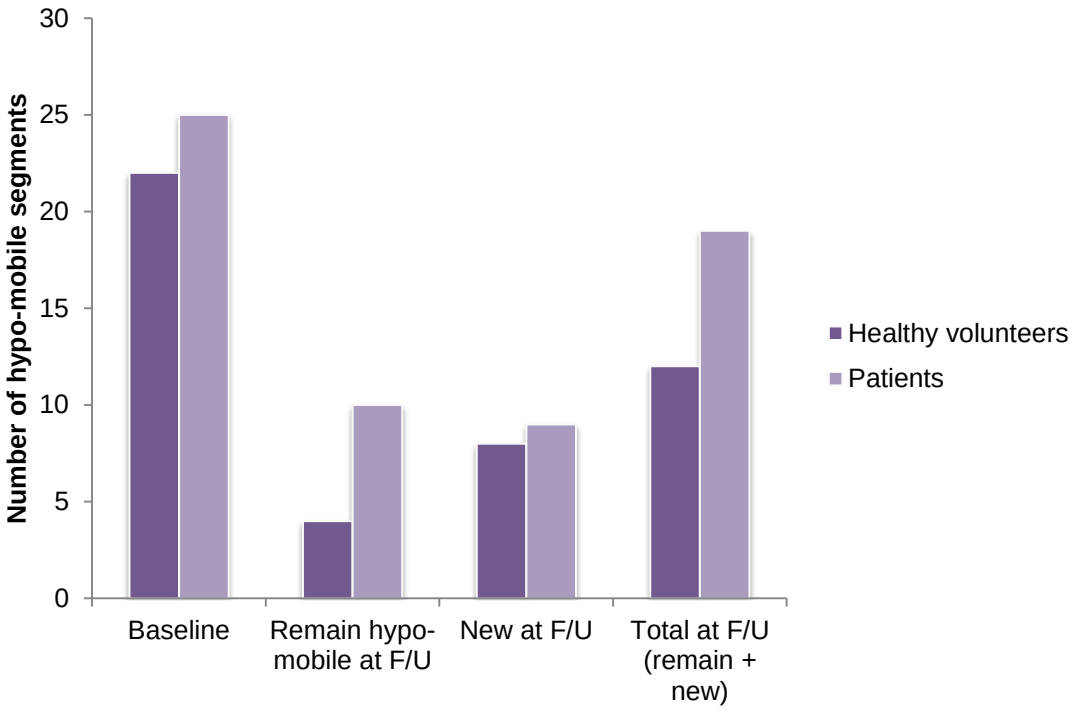
	Sensitivity (95%CI)	Specificity (95%CI)	Likelihood ratio (positive test)
C2/3	0.55 (0.234 to 0.833)	0.22 (0.064 to 0.476)	0.70 (0.349 to 1.181)
C3/4	0.33 (0.043 to 0.778)	0.70 (0.471 to 0.868)	1.10 (0.286 to 3.196)
C4/5	0.75 (0.349 to 0.968)	0.67 (0.430 to 0.854)	2.25 (1.025 to 4.672)
Pooled	0.56 (0.349 to 0.756)	0.55 (0.417 to 0.675)	1.24 (0.767 to 1.882)

Table 32: Sensitivity and specificity of palpation for identifying hypo-mobility (<5°) in flexion or extension at the identified or adjacent segment

8.3.6 The prevalence of hypo-mobile segments at baseline and follow-up

There were three tracking failures of C5/6 in two patients at follow-up (Appendix 29). The number of inter-vertebral levels classed as hypo-mobile at baseline and follow-up in patients are displayed in Figure 52, along with those levels from the intra-subject reproducibility study in healthy volunteers (section 7.3.3 page 157) for comparison. While most of these segments in patients were no longer classed as hypo-mobile at follow-up, nine segments were hypo-mobile that had been within normal range at baseline.

There was no significant difference in the prevalence of hypo-mobility at baseline (two-sided p = 0.76, Fisher's Exact test) or follow-up (two-sided p = 0.27, Fisher's Exact test) between groups. Within-group change was similarly not significant (healthy volunteers: two-sided p = 0.11; patients: two-sided p = 0.43).



F/U, follow-up

Figure 52: The prevalence of hypo-mobile segments at baseline and follow-up in patients and healthy volunteers

Of the 15 segments in patients no longer hypo-mobile at follow-up only one increased in range greater than the MDC for that level (Figure 53). This segment received three manipulations over the study period, including one at the final treatment visit.

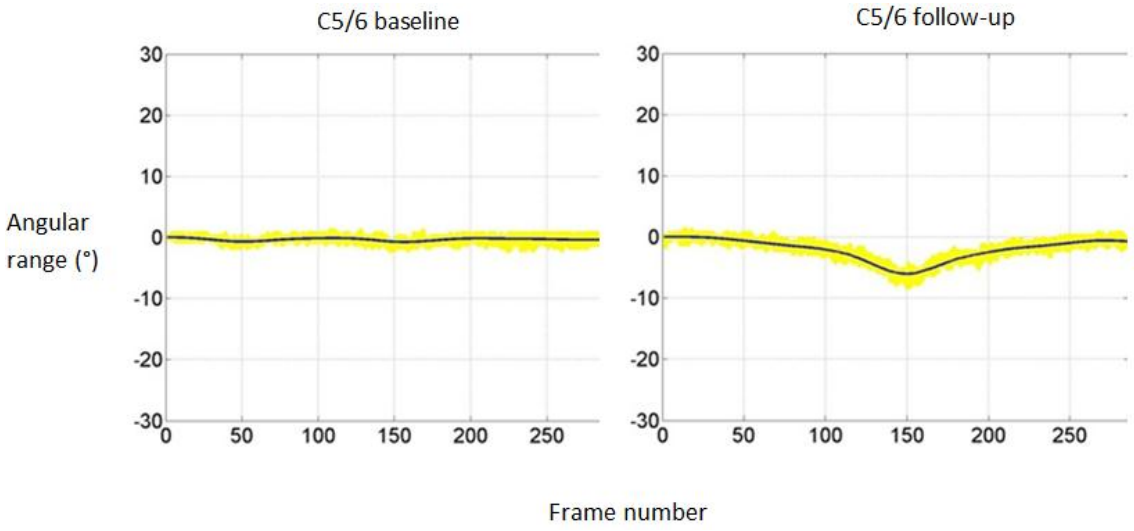
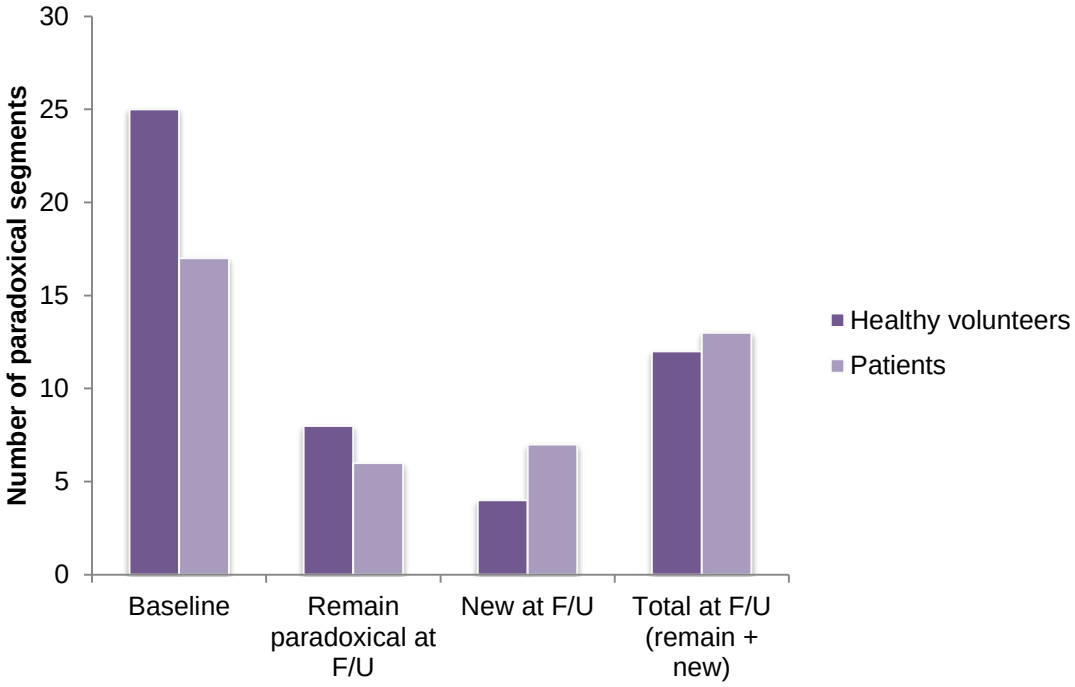


Figure 53: Baseline and follow-up motion graphs showing freeing of a hypo-mobile C5/6 segment

8.3.7 The prevalence of paradoxical motion at baseline and follow-up

The prevalence of paradoxical motion segments at baseline and follow-up is shown in Figure 54, along with healthy volunteers' data for comparison (section 7.3.3, 157). Most of these segments in patients were no longer classed as paradoxical at follow-up; seven segments were newly paradoxical that had not been at baseline. There was no significant difference in the prevalence of paradoxical motion segments at baseline (two-sided p = 0.20, Fisher's Exact test) or follow-up (two-sided p >0.99, Fisher's Exact test) between groups. Within-group change was not significant in the patient group (two-sided p = 0.57, Fisher's Exact test) but was in the healthy volunteer group two-sided p = 0.04, Fisher's Exact test).



F/U, follow-up

Figure 54: The prevalence of paradoxical segments at baseline and follow-up in patients and healthy volunteers

8.3.8 Changes in cervical angular inter-vertebral motion

While the mean IV-RoM of the five inter-vertebral levels increased for 4/5 levels in flexion and 4/5 levels in extension between baseline and follow-up (see Appendix 29), these changes were small and not significant except for C3/4 in flexion, which increased in range on average by 1.2° (p=0.01). As shown in Figure 55 (flexion) and Figure 56 (extension), these small amounts of change occurred in both directions and in many segments.

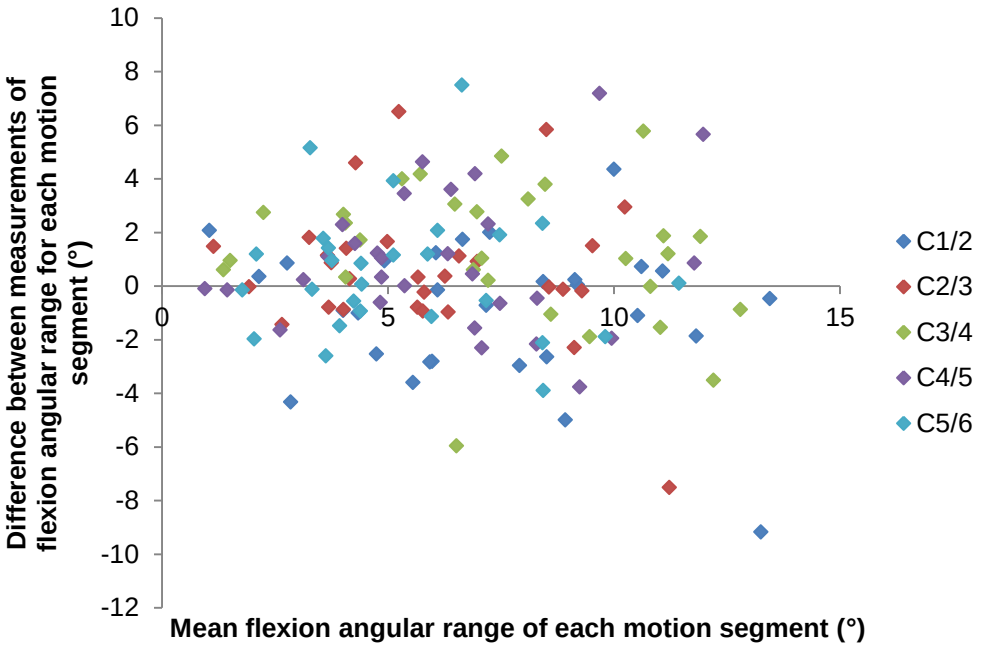


Figure 55: Difference against mean flexion angular range of each motion segment in patients with neck pain (n= 148 segments)

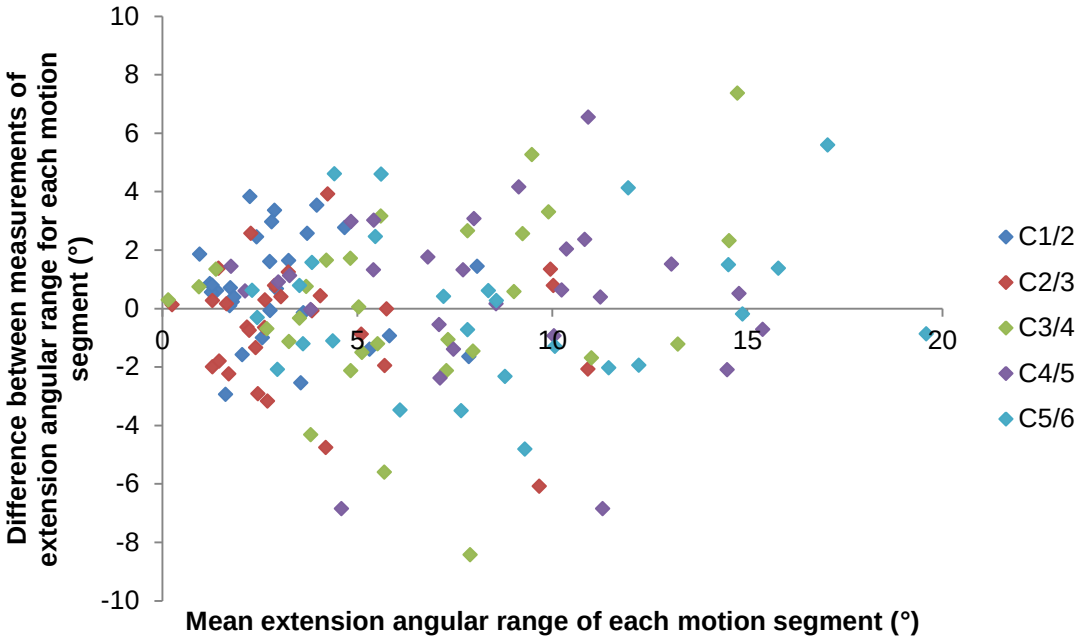


Figure 56: Difference against mean extension angular range of each motion segment in patients with neck pain (n= 148 segments)

However in 12/29 of the patients (41%), 17/148 segments (11.5%) increased their ranges above MDC in flexion and 3/148 segments (2.0%) in extension after treatment. The 20 segments (flexion and extension) that increased in range above MDC were categorised as hypo-mobile (≤ mean-2SD), hyper-mobile (> mean+2SD) or normal (> mean-2SD and < mean+2SD) at baseline and follow-up based on healthy control data (Deitz et al. 2011), and these are shown in Figure 57.

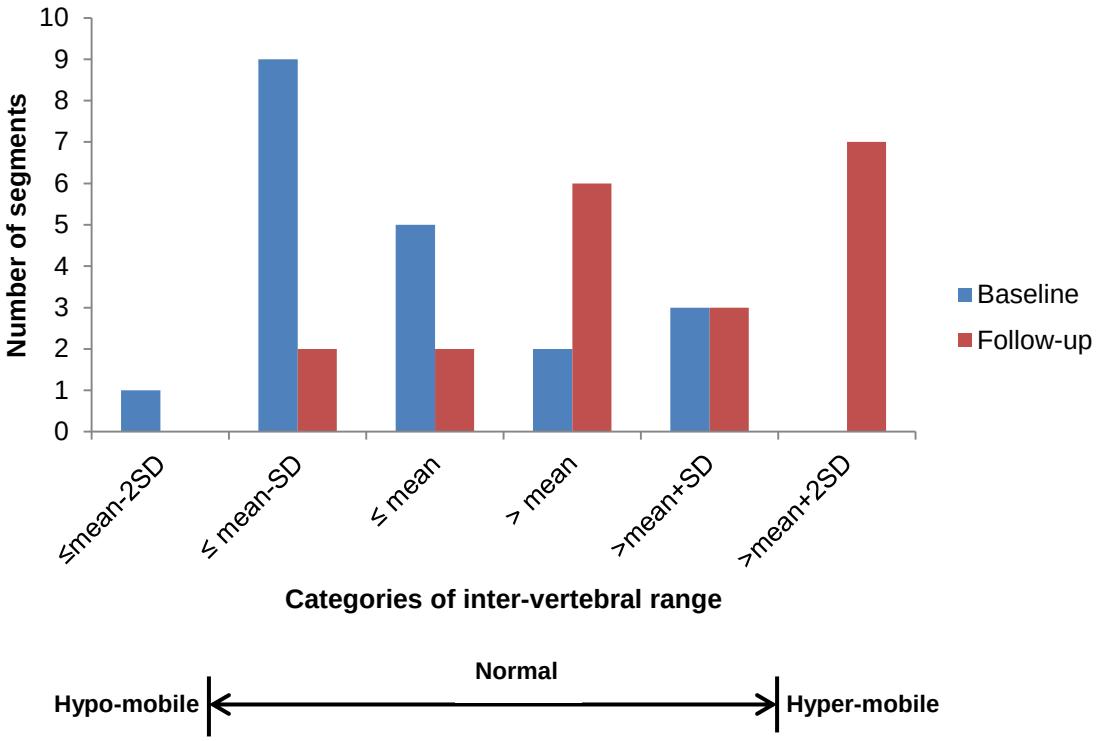


Figure 57: Baseline and follow-up angular range classification of segments that increased in range (n=20 segments)

This figure shows that only one out of the 20 segments that became more mobile exhibited hypo-mobility at baseline (see page 138 for further description of hypo-mobility). Indeed all other segments were within normal range at baseline. At follow-up, 13 of these 20 levels had not increased their range to the extent of being hyper-mobile. However, the remaining seven levels in four patients were now hyper-mobile.

There was no correlation between increased range at these levels and corresponding decreases in range beyond the MDC within patients at other levels (Rho = 0.05 (95% CI: -0.326 to 0.406) two-sided p = 0.41). This opens the question of whether manipulation in these patients could have resulted in the hyper-mobility.

8.3.9 The association between increased cervical IV-RoM and spinal manipulation

Of the 20 inter-vertebral levels that did increase in range after treatment, only four were the recorded targets for manipulation given at the final treatment visit. A significantly higher proportion (13/29, 44.8%) of targeted or adjacent segments in patients who received at least four manipulations over the study period increased in range compared with the same segments in the untreated healthy volunteers (2/27, 7.4%), (two-sided Fisher's Exact test p = 0.002), again suggesting a link between increased segmental mobility and spinal manipulation.

Finally, in Figure 58 the number of manipulations received by each patient is plotted against the number of levels that increased in range above the MDC in either flexion or extension in all patients.

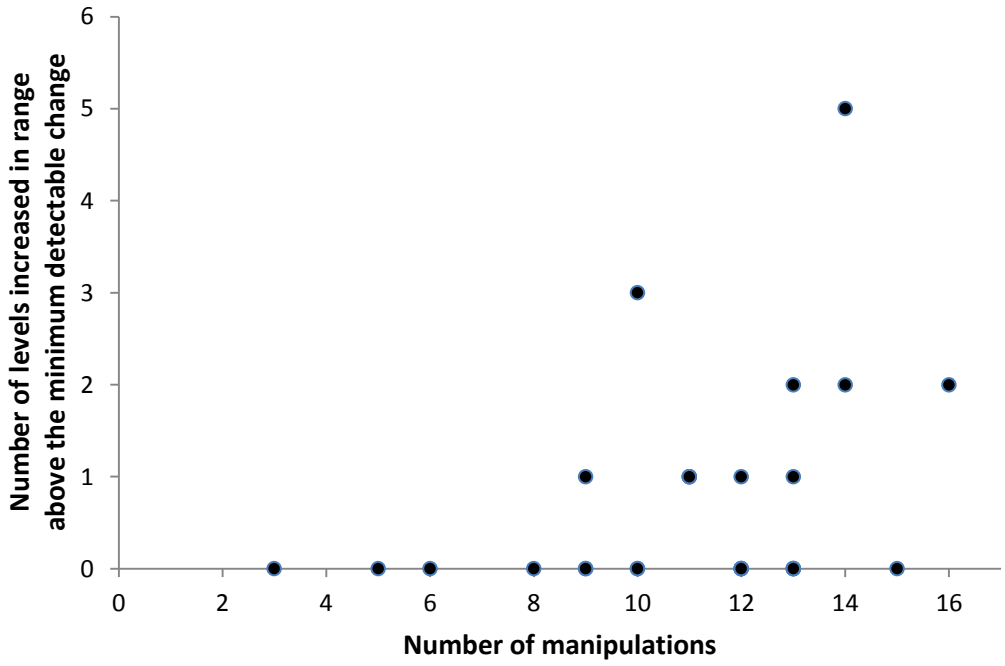


Figure 58: The number of manipulations received by patients versus the number of inter-vertebral levels that increased above the MDC

As shown, the number of manipulations received was weakly but positively correlated with the number of levels that increased their inter-vertebral range in a dose-response manner (Rho = 0.39 (95% CI: 0.014 to 0.663), upper side p = 0.04). Conversely, this number of manipulations was not associated with the number of levels that *decreased* their ranges in excess of the MDC (Rho = -0.18 (-0.520 to 0.205), upper side p = 0.82).

Despite this, nine patients experienced no increase in segmental range at any level, even when they received at least nine manipulations which, as suggested by Figure 58, was the number of manipulation below which no levels increased above MDC.

8.3.10 Correlating increased cervical IV-RoM with patient-reported outcomes

In Table 33 are shown patients' changes in pain, disability, quality of life and global impression of change scores, which were all significantly improved at follow-up. However, there was no correlation between increased cervical IV-RoM and any of these outcomes.

PROM	Baseline Mean (SD)	Follow-up Mean (SD)	Sig. (p) †	Percentage Change Score (95%CI)	Correlation of Percentage Change and increased IV-RoM **	Sig. (p) ‡
NRS/10	5 (1.5)	2 (1.6)	p<0.0001	52% (40.6 to 63.4%)	0.02 (-0.350 to 0.383)	0.92
NDI/50	13 (6.7)*	6 (4.9)	p<0.0001	48% (36.2 to 59.8%)	0.12 (-0.260 to 0.464)	0.54
EQ-5D-5L VAS/100	75 (15.5)	84 (14.9)	p=0.001	6% (-10.0 to 22.0%)	-0.12 (-0.465 to 0.259)	0.54
EQ-5D-5L Index/-0.59 to 1.0	0.744 (0.099)	0.819 (0.105)	p<0.0001	9% (4.4 to 13.6%)	-0.19 (-0.518 to 0.192)	0.33
PGIC/ -10 to +10	-	87% 'improved'***	-	-	-0.05 (-0.407 to 0.325)	0.81

PROM, patient-reported outcome measure; *Sig*, significance; *p*, two-sided p-value; †, Wilcoxon signed rank test; ‡, Spearman's rank correlation coefficient; *normally distributed; **Increased IV-RoM = number of inter-vertebral levels increased in range above MDC ***At least 30% improvement

Table 33: Correlations between patient-reported outcomes and increased cervical inter-vertebral angular motion

Twenty-six of the 29 patients (90%) were 'very' or 'extremely' satisfied with the results of their treatment for neck pain, two were 'somewhat' satisfied, and one was 'mixed' (approximately equal satisfaction and dissatisfaction).[29]

[29] The 30th patient, for whom cervical IV-RoM data was not available due to a technical error, also reported a 'mixed' level of satisfaction. While a clinically significant reduction in pain was reported, a large temporary increase in symptoms was experienced by this patient during the study period.

Levels of satisfaction were not correlated with increased cervical IV-RoM (Rho = -0.26 (95%CI: -0.574 to 0.130) two sided p = 0.19).

8.3.11 Clinically important differences in patient-reported outcomes and increased cervical IV-RoM

PROM	Clinically improved*	Not clinically improved	Sig. (p)	Clinically improved*	Not clinically improved	Sig. (p)
	Proportion of patients with increased IV-RoM** (n=29)			Proportion of segments with increased IV-RoM (n=286)		
NRS	32% (8/25)	50% (2/4)	0.59	5% (13/247)	15% (6/39)	0.03
NDI	35% (7/20)	33% (3/9)	>0.99	5% (10/199)	10% (9/87)	0.12
EQ-5D-5L VAS	33% (1/3)	35% (9/26)	0.22	3% (1/30)	7% (18/256)	0.70
EQ-5D-5L Index	18% (1/8)	43% (9/21)	0.20	3% (2/80)	8% (17/206)	0.11

Sig, significance; *p*, two-sided (by summation) Fisher's Exact test

*Clinically improved defined as follows: *NRS and EQ-5D-5L VAS,* ≥ 30% reduction (Pool et al. 2007; Ostelo et al. 2008); *NDI,* ≥ 14% reduction (MacDermid et al. 2009b); *EQ-5D-5L Index,* ≥ 0.083 (the mean change score of those 'improved' based on the PGIC; **at least one level increased above MDC

Table 34: Increased cervical inter-vertebral angular motion in patients clinically improved and not clinically improved

Table 34 compares the proportion of patients who were clinically improved and had increased IV-RoM against those who had increased IV-RoM but were not clinically improved; there were no significant differences for any of the PROMs. When the number of segments that increased in angular range in those who were clinically improved were compared to the same segments in those not clinically improved, the only significant difference was for pain, where a greater proportion of segments were increased in those whose pain had not improved or worsened.

As shown in Table 34, the majority (25) of patients (87%) reported clinically significant reductions in pain;[30] this included two patients who had hyper-mobile segments at follow-up (one and three levels respectively). Four patients (13%) reported no change or worsening of their neck pain.

Two of these four individuals had no increases in cervical IV-RoM while the other two patients did. In the two cases of no cervical IV-RoM change, pain was increased (by 30%). One of these two patients had no detectable change in disability, while the other had a clinically significant decrease in disability score.

Of the two clinically unchanged/worsened patients who had increases in IV-RoM above MDC, the first had one segment that increased in range and was classed as hyper-mobile at follow-up; the second patient had five levels increased, two of which were hyper-mobile at follow-up (no change in pain in both cases; disability was clinically improved in the first and unchanged in the second patient).

In five patients clinically important differences (CID) in disability could not be detected, as their NDI baseline scores were less than the CID of 7 (MacDermid et al. 2009b), and so these scores were subject to floor effects. Despite this, most patients (69%) had a clinically significant improvement in disability.

Quality of life as measured with the EQ-5D-5L significantly improved at the group level, but this was not significant for the VAS when baseline values were accounted for in the percentage change scores (Table 33). Only three patients had at least a 30% improvement in this score. The mean baseline VAS of 75% (SD 15.5%) meant that this score was subject to ceiling effects, precluding the detection of meaningful improvement in some patients (mean change score was 5%, SD 43%). It also meant that in this cohort that quality of life appeared not to be significantly impacted by neck pain.

The mean change score for the EQ-5D-5L Index values was significant but small (9%). The CID for the *EQ-5D-3L* Index has been calculated from a back pain trial (mean minimally important difference for improvement = 0.046, SD 0.109; standardised response mean = 0.25) (Walters and Brazier 2005) but not for neck pain nor for the EQ-5D-5L, which is intended to be more responsive than the original three level version (Herdman et al. 2011). [31]

[30] NRS reduction: ≥ 50% (21/29 patients), ≥ 70% (9/29 patients), = 100% (2/29 patients)
[31] For information: EQ-5D-3L Index data were collected in a randomised trial of physiotherapy interventions for neck pain (Klaber Moffett et al. 2005). The mean raw Index change score (at three months) from a mean baseline of 0.696 was 0.016 (Manca et al. 2006). In this present study, the mean raw Index change score (at four weeks) was 0.075.

Based on the mean change score of Index values reported in this present study for those ‘improved’ based on the PGIC, eight patients had a clinically important improvement in their quality of life score.

8.4 Discussion

This study has shown for the first time that spinal manipulation is associated with increasing cervical inter-vertebral angular motion, albeit the association was weak (Figure 58). Previous research has found increases in regional cervical ROM immediately after manipulation (Cassidy et al. 1992; Martinez-Segura et al. 2006), one week after manipulation (Saavedra-Hernandez et al. 2012) and after a course of cervical manipulation (Whittingham and Nilsson 2001). It is possible however that the changes in regional ROM observed in these studies may not have been attributable to any mechanical changes due to manipulation, but could have been due to a change in participants’ behaviour (Bahat et al. 2014). The cross-sectional study by Bahat et al. (2014) found fear of motion to be consistently associated with decreased flexion, extension and left/right rotation (Bahat et al. 2014). Fear of motion was also correlated with pain intensity, so this could have been a covariate for the reduced extension ROM which had been correlated with pain in that study.

At baseline in this present work, while regional cervical ROM was significantly reduced in patients compared to healthy volunteers (Chapter 6, Table 14, page 135), neither regional ROM nor cervical IV-RoM were correlated with baseline severity of pain or disability. The encouragement to patients to move as far as they could, through the pain if possible, may have overcome any fear of movement, or it may be that flexion and extension were not the most pain-provoking movements. The only correlation in this present study between baseline outcome measures and motion, regional or inter-vertebral, was that patients reporting higher levels of pain had fewer lax segments. This suggests that segments in patients with more pain were more likely to be slowly moving, at least in the corresponding first 10° of neck motion.

It was assured that all participants were moving at the same velocity by following the face-rest attached to the motion frame during image acquisition (Figure 17) and the angular velocity differences at segmental levels can be considered true inter-vertebral differences. Although patients were asked to inform the researcher if their face was sliding on the face-rest during motion there is the possibility of some differences in gross head movement between participants.

Lax segments were most commonly observed at C1/2 in extension, and it might be that the speed of the head nodding back during extension was perhaps not as well controlled as was the rest of the neck motion. Because of the relatively large mass of the head, active cervical ROM has been characterised as essentially passive at end-range (Nilsson et al. 1996b). Any lack of motor control or muscle recruitment impairment present in some patients could perhaps contribute to poor head control (Tsang et al. 2014).

In this study regional cervical ROM was standardised with the intention of taking all segments through their full range, and this range was not significantly different between baseline and follow-up; and, since increased IV-RoM was determined based on the MDC over the four-week study period, the segmental increases can be considered true changes with some confidence. However, only one level that increased in range was hypo-mobile at baseline.

8.4.1 Hypo-mobility

There was little agreement between palpation findings of hypo-mobility and that measured by QF, even when the threshold for hypo-mobility was increased to five degrees. It has been previously shown that congenital block vertebrae can be reliably identified as the most hypo-mobile segments with motion palpation by even relatively inexperienced palpators (final year chiropractic students) (Humphreys et al. 2004). However, congenital blocks are effectively immobile; the discrepancy in motion between a segment that is not moving, and those that are, will be more readily palpated than that of a moveable segment whose motion is reduced.

The findings from this present study, using QF as the reference standard, are more representative of the usual clinical scenario where congenital blocks are rare. Hypo-mobility was palpated far more frequently than it was measured. Dvorak et al. (2008) has cautioned against placing too much significance on the finding of segmental hypo-mobility in the absence of symptom-provocation, particularly in older patients where mobility has probably decreased as a function of aging (Dvorak et al. 2008). The presence of hypo-mobility in this present study was not associated with the age of patients (Rho 0.21; 95%CI: -0.170 to 0.535), p = 0.27), so was not being erroneously identified in older patients.

In a study that compared motion palpation findings of *hyper-mobility* in patients with LBP with measurements from flexion-extension radiography, palpation was specific but not sensitive at detecting hyper-mobility; the detection of hypo-mobility was not performed (Abbott et al. 2005).

In this study, the palpation of hypo-mobility was only sensitive and specific at C4/5, in extension. Some concurrent validity is lent to this finding when the influence of anatomical structures during flexion and extension are considered. During cervical flexion the posterior muscles and ligaments stretch and there is eccentric contraction of the stabilising musculature, which make it difficult to palpate joint movements, while in extension, these structures are relaxed and the joints can be better discerned by palpation.

However, as Abbott et al. (2005) found for hyper-mobile segments, hypo-mobile segments were more often palpated than measured. It might be that palpated and measured hypo-mobility are two different constructs. Rather than palpation being a method of measuring IV-RoM, it is likely that a dichotomous decision is being made - hypo-mobile or not - this being decided based on the motion relative to other cervical levels within the same patient. When Abbott et al (2006) took into account within-subject variability, the presence of hypo-mobility as determined from flexion-extension x-rays was found to be more discriminatory between patients and controls (Abbott et al. 2006). It was not possible to follow that methodology in this present study as the data were not always normally distributed. Also, the approach and the intent of practitioners can vary regarding the relative importance of interpreting palpatory findings (Abbott et al. 2009) which adds a layer of variability that makes comparisons with a standardised measurement method problematic.

The presence of (palpated) hypo-mobility is an important feature of a proposed clinical prediction rule (CPR) thought to predict a favourable response to spinal manipulation for LBP (Childs et al. 2004a). While hypo-mobility is not a direct feature of a clinical prediction rule developed to predict neck pain patients' likelihood of a positive outcome with cervical manipulation (see section 2.4.2 page 16), patients in the study where this rule was developed had manipulation directed to the level found to be most "restricted" (Puentedura et al. 2012a), not the most symptomatic.

It is not known how many of the patients in this present study will have met the condition of that CPR; certainly, most had symptoms longer than 38 days. A shorter duration of symptoms is a predictor of improvement independent of manipulation (Carroll et al. 2008b), so the group of patients identified by this rule will include patients who are likely to improve irrespective of treatment. Furthermore, in a study by Haas et al. (2003) 104 patients with neck pain were randomised to receive cervical manipulation directed either to restricted levels identified by palpation or to levels selected at random by a computer.

Both groups showed immediate clinically important improvements in pain and stiffness with no differences between groups (Haas et al. 2003). The study authors' concluded that, "pain modulation may not be limited to mechanisms associated with manipulation of putative motion restrictions" (Haas et al. 2003).

In this present study segments exhibiting hypo-mobility or paradoxical motion, both considered to be indications for spinal manipulation (Schafer and Faye 1989; Peterson and Bergmann 2011), were observed to come and go with no more or less frequency than in healthy volunteers receiving no manipulation (Appendix 24), casting further doubt on their clinical importance.

The clinical importance of increased IV-RoM, at least in the sagittal plane, is also under question since there was no correlation between increased IV-RoM and any of the patient-reported outcomes of pain, disability, quality of life or patient global impression of change. It might have been that increases in IV-RoM were important for pain reduction in some patients, but not for others. However, it is not currently possible to distinguish between these patients at baseline.

8.4.2 Other possible mechanisms of manipulation

It is possible that clinically important changes in IV-RoM occurred at levels (C0/1, C7/T1, thoracic spine), or in directions (coronal plane, transverse plane) that were not measured. Changes in kinematic variables other than angular range, such as IAR (Hwang et al. 2008) or phase lag (Bogduk and Mercer 2000) could be more clinically important. Alternatively, a different mechanism(s) that could account for the clinical improvements observed after manipulation may be have been involved (see Figure 13).

• Other reasons for recovery

Other possible reasons for improvement that cannot be ruled out in an observational study like this one include: placebo effect (patient's expectations of benefit from an intervention that might be therapeutically inert, for them), curabo effect (positive nature of the practitioner increasing the patient's confidence in the therapy) (Graz et al. 2005) and the natural history (regression to the mean) of neck pain, or if pain was muscular in origin, trigger point therapy and light massage may have been therapeutic without influencing IV-RoM. The rationale for including these treatments was to reduce the risk of drop-out of those participants with muscle pain not experiencing adequate pain relief. If a broad definition of spinal manipulation is taken it can be argued that these muscle treatments fall under the aegis of 'spinal manipulation' (Harvey et al. 2003).

Additionally, the use of cold/hot packs and analgesia by some patients may have contributed to symptomatic improvement.

Even in a controlled study it is difficult or impossible to completely remove non-specific effects. One study attempted to control for these non-specific effects by anaesthetising six patients with LBP who were then placed on their sides and SMT was delivered to half the group (Kawchuk et al. 2009). When patients woke up they were unaware of whether they had received SMT or not, and those who had received the intervention reported greater pain reduction than the controls, providing some preliminary evidence of a true therapeutic effect. However, while encouraging, these are only preliminary findings from a small study sample and the possibility of the anaesthetic agents having an analgesic effect have yet to be ruled out (Kawchuk et al. 2009).

8.4.3 Patients who did not improve

• Heterogeneity of cohort

While neck pain was the cardinal symptom in all patients the majority had pain at other body sites, so the group was not symptomatically homogeneous. Patients with multi-site pain are less likely to report symptomatic improvement (Michaelson et al. 2004), whether or not any changes have occurred in cervical inter-vertebral motion after treatment. However, with 25/29 patients reporting clinically significant decreases in pain, multi-site pain appears not to have been an important confounder. Also, in a study that measured regional cervical ROM with an electromagnetic tracker system no differences in this motion were found between patients with neck pain and patients with neck pain and LBP (Rudolfsson et al. 2012). This suggests that additional pain, at least LBP, probably does not affect cervical IV-RoM.

Including patients with pain in addition to the neck is likely to be more reflective of clinical practice (Bolton and Hurst 2011) which can make results more generalisable. In a large population-based survey in Norway with 1,144 returned questionnaires, 34.4% of respondents reported neck pain in the previous week, but only 1.4% reported pain confined to the neck (Natvig et al. 2010). 15.9% had “regional neck pain” (pain in head, shoulder or upper back), 14.8% reported “neck pain as part of widespread pain” (pain in one to three additional pain sites distant from the neck) and 2.4% had “neck pain as part of scattered pain” (pain in four or more of nine sites other than the neck) (Natvig et al. 2010).

The response rate in this survey was only 54.4% so the results must be interpreted with caution due to the risk of responder bias; for example, those with more problematic widespread pain problems are perhaps more likely to return such a survey.

However these findings do echo that of the multisite pain commonly reported by patients presenting with chronic musculoskeletal pain to primary care (Carnes et al. 2007). In a survey of AECC outpatient clinic records between 1997-1999, 50% of patients reported having one area of complaint; for example, the neck or low back alone (Wagennaar 2000). Therefore confining recruitment to those with neck pain alone would have had a restrictive effect on the recruitment rate.[32]

• Negative prognostic factors

Four patients did not symptomatically improve, two of whom had increased cervical IV-RoM at follow-up. This group exhibited a number of negative prognostic factors for neck pain, independent of any intervention (Appendix 30) as shown in Figure 59, which may have contributed to the poor outcomes. While a study which studied the results from three randomised trials of treatments for neck pain found that older age was associated with an increasing likelihood of recovery with SMT in the longer term versus 'usual care', this benefit was negated in the presence of co-morbid LBP (Schellingerhout et al. 2008). Conversely, the probability of recovery with SMT diminished with increasing baseline NRS pain scores (>7/10) (Schellingerhout et al. 2008).

	Negative prognostic factors for neck pain (Carroll et al. 2008b)					
Patient	Female	Older age*	Pain > 6 months	Co-morbid LBP	Greater baseline pain**	Greater baseline disability**
P04	✓	×	✓	✓	×	✓
P05	✓	×	✓	×	×	✓
P11	×	×	×	✓	×	✓
P28	✓	✓	✓	×	✓	✓

*Particularly in 45-59 age-group (Hill et al. 2004); **greater than mean NRS or NDI scores for the cohort

Figure 59: Known negative prognostic factors present in patients who did not improve

[32] It is also worth noting that the vast majority of patients approached (n=161) regarding participation in this study were excluded (Figure 46 page 124).

While three of these patients experienced temporary increases in symptoms during the study period, adverse events after cervical SMT which are typically mild-moderate, are not believed to negatively affect clinical outcomes, at least not at three months (Rubinstein et al. 2007); however, patients were not followed-up beyond the four-week study period.

Four weeks of passive treatment proved insufficient for this group who may have benefited from the addition of exercise rehabilitation (Falla et al. 2012; Vincent et al. 2013) or perhaps alternative treatment. One patient did not improve despite receiving treatment out-with the study protocol (thoracic SMT) which has been shown to be efficacious for neck pain (Cross et al. 2011).

The presence of occupational risk factors for recovery in this cohort, such as lack of control in the workplace (Carroll et al. 2008a), are unknown. Equally unknown are the presence or absence of positive prognostic factors for recovery from neck pain, such as having a good social support network (Bergstrom et al. 2012) and a propensity towards physical activity (Rasmussen-Barr et al. 2013).

None of the patients had evidence of central pain hypersensitivity, based on algometry testing, at baseline (Table 26 page 168) which could have been an additional negative prognostic factor for recovery with passive treatment. It may be that this is a feature more related to whiplash-associated neck pain, rather than idiopathic neck pain (Walton et al. 2013; Smith et al. 2014). Algometry data was missing for two of the patients who did not improve. Additionally, while the same model of algometer was used as in a large study that derived reference values for pain-pressure thresholds (Neziri et al. 2011), the handle was susceptible to sticking so may not have been particularly sensitive at detecting pain at small pressures. Therefore, the possibility of some patients having central hypersensitivity cannot be entirely discounted.

Three of the four patients who did not improve did have a prior history of whiplash-associated disorders which can also be associated with post-traumatic stress that can further hamper recovery (Walton et al. 2013). Other negative psychological prognostic factors, the presence of which were unknown, include catastrophising and anxiety (Hill et al. 2007). Abnormal illness behaviour was not suspected in any of the patients and was not tested for (Vernon et al. 2010).

• Non-mechanical neck pain

The likelihood of any of the patients having non-mechanical neck pain is very small (NHMRC. 2003). However it is possible that some patients had excessive inflammation (Teodorczyk-Injeyan et al. 2011) that would better respond to an anti-inflammatory strategy. Also, evidence has emerged that Modic type 1 changes at inter-vertebral end-plates have an important role to play in a small sub-group of LBP sufferers (Albert et al. 2013) and these changes are known to occur in the cervical spine (Mann et al. 2014) although their role in the evolution of neck pain has yet to be elucidated.

8.4.4 Additional limitations

Due to the observational design of this study increases in IV-RoM can only be associated and not causally linked with treatment nor with HVLA manipulation, since soft tissue treatment was also received by most patients. The increases in IV-RoM may be related to decreases in pain, and pain may have reduced for reasons other than treatment, such as natural history. However, since regional cervical ROM was unchanged at follow-up, increases at the segmental level are not readily explained by reduced pain alone but suggest mechanical changes have occurred. Changes in segmental motion in planes other than the sagittal plane may have occurred and may be symptomatically important, but these could not be measured.

Hypo-mobility as documented by chiropractic interns was retrospectively extracted from patient's files. Palpation is known to be unreliable in the absence of pain provocation (Triano et al. 2013) and hypo-mobile levels were frequently not identified as being tender. Further, the direction of segmental hypo-mobility was not documented, and may not have been palpated in flexion or extension. Although it has been suggested that if motion is reduced in the sagittal plane it is probably also reduced in other planes (Hipp and Wharton 2008), this is not necessarily the typical finding in manual therapy practice. Had there been a more standardised protocol followed by examiners then agreement between palpated and measured hypo-mobility may have been better. However, the strength of there not having been a study protocol is that the data were untarnished by the Hawthorne effect as interns did not know these data were to be collected.

Similarly the palpation methods used by the chiropractors to determine the target segments for manipulation and the manipulative technique used were not standardised.

While it was routine practice at the AECC outpatient clinic to use motion palpation, there remains the possibility of alternative approaches being used. However, the use of HVLA manipulation was stipulated.

Follow-up IV-RoM and PROMs data were collected immediately after the final treatment session so it is possible that changes in IV-RoM were a reflection of the final treatment although the significant dose-response found between the number of manipulations and increased IV-RoM would suggest that changes were cumulative. It is possible that any IV-RoM changes were only short-term as is the case with changes in passive regional cervical ROM after SMT (Nilsson et al. 1996a). Finally, changes in clinical outcomes were not collected beyond the four-week study period therefore longer-term benefits are unknown.

8.5 Conclusion

There was little overall change in inter-vertebral range of motion in the patient group following cervical manipulation, although inter-vertebral motion did increase in some individuals. However, some segments which were not hyper-mobile at baseline became hyper-mobile after treatment. These did not seem to be accompanied by compensatory decreases at other levels and were not necessarily the levels targeted for manipulation. The number of segments that increased in range seems to have been related to the number of manipulations received.

Overall, the effects of cervical manipulation on inter-vertebral motion appear to be towards increasing mobility, but only in some patients and not necessarily to increase the range of hypo-mobile levels. Furthermore, increased segmental motion was not correlated to patient-reported outcomes so these segmental changes were not clearly related to clinical benefit.

Chapter 9. General Discussion

The Global Burden of Disease (2010) survey highlighted the growing problem of neck pain-related disability (page 6) while the Neck Pain Task Force identified the continuing difficulties in accurately diagnosing most cases of neck pain (page 7). Systematic reviews have concluded that a small number of treatments, including spinal manipulation, can be effective when included in the management of neck pain, but effect sizes are small and trial results sometimes conflicting (pages 35 – 43). This is perhaps indicative of the difficulties in appropriately targeting treatment to a heterogeneous group of patients, coupled with a lack of understanding of the mechanism behind the clinical effects of these treatments. This thesis adds to the body of evidence examining the mechanism of spinal manipulation (pages 25 – 34). The following issues stand out as factors contributing to the implications of the findings from this work.

9.1 Sequencing of studies and limitations of research designs

When measuring inter-vertebral motion in living subjects the standardisation of spinal motion is essential to reduce variability where possible, both between and within participants. This was approached through the use of standardised instructions and a stabilisation and motion-frame (Figure 18). This level of standardisation is considered an advance on methods used in previous cervical inter-vertebral motion studies (Bogduk and Mercer 2000; Anderst et al. 2011). The lack of differences found in the kinematic variables measured between patients with neck pain and healthy volunteers was therefore less likely to be due to incorrect positioning of participants (Chapter 6), nor did the presence of radiographic skeletal variants in each group appear to be important confounders (page 134). Additionally, QF was found to be more repeatable than plain-film flexion-extension radiography for IV-RoM (Table 6) lending further confidence to the interpretation of the study findings.

As a quality control measure the sagittal alignment of the cervical spine (lordosis) was measured and was not significantly different between groups although large variability was present between individual participants (Table 4). Despite the control introduced by the motion-frame, participants' motion remained voluntary which can be considered a reasonable compromise and may account for this variability; inducing neck motion in participants could risk injury as well as making findings less transferrable to normal everyday neck movements.

Hypo-mobility was defined as motion at or below the 2.5th percentile for that segment and direction. These thresholds were calculated from the data of published plain-film studies due to data from this present study not always exhibiting a normal distribution (page 138). Since the thresholds were calculated from studies that measured regional end-range motion rather than true inter-vertebral end-ranges (van Mameren et al. 1990), these values might vary from that had they been calculated with this present study's methodology. However, hypo-mobility thresholds were calculated from the studies considered to have the most sound methodology and reporting (Deitz et al. 2011). Furthermore, although the hypo-mobile thresholds may be considered small (Table 18), congenital fusions present in two healthy volunteers were correctly identified as hypo-mobile so lending the thresholds validity.

Attainment rate as defined in this thesis (Figure 34) was intended as an *in vivo* proxy for neutral zone laxity, although this is yet to be validated (Breen et al. 2012). However, this was considered to be worthy of exploration in this study given that previous cervical spine studies have not been particularly successful in identifying motion differences between patients and controls (Bogduk and Mercer 2000) and attainment rate can only currently be measured with QF. The only significant difference in this measurement between patients and healthy volunteers in this study was C1/2 in flexion which on average had a lower attainment rate in patients (Table 20). The patient group appeared to have less lax levels although the clinical significance of this is unknown. It is suggested that segmental stiffness may have been more prevalent in the patient group and so might be an important variable for future research that could include the measurement of spinal stiffness.

The lack of differences in the kinematic parameters measured at baseline created uncertainty regarding the likelihood of identifying clinically meaningful changes in these parameters in the patients. Time and resources did not allow for the analysis of alternative variables such as translation, and IAR location was not sufficiently repeatable (Chapter 5). It remained unknown however, whether changes in IV-RoM might be greater in the patients versus healthy volunteers, so follow-up studies were pursued.

9.2 The minimum detectable change

Despite the use of measures to minimise measurement variability the MDC, as calculated from the healthy volunteers, was high (Table 24), highlighting the difficulties inherent in this type of research (Appendix 1). In order to replicate measurement conditions at four-week follow-up a number of measurements were taken of the stabilisation and motion-frame (Figure 20).

This was sometimes awkward to do, with the operator taking the measurements while wearing a lead-apron and within the confined space produced by the C-arm and motion-frame while the participant sat still. Therefore, while QF represents an improvement on the participant positioning reported in previous studies (van Mameren et al. 1990; Anderst et al. 2014) the potential for human error in these measurements may have contributed to measurement variability. Automating these measurements, where apparatus positioning might be memorised by the computerised motion-frame, would enhance replication of participant positioning, and perhaps reduce MDC.

Compromises were made in the calculation of the MDC (see pages 158-159); some of the IV-RoM data was not normally distributed and on two occasions the within-subject standard deviation was not independent of the mean, both of which are pre-conditional on appropriate calculation of the MDC. However this was a justifiable compromise in order to detect changes in the patient group. Since all MDCs were of a similar order of magnitude this compromise is not considered to have had an important influence on the study findings.

Measurement variability may also have been introduced due to repositioning of the face-rest, between flexion and extension motion sequences, during which the participants were required to stay absolutely still. It might be possible to develop a face-rest that does not require re-positioning between sequences, which would further reduce erroneous measurement variability. Despite these positioning limitations, sagittal alignment of the cervical spine was not significantly different between sessions in healthy volunteers, suggesting participant positioning was standardised.

Despite the large MDC, changes in cervical IV-RoM were observed in the patient group, in association with the number of manipulations received in a dose-response manner (Figure 58). The above limitations notwithstanding, these changes are less likely to have been detected only by chance. However, changes were not correlated with the PROMs measured (Table 33).

The lack of baseline differences between patients and healthy volunteers also suggests that the changes were not clinically meaningful. On the other hand, in an older or more disabled group than the cohort in this present study, where restricted motion might be more prevalent, increases in IV-RoM could be clinically important and merits further study in such populations.

9.3 Alternative research designs

The healthy volunteer group was not a “true” control group; that would necessitate a group recruited on the same inclusion/exclusion criteria as the patient group (Tables 11 and 12), but not receiving manipulation. Any IV-RoM changes in the manipulation group not exhibited in the control group could therefore be more confidently ascribed to the intervention and not to intrinsic group differences. Ideally all participating patients would be randomised to receive real or sham manipulation to further reduce confounding (self-selection and allocation bias particularly) (Howick 2011) but appropriate sham conditions for cervical SMT have yet to be validated (Vernon et al. 2012; Vernon et al. 2013). The control group could have included treatment that was not intended to have an effect on IV-RoM, such as analgesia. However, the time and resources required to recruit the patient cohort in this study, which took 18 months, could not have been extended to cover the recruitment of an additional 30 eligible patients (Figure 46). Further, if patients were denied their treatment preference this could have increased the drop-out rate and risked biasing the study findings; in this study there was no loss to follow-up.

While the small sample size and the exclusion of the majority of potential participants (Figure 46) limits the generalizability of the study’s findings, the sample needed to be well-defined so that the data might be interpreted with confidence.

9.4 Clinical Implications

In this study, no differences in IV-RoM (flexion/extension) were detected between patients with mild to moderately-disabling neck pain and healthy volunteers with no neck pain. It therefore remains that it is not possible to diagnose or sub-group patients with neck pain on the basis of sagittal IV-RoM. Since differences in IV-RoM could not be detected using an accurate and reproducible method of measurement (QF), it is unlikely that measurement methods used for this in the clinical setting, such as motion palpation, can alone provide clinically important information in patients similar to that from this study. Rather, the palpation of tenderness and the reproduction of pain with provocative testing may be thought to be more clinically informative.

Compared to QF, inter-vertebral hypo-mobility was far more likely to be registered with motion palpation suggesting that this finding might be over-identified in practice and its clinical importance therefore, over-emphasised. It might also be that reduced or altered IV-RoM is only important in patients with higher levels of neck pain-related disability or in an older population than those included in this thesis. It is also unknown whether IV-RoM in directions of motion other than that measured in this study, or different motion parameters, such as IAR location or laxity, might be of greater clinical importance.

Most patients did not have segmental motion restrictions, at least not in the sagittal plane. Therefore practitioners should consider other grounds on which to base the diagnosis of neck pain than joint restriction. A promising route for researching this might be electromyography and muscle fatigue studies to explore the role of lactate build-up as a neck pain generator. Other kinematic parameters, such as IAR location, laxity and segmental motion pattern variability cannot currently be measured except by using QF. If future QF studies find that any of these are different in populations like the one studied here then palpation results of joint motion are going to be seen as redundant for not detecting the important elements. Practitioners should consider what else they might be feeling when they palpate, for example, anisotropic muscle.

Regional flexion and extension cervical ROM was significantly reduced in patients compared to healthy volunteers. In the absence of any IV-RoM differences the regional ROM differences are likely due to the presence of pain which may not exhibit an effect on segmental motion. This assumes that IV-RoM was not reduced in patients at levels not measured (C0/1, C6/7, upper thoracic spine). The apparent smaller number of lax segments (based on attainment rate) in patients suggested the presence of more segmental stiffness in the patient group, which might respond favourably to manipulation, but this was not measured.

While it was going to be difficult to detect IV-RoM changes in patients since the MDC was large, increased IV-RoM was weakly correlated with SMT in a dose-response manner. In other words, the more manipulations a patient received, the more likely that individual was to have had levels increased in range. However, only one out of 20 levels that increased in range was classed as hypo-mobile at baseline. Further, increases in IV-RoM were not correlated with improvement based on the PROMs used in this study. The continued use of manipulation in the absence of pain, or for very low-levels of pain, may not be clinically justified since there is the possibility of inducing segmental hyper-mobility, which could be detrimental to a patient's prognosis.

In summary, based on the key findings, including the limitations, of this thesis, the determination of whether or not to apply cervical SMT to a patient with neck pain, or to assess the outcome of SMT, cannot currently be based on IV-RoM. Rather, as recommended in the literature, this should be determined via a process of clinical reasoning that seeks to rule out non-mechanical causes of neck pain (Taylor and Kerry 2010; Rushton et al. 2014), takes account of the risks and benefits of treatment, the practitioner's experience and the preferences of patients.

9.5 Summary of main findings

It was the intention within this thesis to explore the theory that spinal manipulative therapy changes inter-vertebral motion and that this is linked to patient-reported outcomes. Quantitative fluoroscopy was identified as an objective and reproducible method for measuring inter-vertebral motion that might be used to explore this theory, but it had been validated only in the lumbar spine. Therefore it was necessary to validate it for measuring inter-vertebral motion in the cervical spine prior to its use with study participants. The following points constitute the new contributions to knowledge provided by this thesis.

- Quantitative fluoroscopy was found to be a valid and repeatable method for measuring cervical inter-vertebral rotational range of motion. However, further development is required to improve the repeatability of measuring instantaneous axis of rotation locations.
- There were no significant differences between patients and healthy controls in sagittal plane inter-vertebral rotational range of motion parameters at baseline. This meant that neither inter-vertebral rotational range of motion, hypo-mobile levels nor paradoxical motion segments differentiated patients with neck pain from healthy volunteers without neck pain.
- Attainment rate/laxity was only significantly different at one motion segment in one direction (C1/2 in extension) where it was, on average, more lax in the healthy volunteers. Lax levels, defined as those segments with attainment rates in excess of the upper reference level, were more common in the healthy volunteer group suggesting a degree of stiffness of motion in the neutral zone in patients. It was speculated that patients might have been exhibiting higher levels of resting tone in the cervical musculature causing this relative stiffness, but this was not measured.
- The minimum detectable change in inter-vertebral rotational range of motion over four weeks was calculated from healthy volunteers. This was large and consistently greater in extension, meaning that the detection of small changes in inter-vertebral motion is currently not possible.
- Spinal manipulation was weakly associated with increasing inter-vertebral rotational motion in a dose-response manner. However, only one motion segment that increased its range was hypo-mobile at baseline, bringing into question the theory that spinal manipulation restores motion to hypo-mobile segments.

- The presence of hypo-mobility was overestimated by palpation when compared to that measured by quantitative fluoroscopy, the first time palpation has been compared to a criterion standard.
- Changes in inter-vertebral rotational range of motion were not correlated with changes in pain, disability, quality of life, patient global impression of change or satisfaction. Therefore, according to these findings, increased range in the sagittal plane is not associated with clinical benefit.

9.6 Recommendations for future research

In the literature review it was highlighted that neck pain likely represents a group of as yet undiagnosed disorders, and this is possibly a major reason for some patients responding well to spinal manipulation while others do not. Any future work intending to research the mechanism of SMT could benefit from a more disabled population and where important confounders to a positive treatment response are controlled for. This should include the ruling out of: hypersensitivity, which might be better identified with more extensive testing than that used in this study and could involve algometry to more than one body site and cold tolerance; local inflammation, as recognised in the patient history by the presence of night pain; and psychosocial factors such as fear avoidance which can be measured by a validated questionnaire (e.g. Tampa scale for Kinesiophobia). Once these are ruled out this might increase the chance of identifying biomechanical predictors for a positive response to manipulation.

If future work were to further explore the possibility that SMT affects inter-vertebral function, improved standardisation of the acquisition procedure is needed to reduce intra- and inter-subject variability thereby increasing the chances of inter-vertebral motion changes being identified.

Furthermore, changes should not be sought solely in rotational range of motion but also in proportional rotational motion, motion pattern variation, IAR, laxity and/or phase lag. Further development is indicated to improve the reliability of tracking codes for IAR measurement and quantitative fluoroscopy has a rich potential for achieving this. Additionally, a normative database of continuous cervical inter-vertebral motion is required against which can be compared data from patients. Repeatability (agreement and reliability) will also be improved by calculating this from a larger normative sample.

The combining of different functional measurement technologies might be a logical step in forwarding our understanding of spinal function, and the effects of therapy on that function. For instance, simultaneous measurements with quantitative fluoroscopy and electromyography in the same participant would allow an exploration of the relationships between inter-vertebral motion and muscle function. Combining quantitative fluoroscopy with MRI would allow soft tissue findings such as disc degeneration to be explored in relation to inter-vertebral motion. This latter combination holds the potential for creating a three-dimensional reconstruction of a participant's spine in motion, which would provide a rich supply of information about spinal mechanical function beyond that which is currently available to researchers and clinicians.

Finally, future research exploring the mechanism of SMT ought to seek to link mechanisms with patient-reported outcomes. The importance of discovering mechanisms will only be fully realised if they lead to improvements in the understanding and management of patients' pain.

References

AANTTA., 1997. Assessment: Dermatomal somatosensory evoked potentials. *Neurology*, 49, 1127-1130.

Abbott, J. H., Flynn, T. W., Fritz, J. M., Hing, W. A., Reid, D. and Whitman, J. M., 2009. Manual physical assessment of spinal segmental motion: Intent and validity. *Manual Therapy*, 14 (1), 36-44.

Abbott, J. H., Fritz, J., McCane, B., Shultz, B., Herbison, P., Lyons, B., Stefanko, G. and Walsh, R., 2006. Lumbar segmental mobility disorders: comparison of two methods of defining abnormal displacement kinematics in a cohort of patients with non-specific mechanical low back pain. *BMC Musculoskeletal Disorders*, 7 (1), 45.

Abbott, J. H., McCane, B., Herbison, P., Moginie, G., Chapple, C. and Hogarty, T., 2005. Lumbar segmental instability: a criterion-related validity study of manual therapy assessment. *BMC Musculoskeletal Disorders*, 6 (1), 56.

Adams, M. A., Bogduk, N., Burton, K., Dolan, P. and Freeman, B. J. C., 2013. *The Biomechanics of Back Pain*. 3rd. Edinburgh: Churchill Livingstone Elsevier.

Adams, M. A., Dolan, P. and Hutton, W. C., 1987. Diurnal variations in the stresses on the lumbar spine. *Spine*, 12, 130-137.

Adams, M. A., Dolan, P., Hutton, W. C. and Porter, R. W., 1990. Diurnal changes in spinal mechanics and their clinical significance. *Journal of Bone & Joint Surgery* 72, 266-270.

Aho, A., Vartianinen, O. and Salo, O., 1955. Segmentary antero-posterior mobility of the cervical spine. *Annales Medicinae Internae Fenniae*, 44, 287-299.

Albert, H. B., Sorensen, J. S., Christensen, B. S. and Manniche, C., 2013. Antibiotic treatment in patients with chronic low back pain and vertebral bone edema (Modic type 1 changes): a double-blind randomized clinical controlled trial of efficacy. *European Spine Journal*, 22 (4), 697-707.

Amevo, B., Aprill, C. and Bogduk, N., 1992. Abnormal instantaneous axes of rotation in patients with neck pain. *Spine*, 17 (7), 748-756.

Amevo, B., Macintosh, J. E., Worth, D. and Bogduk, N., 1991a. Instantaneous axes of rotation of the typical cervical motion segments: I. an empirical study of technical errors. *Clinical Biomechanics*, 6, 31-37.

Amevo, B., Worth, D. and Bogduk, N., 1991b. Instantaneous axes of rotation of the typical cervical motion segments. II. optimisation of technical errors. *Clinical Biomechanics*, 6, 38-46.

Amevo, B., Worth, D. and Bogduk, N., 1991c. Instantaneous axes of rotation of the typical cervical motion segments: a study in normal volunteers. *Clinical Biomechanics*, 6, 111-117.

Anderst, W. J., Baillargeon E., Donaldson, W. F., Lee, J. Y. and Kang, J. D., 2011. Validation of a noninvasive technique to precisely measure in vivo three-dimensional cervical spine movement. *Spine*, 36 (6), E393-E400.

Anderst, W. J., Donaldson, W. F., Lee, J. Y. and Kang, J. D., 2013. Cervical motion segment percent contributions to flexion-extension during continuous functional movement in control subjects and arthrodesis patients. *Spine*, 38 (9), E533-539.

Anderst, W. J., Donaldson, W. F., Lee, J. Y. and Kang, J. D., 2014. Continuous cervical spine kinematics during in vivo dynamic flexion-extension. *The Spine Journal*, 14 (7), 1221-1227.

Anderst, W. J., Vaidya, R. and Tashman, S., 2008. A technique to measure three-dimensional in vivo rotation of fused and adjacent lumbar vertebrae. *The Spine Journal*, 8 (6), 991-997.

Antonaci, F., Bulgheroni, M., Ghirmai, S., Lanfranchi, S., Dalla Toffola, E., Sandrini, G. and Nappi, G., 2002. 3D kinematic analysis and clinical evaluation of neck movements in patients with whiplash injury. *Cephalalgia*, 22, 533-542.

Assendelft, W. J. J., Bouter, L. M. and Knipschild, P. G., 1996. Complications of spinal manipulation: A comprehensive review of the literature. *The Journal of Family Practice*, 42 (5), 475-480.

ASTM, 1996. Standard practice for use of the terms precision and bias in ASTM test methods. West Conshohocken: American Society for Testing and Materials.

Audette, E., Dumas, J.-P., Cote, J. and De Serres, S. J., 2010. Validity and between-day reliability of the cervical range of motion (CROM) device. *Journal of Orthopaedic & Sports Physical Therapy*, 40 (5), 318-323.

Bahat, H. S., Weiss, P. L., Sprecher, O. T. E., Krasovsky, A. and Laufer, P. T. Y., 2014. Do neck kinematics correlate with pain intensity, neck disability or with fear of motion? *Manual Therapy*, 19 (3), 252-258.

Baillargeon, E. and Anderst, W. J., 2013. Sensitivity, reliability and accuracy of the instant center of rotation calculation in the cervical spine during in vivo dynamic flexion-extension. *Journal of Biomechanics*, 46 (4), 670-676.

Baker, D. J., Pynsent, P. B. and Fairbank, C. T., 1989. The Oswestry Disability Index revisited: its reliability, repeatability and validity and a comparison with the St Thomas's Disability Index. *In:* Roland, M. O., and Jenner, J. R., eds. *Back Pain: New approaches to rehabilitation and education.* Manchester UK: Manchester University Press, 174-186.

Bartlett, J. W. and Frost, C., 2008. Reliability, repeatability and reproducibility: analysis of measurement error in continuous variables. *Ultrasound in Obstetrics & Gynecology* 31, 466-475.

Beattie, P. F., Donley, J. W., Arnot, C. F. and Miller, R., 2009. The Change in the Diffusion of Water in Normal and Degenerative Lumbar Intervertebral Discs following Joint Mobilization Compared to Prone Lying. *Journal of Orthopaedic & Sports Physical Therapy*, 39 (1), 4-11.

Begg, A. C. and Falconer, M. A., 1949. Plain radiography in intraspinal protrusion lumbar intervertebral disks; a correlation with operative findings. *British Journal of Surgery*, 36 (143), 225-239.

Bergstrom, C., Jensen, I., Hagberg, J., Busch, H. and Bergstrom, G., 2012. Effectiveness of different interventions using a psychosocial subgroup assignment in chronic neck pain back patients: a 10-year follow-up. *Disability & Rehabilitation*, 34 (2), 110-118.

Bhalla, S. K. and Simons, E. H., 1969. Normal ranges of intervertebral joint motion of the cervical spine. *Canadian Journal of Surgery*, 12, 181-187.

Bialosky, J. E., Bishop, M. D., Price, D. D., Robinson, M. E. and George, S. Z., 2009. The mechanisms of manual therapy in the treatment of musculoskeletal pain: A comprehensive model. *Manual Therapy*, 14, 531-538.

Binder, A., 2008. Neck Pain. *Clinical Evidence*, (08), 1103.

Bishop, M. D., Mintken, P. E., Bialosky, J. E. and Cleland, J. A., 2013. Patient expectations of benefit from interventions for neck pain and resulting influence on outcomes. *Journal of Orthopaedic & Sports Physical Therapy*, 43 (7), 457-465.

Bland, J. M., 1996. *An Introduction to Medical Statistics*. 2nd. Oxford: Oxford University Press.

Bland, J. M. and Altman, D. G., 1986. Statistical methods for assessing agreement between two methods of clinical measurement. *The Lancet*, (February 8), 307-310.

Bland, J. M. and Altman, D. G., 1996a. Statistics Notes: Measurement error. *British Medical Journal*, 313 (744).

Bland, J. M. and Altman, D. G., 1996b. Statistics Notes: Measurement error proportional to the mean. *British Medical Journal*, 313 (7049), 106.

Bland, J. M. and Altman, D. G., 1996c. Statistics Notes: Transforming data. *British Medical Journal*, 312 (7033), 770.

Boden, S. D., Davis, D. O., Dina, T. S., Patronas, N. J. and Wiesel, S. W., 1990. Abnormal Magnetic-Resonance Scans of the Lumbar Spine in Asymptomatic Subjects. *The Journal of Bone and Joint Surgery (American)*, 72, 403-408.

Bogduk, N., 1984. Neck Pain. *Australian Family Physician*, 13 (1), 26-30.

Bogduk, N., 2003. Spinal manipulation for neck pain does not work. *The Journal of Pain*, 4 (8), 427-428.

Bogduk, N., 2011. The Anatomy and Pathophysiology of Neck Pain. *Physical Medicine & Rehabilitation Clinics of North America*, 22 (3), 367-382.

Bogduk, N., Amevo, B. and Pearcy, M., 1995. A Biological basis for instantaneous centres of rotation of the vertebral column. *Proceedings of the Institute of Mechanical Engineers*, 209, 177-183.

Bogduk, N. and Mercer, S., 2000. Biomechanics of the cervical spine, I: Normal kinematics. *Clinical Biomechanics*, 15, 633-648.

Bolton, J. E., 2001. The evidence in evidence-based practice: What counts and what doesn't count? *Journal of Manipulative and Physiological Therapeutics*, 24 (5), 362-366.

Bolton, J. E., 2004. Sensitivity and specificity of outcome measures in patients with neck pain: detecting clinically significant improvement. *Spine*, 29 (21), 2410-2417.

Bolton, J. E. and Breen, A. C., 1999. The Bournemouth Questionnaire: a short-form comprehensive outcome measure: I. Psychometric properties in back pain patients. *Journal of Manipulative and Physiological Therapeutics*, 22 (8), 503-510.

Bolton, J. E. and Hurst, H. C., 2011. Prognostic factors for short-term improvement in acute and persistent musculoskeletal pain consulters in primary care. *Chiropractic & Manual Therapies*, 19, 27.

Bombardier, C., 2000. Outcome assessments in the evaluation of treatment of spinal disorders. *Spine*, 25 (24), 3100-3103.

Borghouts, J., Janssen, H., Koes, B., Muris, J., Metsemakers, J. and Bouter, L., 1999a. The management of chronic neck pain in general practice. A retrospective study. *Scand J Prim Health Care*, 17 (4), 215-220.

Borghouts, J. A. J., Koes, B. W., Vondeling, H. and Bouter, L. M., 1999b. Cost-of-illness of neck pain in The Netherlands in 1996. *Pain*, 80, 629-636.

Bossuyt, P. M., Reitsma, J. B., Bruns, D. E., Gatsonis, C. A., Glasziou, P. P., Irwig, L. M., Lijmer, J. G., Moher, D., Rennie, D. and de Vet, H. C. W., 2003. Towards Complete and Accurate Reporting of Studies of Diagnostic Accuracy: The STARD Initiative. *American Journal of Roentgenology*, 181, 51-56.

Bot, S. D. M. M., van der Waal, J. M. M., Terwee, C. B. P., van der Windt, D. A. W. M. P., Scholten, R. J. P. M. M. D. P., Bouter, L. M. P. and Dekker, J. P., 2005. Predictors of Outcome in Neck and Shoulder Symptoms: A Cohort Study in General Practice. *Spine*, 30 (16), E459-E470.

Botsford, D. J., Esses, S. I. and Ogilvie-Harris, D. J., 1994. In vivo diurnal variation in intervertebral disc volume and morphology. *Spine*, 19, 935-940.

Breen, A., Muggleton, J. and Mellor, F., 2006. An objective spinal motion imaging assessment (OSMIA): reliability, accuracy and exposure data. *BMC Musculoskeletal Disorders*, 7 (1), 1-10.

Breen, A. C., 2013. *Low back pain: Identifying sub-groups, clinical prediction rules and measuring results.* Paper presented at the World Federation of Chiropractic Biennial Cogress, Durban, South Africa.

Breen, A. C., Allen, R. and Morris, A., 1988. An image processing method for spine kinematics-preliminary studies. *Clinical Biomechanics*, 3, 5-10.

Breen, A. C., Carr, E., Langworthy, J. E., Osmond, C. and Worswick, L., 2011. Back pain outcomes in primary care following a practice improvement intervention: - a prospective cohort study. *BMC Musculoskeletal Disorders*, 12 (1), 28-37.

Breen, A. C., Muggleton, J., Kondracki, M., Wright, J. and Morris, A., 2002. Lumbar spine motion palpation compared with objective intervertebral motion analysis: preliminary findings. *European Journal of Chiropractic*, 50, 27-32.

Breen, A. C., Teyhen, D. S., Mellor, F. E., Breen, A. C., Wong, K. W. N. and Deitz, A., 2012. Measurement of InterVertebral Motion Using Quantitative Fluoroscopy: Report of an International Forum and Proposal for Use in the Assessment of Degenerative Disc Disease in the Lumbar Spine. *Advances in Orthopaedics*, 2012 (802350).

Brodin, H., 1984. Cervical pain and mobilization. *International Journal of Rehabilitation Research*, 7 (2), 190.

Bronfort, G., Evans, R., Anderson, A. V., Svendsen, K. H., Bracha, Y. and Grimm, R. H., 2012. Spinal Manipulation, Medication, or Home Exercise with Advice for Acute and Subacute Neck Pain. *Annals of Internal Medicine*, 156 (1), 1-10.

Bronfort, G., Evans, R., Nelson, B., Aker, P. D., Goldsmith, C. H. and Vernon, H., 2001. A Randomized Clinical Trial of Exercise and Spinal Manipulation for Patients With Chronic Neck Pain. *Spine*, 26 (7), 788-799.

Bronfort, G., Haas, M., Evans, R., Leininger, B. and Triano, J., 2010. Effectiveness of manual therapies: the UK evidence report. *Chiropractic & Osteopathy*, 18, 3.

Burns, D. K. and Wells, M. R., 2006. Gross range of motion in the cervical spine: the effects of osteopathic muscle energy technique in asymptomatic subjects. *Journal of The American Osteopathic Association*, 106 (3), 137-142.

Carlesso, L., MacDermid, J., C.,, Gross, A., R.,, Walton, D., M., and Santaguida, P., L., 2014. Treatment preferences amongst physical therapists and chiropractors for the management of neck pain: results of an international survey. *Chiropractic & Manual Therapies*, 22 (11).

Carlesso, L. C., Gross, A. R., Santaguida, L., Burnie, S., Voth, S. and Sadi, J., 2010. Adverse events associated with the use of cervical manipulation and mobilization for the treatment of neck pain in adults: A systematic review. *Manual Therapy*, 15, 434-444.

Carnes, D., Mars, T. S., Mullinger, B., Froud, R. and Underwood, M., 2010a. Adverse events and manual therapy: A systematic review. *Manual Therapy*, 15 (4), 355-363.

Carnes, D., Mullinger, B. and Underwood, M., 2010b. Defining adverse events in manual therapies: A modified Delphi consensus study. *Manual Therapy*, 15 (1), 2-6.

Carnes, D., Parsons, S., Ashby, D., Breen, A., Foster, N. E., Pincus, T., Vogel, S. and Underwood, M., 2007. Chronic musculoskeletal pain rarely presents in a single body site: results from a UK population study. *Rheumatology*, 46 (1), 1168-1170.

Carragee, E., Hurwitz, E., Cheng, I., Carroll, L., Nordin, M., Guzman, J., Peloso, P., Holm, L., Cote, P., Hogg-Johnson, S., van der Velde, G., Cassidy, J. D. and Haldeman, S., 2008. Treatment of Neck Pain: Injections and Surgical Interventions: Results of the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. *Spine*, 33(4S) Neck Pain Task Force (Supplement), S153-S169.

Carroll, L., Hogg-Johnson, S., Cote, P., van der Velde, G., Holm, L., Carragee, E., Hurwitz, E., Peloso, P., Cassidy, J. D., Guzman, J., Nordin, M. and Haldeman, S., 2008a. Course and Prognostic Factors for Neck Pain in Workers: Results of the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. *Spine*, 33(4S) Neck Pain Task Force (Supplement), S93-S100.

Carroll, L., Hogg-Johnson, S., van der Velde, G., Haldeman, S., Holm, L., Carragee, E., Hurwitz, E., Cote, P., Nordin, M., Peloso, P., Guzman, J. and Cassidy, J. D., 2008b. Course and Prognostic Factors for Neck Pain in the General Population: Results of the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. *Spine*, 33(4S) Neck Pain Task Force (Supplement), S75-S82.

Carroll, L., Holm, L., Hogg-Johnson, S., Cote, P., Cassidy, J. D., Haldeman, S., Nordin, M., Hurwitz, E., Carragee, E., van der Velde, G., Peloso, P. and Guzman, J., 2008c. Course and Prognostic Factors for Neck Pain in Whiplash-Associated Disorders (WAD): Results of the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. *Spine*, 33(4S) Neck Pain Task Force (Supplement), S83-S92.

Casanova-Mendez, A., Oliva-Pascual-Vaca, A., Rodriguez-Blanco, C., Heredia-Rizo, A., M.,, Gogorza-Arroitaonandia, K. and Almazan-Campos, G., 2014. Comparative short-term effects of two thoracic spinal manipulation techniques in subjects with chronic mechanical neck pain: A randomised controlled trial. *Manual Therapy*.

Cassidy, J. D., Boyle, E., Cote, P., He, Y., Hogg-Johnson, S., Silver, F. L. and Bondy, S. J., 2008. Risk of Vertebrobasilar Stroke and Chiropractic Care: Results of a Population-Based Case-Control and Case-Crossover Study. *Spine*, 33(4S) Neck Pain Task Force (Supplement), S176-S183.

Cassidy, J. D., Lopes, A. A. and Yong-Hing, K., 1992. The immediate effect of manipulation versus mobilisation on pain and range of motion in the cervical spine: a randomised controlled trial. *Journal of Manipulative & Physiological Therapeutics*, 15 (9), 570-575.

Cattrysse, E., Provyn, S., Kool, P., Gagey, O., Clarys, J. P. and Van Roy, P., 2009. Reproducibility of kinematic motion coupling parameters during manual upper cervical axial rotation mobilization: A 3-dimensional in vitro study of the atlanto-axial joint. *Journal of Electromyography and Kinesiology*, 19, 93-104.

Chapman-Smith, D., 2012. *The Chiropractic Report - Best Treatments for Neck Pain*. Toronto, Canada.

Childs, J. D., Cleland, J. A., Elliott, J. M., Teyhen, D. S., Wainner, R. S., Whitman, J. M., Sopky, B. J., Godges, J. J. and Flynn, T. W., 2008. Neck Pain: Clinical Practice Guidelines. *Journal of Orthopaedic & Sports Physical Therapy*, 38 (9), A1-A34.

Childs, J. D., Fritz, J. M., Flynn, T. W., Irrgang, J. J., Johnson, K. K., Majkowski, G. R. and Delitto, A., 2004a. A clinical prediction rule to identify patients with low back pain most likely to benefit from spinal manipulation: a validation study. *Annals of Internal Medicine*, 141 (12), 920-928.

Childs, J. D., Fritz, J. M., Piva, S. R. and Whitman, J. M., 2004b. Proposal of a classification system for patients with neck pain. *Journal of Orthopaedic & Sports Physical Therapy*, 34, 686-700.

Chinn, S., 1990. The assessment of methods of measurement. *Statistics in Medicine*, 9, 351-362.

Chung, C. L., Cote, P., Stern, P. and L'Esperance, G., 2014. The Association Between Cervical Spine Manipulation and Carotid Artery Dissection: A Systematic Review of the Literature. *Journal of Manipulative & Physiological Therapeutics* [online], In Press. Available from: http://www.jmptonline.org/article/S0161-4754(13)00273-X/pdf [Accessed 4 May 2014].

Clar, C., Tsertsvadze, A., Court, R., Lewando Hundt, G., Clarke, A. and Sutcliffe, P., 2014. Clinical effectiveness of manual therapy for the management of musculoskeletal and non-musculoskeletal conditions: systematic review and update of UK evidence report. *Chiropractic & Manual Therapies*, 22 (12).

Cleland, J. A., Childs, J. D., Fritz, J. and Whitman, J., 2008. Interater reliability of the history and physical examination in patients with mechanical neck pain. *Archives of Physical Medicine and Rehabilitation*, 87 (10), 1388-1395.

Cleland, J. A., Childs, J. D., Fritz, J. M., Whitman, J. M. and Eberhart, S. L., 2007. Development of a Clinical Prediction Rule for Guiding Treatment of a Subgroup of Patients With Neck Pain: Use of Thoracic Spine Manipulation, Exercise, and Patient Education. *Physical Therapy*, 87 (1), 9-23.

Cleland, J. A., Fritz, J. M., Kulig, K., Davenport, T. E., Eberhart, S., Magel, J. and Childs, J. D., 2009. Comparison of the effectiveness of three manual physical therapy techniques in a subgroup of patients with low back pain who satisfy a clinical prediction rule. *Spine*, 34 (25), 2720-2729.

Cleland, J. A., Mintken, P. E., Carpenter, K., Fritz, J. M., Glynn, P., Whitman, J. and Childs, J. D., 2010. Examination of a Clinical Prediction Rule to Identify Patients With Neck Pain Likely to Benefit From Thoracic Spine Thrust Manipulation and a General Cervical Range of Motion Exercise: Multi-Center Randomized Clinical Trial. *Physical Therapy*, 90, 1239-1250.

Coronado, R. A., Gay, C. W., Bialosky, J. E., Carnaby, G. D., Bishop, M. D. and George, S. Z., 2012. Changes in pain sensitivity following spinal manipulation: A systematic review and meta-analysis. *Journal of Electromyography and Kinesiology*, 22 (5), 752-767.

Costa-Santos, C., Bernardes, J., Ayres-de-Campos, D., Costa, A. and Costa, C., 2011. The limits of agreement and the intraclass correlation coefficient may be inconsistent in the interpretation of agreement. *Journal of Clinical Epidemiology*, 64, 264-269.

Costa Santos, C., Bernardes, J. and Ayres-de-Campos, D., 2011. Observer reliability and agreement: differences, difficulties, and controversies. *Journal of Clinical Epidemiology*, 64 (6), 702.

Cote, P., Cassidy, J. D., Carroll, L. J. and Kristman, V., 2004. The annual incidence and course of neck pain in the general population: a population-based cohort study. *Pain*, 112, 267-273.

Cote, P., Hogg-Johnson, S., Cassidy, J. D., Carroll, L. and Frank, J. W., 2001. The association between neck pain intensity, physical functioning, depressive symptomatology and time-to-claim-closure after whiplash. *Journal of Clinical Epidemiology*, 54 (3), 275-286.

Cote, P., van der Velde, G., Cassidy, J. D., Carroll, L., Hogg-Johnson, S., Holm, L., Carragee, E., Haldeman, S., Nordin, M., Hurwitz, E., Guzman, J. and Peloso, P., 2008a. The Burden and Determinants of Neck Pain in Workers: Results of the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. *Spine*, 33(4S) Neck Pain Task Force (Supplement), S60-S74.

Cote, P. D., Kristman, V., Vidmar, M., Van Eerd, D., Hogg-Johnson, S., Beaton, D. and Smith, P. M., 2008b. The Prevalence and Incidence of Work Absenteeism Involving Neck Pain: A Cohort of Ontario Lost-Time Claimants. *Spine*, 33(4S) Neck Pain Task Force (Supplement), S192-S198.

Cramer, G., Budgell, B., Henderson, C., Khalsa, P. and Pickar, J., 2006. Basic Science Research Related to Chiropractic Spinal Adjusting: The state of the Art and Recommendations Revisited. *Journal of Manipulative and Physiological Therapeutics*, 29 (9), 726-761.

Cramer, G. D., Cambron, J., Cantu, J. A., Dexheimer, J. M., Pocius, J. D., Gregerson, D., Fergus, M., McKinnis, R. and Grieve, T. J., 2013. Magnetic Resonance Imaging Zygapophyseal Joint Space Changes (Gapping) in Low Back Pain Patients Following Spinal Manipulation and Side-Posture Positioning: A Randomized Controlled Mechanisms Trial With Blinding. *Journal of Manipulative and Physiological Therapeutics*, 36 (4), 203-217.

Croft, P. R., Lewis, M., Papageorgiou, A. C., Thomas, E., Jayson, M. I. V., Macfarlane, G. J. and Silman, A. J., 2001. Risk factors for neck pain: a longitudinal study in the general population. *Pain*, 93, 317-325.

Cross, K. M., Kuenze, C., Grindstaff, T. and Hertel, J., 2011. Thoracic Spine Thrust Manipulation Improves Pain, Range of Motion, and Self-Reported Function in Patients with Mechanical Neck Pain: A Systematic Review. *Journal of Orthopaedic & Sports Physical Therapy*, 41 (9), 633-642.

D'Sylva, J., Miller, J., Gross, A., Burnie, S. J., Goldsmith, C. H., Graham, N., Haines, T., Bronfort, G. and Hoving, J. L., 2010. Manual therapy with or without physical medicine modalities for neck pain: a systematic review. *Manual Therapy*, 15, 415-433.

Dagenais, S. and Haldeman, S., 2012. Commentary: Laboring to understand the economic impact of spinal disorders. *The Spine Journal*, 12, 1119-1121.

Dall'Alba, P. T., Sterling, M. M., Treleaven, J. M., Edwards, S. L. and Jull, G. A., 2001. Cervical Range of Motion Discriminates Between Asymptomatic Persons and Those With Whiplash. *Spine*, 26 (19), 2090-2094.

Daltroy, L. H., 1996. The North American Spine Society lumbar spine outcome assessment instrument: reliability and validity tests. *Spine*, 21 (6), 741-749.

de Koning, C. H. P., van den Heuvel, S. P., Staal, J. B., Smits-Engelsman, C. M. and Hendriks, E. J. M., 2008. Clinimetric evaluation of active range of motion measures in patients with non-specific neck pain: a systematic review. *European Spine Journal*, 17, 905-921.

de Vet, H. C. W., 1998. Observer Reliability and Agreement. *In:* Armitage, P., and Colton, T., eds. *Enclyopedia of Statistics.* Chichester: John Wiley & Sons, 3123-3127.

de Vet, H. C. W., Heymans, M. W., Dunn, K. M., Pope, D. P., van der Beek, A. J., Macfarlane, G. J., Bouter, L. M. and Croft, P. R., 2002. Episodes of low back pain: a proposal for uniform definitions to be used in research. *Spine*, 27 (21), 2409-2416.

de Vet, H. C. W., Terwee, C. B., Knol, D. L. and Bouter, L. M., 2006. When to use agreement versus reliability measures. *Journal of Clinical Epidemiology*, 59 (10), 1033-1039.

Deitz, A. K., Breen, A. C., Mellor, F. E., Teyhen, D. S., Panjabi, M. M. and Wong, K. W. M., 2011. Kinematics of the Aging Spine: A Review of Past Knowledge and Survery of Recent Developments, with a Focus on Patient-Management Implications for the Clinical Practitioner. . *In:* Yue, J. J., Guyer, R. D., Johnson, J. P., Khoo, L. T., and Hochschuler, S. H., eds. *The Comprehensive Treatment of the Aging Spine: Minimally Invasive and Advanced Techniques.* 1. Philadelphia: Saunders, 51-62.

Demaille-Wlodyka, S., Chiquet, C., Lavaste, J., Skalli, W., Revel, M. and Poiraudeau, S., 2007. Cervical Range of Motion and Cephalic Kinesthesis: Ultrasonographic analysis by age and sex. *Spine*, 32 (8), E254-E261.

Demyttenaere, K., Bruffaerts, R., Lee, S., Posada-Villa, J., Kovess, V., Angermeyer, M. C., Levinson, D., de Girolamo, G., Nakane, H., Mneimneh, Z., Lara, C., de Graaf, R., Scott, K. M., Gureje, O., Stein, D. J., Haro, J. M., Bromet, E. J., Kessler, R. C., Alonso, J. and Von Korff, M., 2007. Mental disorders among persons with chronic back or neck pain: Results from the world mental health surveys. *Pain*, 129, 332-342.

Deyo, R. A., Battie, M., Beurskens, A. J. H. M., Bombardier, C., Croft, P., Koes, B., Lalmivaara, A., Roland, M., Von Korff, M. and Waddell, G., 1998. Outcome measures for low back pain research. *Spine*, 23 (18), 2003-2013.

Dimnet, J., Pasquet, A., Krag, M. H. and Panjabi, M. M., 1982. Cervical spine motion in the sagittal plane: kinematic and geometric parameters. *Biomechanics*, 15 (12), 959-969.

DOH, 2009. *Reference guide to consent for examination or treatment 2nd Edition*. Department of Health.

Dugailly, P.-M., Beyer, B., Sobczak, S., Salvia, P. and Feipel, V., 2014. Global and regional kinematics of the cervical spine during upper cervical spine manipulation: A reliability analysis of 3D motion data. *Manual Therapy* [online], In Press. Available from: http://www.sciencedirect.com/science/article/pii/S1356689X14000824 [Accessed 31 May 2014], 1-6.

Dunleavy, K. and Goldberg, A., 2013. Comparison of cervical range of motion in two seated postural conditions in adults 50 or older with cervical pain. *Journal of Manual and Manipulative Therapy*, 21 (1), 33-39.

Dunning, J., Mourad, F., Barbero, M., Leoni, D., Cescon, C. and Butts, R., 2013. Bilateral and multiple cavitation sounds during upper cervical thrust manipulation. *BMC Musculoskeletal Disorders*, 14 (24).

Dunning, J. R., Cleland, J. A., Waldrop, M. A., Arnot, C. F., Young, I. A., Turner, M. and Sigurdsson, G., 2012. Upper cervical and upper thoracic thrust manipulation versus nonthrust mobilization in patients with mechanical neck pain: a multicenter randomized clinical trial. *Journal of Orthopaedic and Sports Physical Therapy*, 42 (1), 5-18.

Dvir, Z., Gal-Eshel, N., Shamir, B., Prushansky, T., Pevzner, E. and Peretz, C., 2006. Cervical Motion in Patients With Chronic Disorders of the Cervical Spine: A Reproducibility Study. *Spine*, 31 (13), E394-E399.

Dvorak, J., Dvorak, W., Gilliar, W., Schneider, W., Spring, H. and Tritschler, T., 2008. Segmental Hypomobility and Pain Intensity. *In: Musculoskeletal Manual Medicine.* Stuttgart, Germany: Thieme, 151-152.

Dvorak, J., Froehlich, D., Penning, L., Baumgartner, H. and Panjabi, M. M., 1988. Functional Radiographic Diagnosis of the Cervical Spine: Flexion/Extension. *Spine*, 13, 748-755.

Dworkin, R. H., Turk, D. C., Farrar, J. T., Haythornthwaite, J. A., Jensen, M. P., Katz, N. P., Kerns, R. D., Stucki, G., Allen, R. R., Bellamy, N., Carr, D. B., Chandler, J., Cowan, P., Dionne, R., Galer, B. S., Hertz, S., Jadad, A. R., Kramer, L. D., Manning, D. C., Martin, S., McCormick, C. G., McDermott, M. P., McGrath, P., Quessy, S., Rappaport, B. A., Robbins, W., Robinson, J. P., Rothman, M., Royal, M. A., Simon, L., Stauffer, J. W., Stein, W., Tollett, J., Wernicke, J. and Witter, J., 2005. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain*, 113, 9-19.

Dziedzic, K., Hill, J., Lewis, M., Sim, J., Daniels, J. and Hay, E. M., 2005. Effectiveness of manual therapy or pulsed shortwave diathermy in addition to advice and exercise for neck disorders: A pragmatic randomized controlled trial in physical therapy clinics. *Arthritis Care & Research*, 53 (2), 214-222.

Ernst, E., 2002. Manipulation of the cervical spine: a systematic review of case reports of serious adverse events, 1995-2001. *Medical Journal of Australia*, 176 (15 April), 376-380.

Ernst, E., 2003. Chiropractic spinal manipulation for neck pain: A systematic review. *The Journal of Pain*, 4 (8), 417-421.

Ernst, E., 2010. Vascular accidents after neck manipulation: cause or coincidence. *The International Journal of Clinical Practice*, 64 (6), 673-677.

Euroqol-Group, 1990. Euroquol: A new facility for the measurement of health-related quality of life. *Health Policy*, 16, 199-208.

Evans, D. W., 2002. Mechanisms and effects of spinal high-velocity, low-amplitude thrust manipulation: previous theories. *Journal of Manipulative and Physiological Therapeutics*, 25, 251-262.

Evans, D. W. and Lucas, N., 2010. What is 'manipulation'? A reappraisal. *Manual Therapy*, 15, 286-291.

Evans, R., Bronfort, G., Maiers, M., Hanson, L. and Hartvigsen, J., 2014. Is Satisfaction a Good Outcome? Exploring the Patient Perspective. *Journal of Alternative & Complementary Medicine*, 20 (5), A142.

Evans, R., Bronfort, G., Nelson, B. and Goldsmith, C. H., 2002. Two-Year Follow-Up of a Randomized Clinical Trial of Spinal Manipulation and Two Types of Exercise for Patients with Chronic Neck Pain. *Spine*, 27 (21), 2383-2389.

Evans, R., Bronfort, G., Schulz, C., Maiers, M., Bracha, Y., Svendsen, K., Grimm Jr, R., Garvey, T. and Transfeldt, E., 2012. Supervised exercise with and without spinal manipulation perform similarly and better than home exercise for chronic neck pain: a randomized controlled trial. *Spine*, 37 (11), 903-914.

Fairbank, J. C. T., Couper, J., Davies, J. B. and O'Brien, J. P., 1980. The Oswestry low back pain disability questionnaire. *Physiotherapy*, 66 (8), 271-273.

Falla, D., O'Leary, S., Farino, D. and Jull, G., 2012. The change in deep cervical flexor activity after training is associated with the degree of pain reduction in patients with chronic neck pain. *Clinical Journal of Pain*, 28, 628-634.

Farrar, J. T., Young, J. P., LaMoreaux, L., Werth, J. L. and Poole, R. M., 2001. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain*, 94, 149-158.

Feipel, V., Rondelet, B., LePallec, J. P., DeWitte, O. and Rooze, M., 1999. The use of disharmonic motion curves in problems of the cervical spine. *International Orthopaedics*, 23, 205-209.

Field, A., 2009. *Discovering Statistics Using SPSS. 3rd Edition*. London: Sage.

Fielding, J. W., 1956. Cineradiography of the normal cervical spine. *New York State Journal of Medicine*, Oct, 2984-2986.

Fletcher, J. P. and Bandy, W. D., 2008. Intrarater reliability of CROM measurement of cervical spine active range of motion in persons with and without neck pain. *Journal of Orthopaedic & Sports Physical Therapy*, 38 (10), 640-645.

Flynn, T. W., Fritz, J., Wainner, R. S. and Whitman, J. M., 2003. The audible pop is not necessary for successful spinal high-velocity thrust manipulation in individuals with low back pain. *Archives of Physical Medicine and Rehabilitation*, 84, 1057-1060.

Friedenberg, Z. B. and Miller, W. T., 1963. Degenerative Disc Disease of the Cervical Spine. *The Journal of Bone and Joint Surgery American*, 45 (6), 1171-1178.

Fritz, J. M., Cleland, J. A. and Childs, J. D., 2007. Subgrouping Patients with Low Back Pain: Evolution of a Classification Approach to Physical Therapy. *Journal of Orthopaedic & Sports Physical Therapy*, 37 (6), 290-302.

Fritz, J. M., Koppenhaer, S. L., Kawchuk, G. N., Teyhen, D. S., Hebert, J. J. and Childs, J. D., 2011. Preliminary Investigation of the Mechanisms Underlying the Effects of Manipulation. *Spine*, 36 (21), 1722-1781.

Fritz, J. M., Piva, S. R. and Childs, J. D., 2005. Accuracy of the clinical examination to predict radiographic instability of the lumbar spine. *European Spine Journal*, 14, 743-750.

Frobin, W., Leivseth, G., Biggemann, M. and Brinckmann, P., 2002. Sagittal plane segmental motion of the cervical spine. A new precision measurement protocol and normal motion data of healthy adults. *Clinical Biomechanics*, 17, 21-31.

Froning, E. C. and Frohman, B., 1968. Motion of the lumbosacral spine after laminectomy and spine fusion: Correlation of motion with the result. *Journal of Bone and Joint Surgery*, 50(A), 897-918.

Gatchel, R.J. and Theodore, B.R., 2008. Evidence-based outcomes in pain research and clinical practice. *Pain Practice*, 8(6), 452-460.

GMC, 2008. Consent: Patients and doctors making decisions together. *General Medical Council*.

Gore, D. R., 2001. Roentgenographic Findings in the Cervical Spine in Asymptomatic Persons. *Spine*, 26 (22), 2463-2466.

Gore, D. R., Sepic, S. B. and Gardner, G. M., 1986. Roentgenographic Findings of the Cervical Spine in Asymptomatic People. *Spine*, 11 (6), 521-524.

Gouveia, L. O., Castanho, P. and Ferreira, J. J., 2009. Safety of chiropractic interventions - A systematic review. *Spine*, 34 (11), E405-E413.

Graz, B., Wietlisbach, V., Porchet, F. and Vader, J. P., 2005. Prognosis or "curabo effect?". *Spine*, 30 (12), 1448-1452.

Grip, H., Ohberg, F., Wiklund, U., Sterner, Y., Karlsson, J. S. and Gerdle, B., 2003. Classification of neck movement patterns related to whiplash-associated disorders using neutral networks. *IEEE Transactions on Information Technology in Biomedicine*, 7 (4), 412-418.

Gross, A., Miller, J., D'Sylva, J., Burnie, S. J., Goldsmith, C. H., Graham, N., Haines, T., Bronfort, G. and Hoving, J. L., 2010. Manipulation or mobilisation for neck pain: A Cochrane Review. *Manual Therapy*, 15, 315-333.

Gross, A. R., Haines, T., Goldsmith, C. H., Santaguida, L., McLaughlin, L. M., Peloso, P., Burnie, S., Hoving, J. and Group, C. O., 2009. Knowledge to Action: A Challenge for Neck Pain Treatment. *Journal of Orthopaedic & Sports Physical Therapy*, 39 (5), 351-363.

Gross, A. R., Hoving, J. L., Haines, T. A., Goldsmith, C. H., Kay, T., Aker, P., Bronfort, G. and Group, t. C. O., 2004. A Cochrane Review of Manipulation and Mobilization for Mechanical Neck Disorders. *Spine*, 29 (14), 1541-1548 1510.1097/1501.BRS.0000131218.0000135875.ED.

Guzman, J., Haldeman, S., Carroll, L. J., Carragee, E. J., Hurwitz, E. L., Peloso, P., Nordin, M. P., Cassidy, J. D., Holm, L. W., Cote, P. D., van der Velde, G. D. and Hogg-Johnson, S., 2008a. Clinical Practice Implications of the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders: From Concepts and Findings to Recommendations. *Spine*, 33(4S) Neck Pain Task Force (Supplement), S199-S213.

Guzman, J., Hurwitz, E. L., Carroll, L. J., Haldeman, S., Cote, P. D., Carragee, E., Peloso, P. M., van der Velde, G., Holm, L. W., Hogg-Johnson, S., Nordin, M. P. and Cassidy, J. D., 2008b. A New Conceptual Model of Neck Pain: Linking Onset, Course, and Care: The Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. *Spine*, 33(4S) Neck Pain Task Force (Supplement), S14-S23.

Haas, M., Groupp, E., Panzer, D., Partna, L., Lumbsden, S. and Aickin, M., 2003. Efficacy of cervical endplay assessment as an indicator for spinal manipulation. *Spine*, 28 (11), 1091-1096.

Haas, M., Spegman, A., Peterson, D., Aickin, M. and Vavrek, D., 2010. Dose response and efficacy of spinal manipulation for chronic cervicogenic headache: a pilot randomized controlled trial. *The Spine Journal*, 10 (2), 117-128.

Haas, M., Vavrek, D., Peterson, D., Polissar, N. and Neradilek, M. B., 2014. Dose-response and efficacy of spinal manipulation for care of chronic low back pain: a randomized controlled trial. *The Spine Journal*, 14 (7), 1106-1116.

Haavik-Taylor, H. H. and Murphy, B., 2010. The effects of spinal manipulation on central integration of dual somatosensory input observed after motor training: A crossover study. *Journal of Manipulative & Physiological Therapeutics*, 33 (4), 261-272.

Hagen, K. B., Harms-Ringdahl, K., Enger, N. O., Hedenstad, R. and Morten, H., 1997. Relationship Between Subjective Neck Disorders and Cervical Spine Mobility and Motion-Related Pain in Male Machine Operators. *Spine*, 22 (13), 1501-1507.

Haldeman, S., 1976. The importance of research in the principles and practice of chiropractic. *The Journal of the CCA*, XX (3), 7-10.

Haldeman, S., 2011. Is it time to discard the term "diagnosis" when examining a person with uncomplicated axial neck pain? *The Spine Journal*, 11 (3), 177-179.

Haldeman, S., 2012. Commentary: Is patient satisfaction a reasonable outcome measure? *The Spine Journal*, 12, 1138-1139.

Hancock, M. J., Maher, C. G., Laslett, M., Hay, E. and Koes, B., 2011. Discussion paper: what happened to the 'bio' in the bio-psycho-social model of low back pain? *European Spine Journal*, 20, 2105-2110.

Haneline, M. T., Cooperstein, R., Young, M. and Birkeland, K., 2008. Spinal Motion Palpation: A Comparison of Studies that Assessed Intersegmental End Feel vs excursion. *Journal of Manipulative & Physiological Therapeutics*, 31 (8), 616-626.

Haneline, M. T. and Young, M., 2009. A Review of Intraexaminer and Interexaminer Reliability of Static Spinal Palpation: A Literature Synthesis. *Journal of Manipulative & Physiological Therapeutics*, 32 (5), 379-386.

Harrison, D. E., Harrison, D. D., Cailliet, R., Troyanovich, S. J., Janik, T. J. and Holland, B., 2000. Cobb Method or Harrison Posterior Tangent Method. *Spine*, 25 (16), 2072-2078.

Hart, D., Wall, B. F., Hillier, M. C. and Shrimpton, P. C., 2010. Frequency and Collective Dose for Medical and Dental X-ray Examinations in the UK, 2008. Oxford: Health Protection Agency.

Harvey, E., Burton, A. K., Moffett, J. K. and Breen, A., in collaboration with the UK BEAM trial team, 2003. Spinal manipulation for low-back pain: a treatment package agreed by the UK chiropractic, osteopathy and physiotherapy professional associations. *Manual Therapy*, 8 (1), 46-51.

Haskins, R., Rivett, D. A. and Osmotherly, P. G., 2012. Clinical prediction rules in the physiotherapy management of low back pain: A systematic review. *Manual Therapy*, 17 (1), 9-21.

Hawk, C., Long, C. R., Reiter, R., Davis, C. S., Cambron, J. A. and Evans, R., 2002. Issues in planning a placebo-controlled trial of manual methods: Results of a pilot study. *The Journal of Alternative and Complementary Medicine*, 8 (1), 21-32.

Hebert, J. J. and Fritz, J. M., 2012. Clinical decision rules, spinal pain classification and prediction of treatment outcome: A discussion of recent reports in the rehabilitation literature. *Chiropractic & Manual Therapies*, 20 (19).

Heller, C. A., Stanely, P., Lewis-Jones, B. and Heller, R. F., 1983. Value of x-ray examinations of the cervical spine. *British Medical Journal*, 287, 1276-1278.

Hemmila, H. M., 2005. Bone setting for prolonged Neck Pain: A randomized clinical trial. *Journal of Manipulative & Physiological Therapeutics*, 28 (7), 508-515.

Herdman, M., Gudex, C., Lloyd, A., Janssen, M., Kind, P., Parkin, D., Bonsel, G. and Badia, X., 2011. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Quality of Life Research*, 20 (10), 1727-1736.

Herzog, W., Kats, M. and Symons, B., 2001. The Effective Forces Transmitted by High-Speed, Low-Amplitude Thoracic Manipulation. *Spine*, 26 (19), 2105-2111.

Herzog, W., Zhang, Y. T., Conway, P. J. and Kawchuk, G. N., 1993. Cavitation sounds during spinal manipulative treatments. *Journal of Manipulative & Physiological Therapeutics*, 16 (8), 523-526.

Hestbaeck, L. and Leboeuf-Yde, C., 2000. Are Chiropractic Tests for the Lumbo-Pelvic Spine Reliable and Valid? A Systematic Critical Literature Review. *Journal of Manipulative and Physiological Therapeutics*, 23 (4), 258-275.

Highland, T. R., Dreisinger, T. E., Vie, L. L. and Russell, G. S., 1992. Changes in Isometric Strength and Range of Motion of the Isolated Cervical Spine After Eight Weeks of Clinical Rehabilitation. *Spine*, 17 (6S), S77-S82.

Hill, J. C. and Fritz, J. M., 2011. Psychosocial Influences on Low Back Pain, Disability, and Response to Treatment. *Physical Therapy*, 91 (5), 712-721.

Hill, J. C., Lewis, M., Sim, J., Hay, E. M. and Dziedzic, K., 2007. Predictors of Poor Outcome in Patients With Neck Pain Treated by Physical Therapy. *The Clinical Journal of Pain*, 23 (8), 683-690

Hill, J. M., Lewis, M. P., Papageorgiou, A. C. M., Dziedzic, K. P. and Croft, P. M. D., 2004. Predicting Persistent Neck Pain: A 1-Year Follow-up of a Population Cohort. *Spine*, 29 (15), 1648-1654.

Hino, H., Abumi, K., Kanyama, M. and Kaneda, K., 1999. Dynamic Motion Analysis of Normal and Unstable Cervical Spines Using Cineradiography. *Spine*, 24 (2), 163-168.

Hipp, J. A. and Wharton, N., 2008. Quantative Motion Analysis of Motion Preserving and Fusion Technologies of the Spine. Chapter 10. *In:* Yue, J., J. Ed, ed. *Motion Preservation Surgery of the Spine.* Saunders.

Hipp, J. A. P., Reitman, C. A. M. D. and Wharton, N. M. S., 2005. Defining Pseudoarthrosis in the Cervical Spine With Differing Motion Thresholds. *Spine*, 30 (2), 209-210.

Hogg-Johnson, S., van der Velde, G., Carroll, L., Holm, L. W., Cassidy, J. D., Guzman, J., Cote, P. D., Haldeman, S., Ammendolia, C., Carragee, E., Hurwitz, E., Nordin, M. and Peloso, P., 2008. The Burden and Determinants of Neck Pain in the General Population: Results of the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. *Spine*, 33(4S) Neck Pain Task Force (Supplement), S39-S51.

Holm, L. W., Carroll, L. J., Cassidy, J. D., Hogg-Johnson, S., Cote, P., Guzman, J., Peloso, P., Nordin, M., Hurwitz, E., van der Velde, G., Carragee, E. and Haldeman, S., 2008. The Burden and Determinants of Neck Pain in Whiplash-Associated Disorders After Traffic Collisions: Results of the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. *Spine*, 33(4S) Neck Pain Task Force (Supplement), S52-S59.

Hooper, P. D., 2005. Evolution and basic principles of the chiropractic adjustment and manipulation. *In:* Haldeman S (Ed), ed. *Principles and Practice of Chiropractic. 3rd edition.* New York: McGraw-Hill, 751-754.

Horodyski, M., Weight, M., Conrad, B., Bearden, B., Kimball, J. and Rechtine, G., 2009. Motion generated in the unstable lumbar spine during hospital bed transfers. *Journal of Spinal Disorders & Techniques*, 22 (1), 45-48.

Hou, C.-R., Tsai, L.-C., Cheng, K.-F., Chung, K.-C. and Hong, C.-Z., 2002. Immediate Effects of Various Physical Therapeutic Modalities on Cervical Myofascial Pain and Trigger-Point Sensitivity. *Archives of Physical Medicine and Rehabilitation*, 83 (October), 1406-1414.

Hoving, J. L., de Vet, H. C. W., Koes, B. W., Mameren, H. v., Devillé, W. L. J. M., van der Windt, D. A. W. M., Assendelft, W. J. J., Pool, J. J. M., Scholten, R. J. P. M., Korthals–de Bos, I. B. C. and Bouter, L. M., 2006. Manual Therapy, Physical Therapy, or Continued Care by the General Practitioner for Patients With Neck Pain: Long-Term Results From a Pragmatic Randomized Clinical Trial. *The Clinical Journal of Pain*, 22 (4), 370-377

Hoving, J. L., Koes, B., de Vet, R., van der Windt, D., Assendelft, W. J. J., Marmeren, H. V., Deville, W., Pool, J., Scholten, R. and Bouter, L., 2002. Manual therapy, physical therapy or continued care by a General Practitioner for patients with neck pain: a randomized, controlled trial. *Annals of Internal Medicine*, 136, 713-722.

Hoving, J. L., Pool, J. J. M., van Mameren, H., Deville, W. J. L. M., Assendelft, W. J. J., de Vet, H. C. W., de Winter, A. F., Koes, B. W. and Bouter, L. M., 2005. Reproducibility of cervical range of motion in patients with neck pain. *BMC Musculoskeletal Disorders*, 6 (59).

Howe, J. C. W., 1974. Cineradiographic evaluation of normal and abnormal cervical spine function. *Journal of Clinical Chiropractic*, 4, 42-54.

Howick, J., Galsziou, P. and Aronson, J. K., 2009. The evolution of evidence hierarchies: what can Bradford Hill's 'guidelines for causation' contribute. *Journal of the Royal Society of Medicine*, 102, 186-194.

Howick, J., Glasziou, P. and Aronson, J. K., 2010. Evidence-based mechanistic reasoning. *Journal of the Royal Society of Medicine*, 103 (11), 433-441.

Howick, J., 2011. *The Philosophy of Evidence-based Medicine.* Oxford: Wiley-Blackwell: BMJ Books

Hoy, D. G., Protani, M., De, R. and Buchbinder, R., 2010. The epidemiology of neck pain. *Best Practice & Research Clinical Rheumatology*, 24 (6), 783-792.

HSE, 2009. *Self-reported work-related illness and workplace injuries in 2008/2009: Results form the Labour Force Survey*. Health and Safety Executive.

HSE, 2012. *Self-reported work-related illness (SWI) and workplace injuries: Results from the Labour Force Survey (LFS) - Index of tables* [online]. Available from: http://www.hse.gov.uk/STATISTICS/lfs/index.htm#msd [Accessed 5/4/2014].

Hudak, P. and Wright, J. G., 2000. The Characteristics of Patient Satisfaction Measure. *Spine*, 25 (24), 3167-3177.

Huijbregts, P., 2007. Clinicial Prediction Rules: Time to sacrifice the holy cow of specificity? *The Journal of Manual and Manipulative Therapy*, 15 (1), 5-8.

Humphreys, B. K., Delahye, M. and Peterson, C. K., 2004. An investigation into the validity of cervical spine motion palpation using subjects with congenital block vertebrae as a 'gold standard'. *BMC Musculoskeletal Disorders*, 5 (19).

Hurwitz, E. L., Carragee, E. J., van der Velde, G., Carroll, L. J., Nordin, M., Guzman, J., Peloso, P. M., Holm, L. W., Cote, P., Hogg-Johnson, S., Cassidy, J. D. and Haldeman, S., 2008. Treatment of Neck Pain: Noninvasive Interventions: Results of the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. *Spine*, 33(4S) Neck Pain Task Force (Supplement), S123-S152.

Hurwitz, E. L., Goldstein, M. S., Morgenstern, H. and Chiang, L.-M., 2006. The impact of psychosocial factors on neck pain and disability outcomes among primary care patients: Results from the UCLA Neck Pain Study. *Disability & Rehabilitation*, 28 (21), 1319-1329.

Hurwitz, E. L., Morgenstern, H., Harber, P., Kominski, G. F., Yu, F. and Adams, A. H., 2002. A randomized trial of chiropractic manipulation and mobilization for patients with neck pain: clinical outcomes from the UCLA neck-pain study. *American Journal of Public Health*, 92 (10), 1634-1641.

Hush, J. M., Lin, C., Michaleff, Z. A., Vergagen, A. and Refshauge, K. M., 2011. Prognosis of Acute Idiopathic Neck Pain is Poor: A Systematic Review and Meta-Analysis. *Archives of Physical Medicine and Rehabilitation*, 92 (5), 824-829.

Hutting, N., Verhagen, A. P., Vijverman, V., Keesenberg, M. D., Dixon, G. and Scholten-Peeters, G. G., 2013. Diagnostic accuracy of premanipulative vertebrobasilar insufficiency tests: a systematic review. *Manual Therapy*, 18 (3), 177-182.

Hviid, H., 1965. Functional radiography of the cervical spine. *Annals of the Swiss Chiropractic Association*, 3, 37-65.

Hwang, H., Hipp, J. A., Ben-Galim, P. and Reitman, C. A., 2008. Threshold Cervical Range-of-Motion Necessary to Detect Abnormal Intervertebral Motion in Cervical Spine Radiographs. *Spine*, 33 (8), E261-E267.

ISO5725-1, 1994. Accuracy (trueness and precision) of measurement methods and results - Part 1: General principles and definitions. International Organization for Standardization.

Jasperse, S., M., C., 2013. *Inter-observer repeatability of continuous fluoroscopic measurement using OSMIA of cervical spine inter-vertebral kinematics in the sagittal plane.* Thesis (MChiro). Bournemouth University.

Jensen, M. P. and Karoly, P., 2001. Self report scales and procedures for assessing pain in adults. *In:* Turk, D. C., Melzack, R (Eds), ed. *Handbook of Pain Assessment 2nd Edition.* New York: Guildford Press.

Jensen, T. S., Karppinen, J., Sorensen, J. S., Niinimaki, J. and Leboeuf-Yde, C., 2008. Vertebral endplate signal changes (Modic change): a systematic literature review of prevalence and association with non-specific low back pain. *European Spine Journal*, 17 (11), 1407-1422.

Jordan, A., Bendix, T., Nielsen, H., Hansen, F. R., Høst, D. and Winkel, A., 1998. Intensive Training, Physiotherapy, or Manipulation for Patients With Chronic Neck Pain: A Prospective, Single-Blinded, Randomized Clinical Trial. *Spine*, 23 (3), 311-318.

Jordan, K., 2000. Assessment of Published Reliability Studies for Cervical Spine Range-of-Motion Measurement Tools. *Journal of Manipulative & Physiological Therapeutics*, 23 (3), 180-195.

Jull, G., Trott, P., Potter, H., Zito, G., Niere, K., Shirley, D., Emberson, J., Marschner, I. and Richardson, C., 2002. A Randomized Controlled Trial of Exercise and Manipulative Therapy for Cervicogenic Headache. *Spine*, 27 (17), 1835-1843.

Kaneoka, K., Ono, K., Inami, S. and Hayashi, K., 1999. Motion Analysis of Cervical Vertebrae During Whiplash Loading. *Spine*, 24 (8), 763-770.

Karayannis, N. V., Jull, G. A. and Hodges, P. W., 2012. Physiotherapy movement based classification approaches to low back pain: comparison of subgroups through review and developer/expert survey. *BMC Musculoskeletal Disorders*, 13 (24).

Kawchuk, G. N., Haugen, R. and Fritz, J., 2009. A True Blind for Subjects Who Receive Spinal Manipulation Therapy. *Archives of Physical Medicine and Rehabilitation*, 90 (2), 366-368.

Kay, T. M., Gross, A., Goldsmith, C. H., Rutherford, S., Voth, S., Hoving, J. L., Bronfort, G. and Santaguida, P. L., 2012. Exercises for mechanical neck disorders. *Cochrane Database of Systematic Reviews*, (8).

Khalsa, P. S., Egerhart, A., Cotler, A. and Nahin, R., 2006. The 2005 Conference on the Biology of Manual Therapies. *Journal of Manipulative and Physiological Therapeutics*, 29 (5), 341-346.

Kingston, L., Claydon, L. and Tumilty, S., 2014. The Effects Of Spinal Mobilizations On The Sympathetic Nervous System: A Systematic Review. *Manual Therapy*, 19 (4), 281-287.

Klaber Moffett, J. A., Jackson, D. A., Richmond, S., Hahn, S., Coulton, S., Farrin, A., Manca, A. and Torgerson, D. J., 2005. Randomised trial of a brief physiotherapy intervention compared with usual physiotherapy for neck pain patients: outcomes and patients' preference. *British Medical Journal*, 330 (7482), 75-78.

Koes, B., 2012. [Manual therapy for neck pain: increasing evidence of effectiveness] *Nederlands Tijdschrift voor Geneeskunde*, 15 (A4599).

Koes, B. W., Bouter, L. M., van Mameren, H., Essers, A. H. M., Verstegen, G. J., Hofhuizen, D. M., Houben, J. P. and Knipschild, P. G., 1993. A randomised clinical trial of manual therapy and physiotherapy for persistent back and neck complaints: sub-group analysis and relationship between outcome measures. *Journal of Manipulative & Physiological Therapeutics*, 16 (4), 211-219.

Koes, B. W., Bouter, L. M., van Mameren, H., Essers, A. H. M., Verstegen, G. M. J. R., Hofjuizen, D. M., Houben, J. P. and Knipschild, P. G., 1992. Randomised clinical trial of manipulative therapy and physiotherapy for persistent back and neck complaints: results of one year follow-up. *British Medical Journal*, 304, 601-605.

Koes, B. W., van Tulder, M., Lin, C. W., Macedo, L. G., McAuley, J. and Maher, C., 2010. An updated overview of clinical guidelines for the management of non-specific low back pain in primary care. *European Spine Journal*, 19 (12), 2075-2094.

Kolstad, F., Nygaard, O. and Leivseth, G., 2007. Segmental Motion Adjacent to Anterior Cervical Arthrodesis: A Prospective Study. *Spine*, 32 (5), 512-517.

Koppenhaver, S. L., Fritz, J. M., Hebert, J. J., Kawchuk, G. N., Childs, J. D., Parent, E. C., Gill, N. W. and Teyhen, D. S., 2011. Association between changes in abdominal and lumbar multifidus muscle thickness and clinical improvement after spinal manipulation. *Journal of Orthopaedic & Sports Physical Therapy*, 41 (6), 389-399.

Korthals-de Bos, I. B. C., Hoving, J. L., van Tulder, M. W., Rutten-van Molken, M. P. M. H., Ader, H. J., de Vet, C. W., Koes, B. W., Vondeling, H. and Bouter, L. M., 2003. Cost effectiveness of physiotherapy, manual therapy and general practitioner care for neck pain: economic evaluation alongside a randomised controlled trial. *British Medical Journal*, 326 (26 April), 911-917.

Kottner, J., Audige, L., Brorson, S., Donner, A., Gajewski, B. J., Hrobjartsson, A., Roberts, C., Shoukri, M. and Streiner, D. L., 2011. Guidelines for Reporting Reliability and Agreement Studies (GRRAS) were proposed. *Journal of Clinical Epidemiology*, 64, 96-106.

Kottner, J. and Streiner, D. L., 2011. The difference between reliability and agreement. *Journal of Clinical Epidemiology*, 64 (6), 701-702.

Kovacs, F. M., Bago, J., Royuela, A., Seco, J., Gimenez, S., Muriel, A., Abraira, V., Martin, J. L., Pena, J. L., Gestoso, M., Mufraggi, N., Nunez, M., Corcoll, J., Gomez-Ochoa, I., Ramirez, M. J., Calvo, E., Castillo, M. D., Marti, D., Fuster, S., Fernandez, C., Gimeno, N., Carballo, A., Milan, A., Vazquez, D., Canellas, M., Blanco, R., Brieva, P., Rueda, M. T., Alvarez, L., Gil del Real, M. T., Ayerbe, J., Gonzalez, L., Ginel, L., Ortega, M., Bernal, M., Bolado, G., Vidal, A., Ausin, A., Ramon, D., Mir, M. A., Tomas, M., Zamora, J. and Cano, A., 2008. Psychometric characteristics of the Spanish version of instruments to measure neck pain disability. *BMC Musculoskeletal Disorders*, 9 (42).

Kristjansson, E., Leivseth, G., Brinckmann, P. and Frobin, W., 2003. Increased sagittal plane segmental motion in the lower cervical spine in women with chronic whiplash-associated disorders, Grades I-II. *Spine*, 28 (19), 2215-2221.

Latremoliere, A. and Woolf, C. J., 2009. Central Sensitization: A Generator of Pain Hypersensitivity by Central Neural Plasticity. *The Journal of Pain*, 10 (9), 895-926.

Leaver, A. M. and Maher, C. G., 2012. In response to: Dunning J. How about an honorable mention for cervical and thoracic thrust manipulation? A passing mention would be more appropriate - Letter to the editor. *Journal of Manual and Manipulative Therapy*, 20 (3), 167-168.

Leaver, A. M., Maher, C. G., Herbert, R. D., Latimer, J., McAuley, J. H., Jull, G. and Refshauge, K. M., 2010. A Randomized Controlled Trial Comparing Manipulation with Mobilization for Recent Onset Neck Pain. *Archives of Physical Medicine and Rehabilitation*, 1313-1318.

Leboeuf-Yde, C., van Dijk, J., Franz, C., Hustad, S. A., Olsen, D., Pihl, T., Robech, R., Vendrup, S. S., Bendox, T. and Kyvik, K. O., 2002. Motion palpation findings and self-reported low back pain in a population-based study sample. *Journal of Manipulative and Physiological Therapeutics*, 25, 80-87.

Lee, H., Nicholson, L. L., Adams, R. D., Maher, C. G., Halaki, M. and Bae, S.-S., 2006. Development and Psychometric Testing of Korean Language Versions of 4 Neck Pain and Disability Questionnaires. *Spine*, 31 (16), 1841-1845.

Lee, M. J., Dettori, J. R., Standaert, C. J., Brodt, E. D. and Chapman, J. R., 2012. The natural history of degeneration of the lumbar and cervical spines: a systematic review. *Spine*, 37 (22 Suppl), S18-30.

Lee, R. Y., McGregor, A. H., Bull, A. M. and Wragg, P., 2005. Dynamic response of the cervical spine to posteronterior mobilisation. *Clinical Biomechanics*, 20, 228-231.

Leivseth, G., Frobin, W. and Brinckmann, P., 2005. Congenital cervical block vertebrae are associated with caudally adjacent discs. *Clinical Biomechanics*, 20, 669-674.

Leivseth, G., Kolstad, F., Nygaard, O. P., Zoega, B., Frobin, W. and Brinckmann, P., 2006. Comparing precision of distortion-compensated and stereophotogrammetric roentgen analysis when monitoring fusion in the cervical spine. *European Spine Journal*, 15, 774-779.

Lidgren, L., 2008. Preface: Neck Pain and the Decade of the Bone and Joint 2000-2010. *Spine*, 33 (4S), S1-S2.

Liebenson, 1998. Spinal stabilization training: the transverse abdominus. *Journal of Bodywork and Movement Therapies*, 2 (4), 218-223.

Lind, B., Sihlbom, H., Nordwall, A. and Malchau, H., 1989. Normal Range of Motion of the Cervical Spine. *Archives of Physical Medicine and Rehabilitation*, 70, 692-695.

Lundh, A. and Gotzsche, P. C., 2008. Recommendations by Cochrane Review Groups for assessment of the risk of bias in studies. *BMC Medical Research Methodology*, 8, 22.

Luo, N., Li, M., Chevalier, J., Lloyd, A. and Herdman, M., 2013. A comparison of the scaling properties of the English, Spanish, French, and Chinese EQ-5D descriptive systems. *Quality of Life Research*, 22 (8), 2237-2243.

MacDermid, J. C., Gross, A. R., Galea, V., McLaughlin, L. M., Parkingson, W. L. and Woodhouse, L., 2009a. Developing Biologically-Based Assessment Tools for Physical Therapy Management of Neck Pain. *Journal of Orthopaedic & Sports Physical Therapy*, 29 (5), 388-399.

MacDermid, J. C., Walton, D. M., Avery, S., Blanchard, A., Etruw, E., McAlpine, C. and Goldsmith, C. H., 2009b. Measurement properties of the Neck Disability Index: A systematic review. *Journal of Orthopaedic & Sports Physical Therapy*, 39 (5), 400-417.

Madson, T. J., Youdas, J. W. and Suman, V. J., 1999. Reproducibility of Lumbar Spine Range of Motion Measurements Using the Back Range of Motion Device. *Journal of Orthopaedic & Sports Physical Therapy*, 29 (8), 470-477.

Maiers, M., Bronfort, G., Evans, R., Hartvigsen, J., Svendsen, K., Bracha, Y., Schulz, C., Schulz, K. and Grimm, R., 2014. Spinal manipulative therapy and exercise for seniors with chronic neck pain. *The Spine Journal* [online], In Press. Available from:

http://www.sciencedirect.com/science/article/pii/S1529943013016306 [Accessed 15/11/2013].

Maigne, J.-Y. and Vautravers, P., 2003. Mechanism of action of spinal manipulative therapy. *Joint Bone Spine*, 70, 336-341.

Maitland, G., Gengeveld, E., Banks, K., English, K., 2005. *Vertebral Manipulation: 7th Edition*. 7th Edition. Oxford: Elsevier Butterworth-Heinemann.

Malmstrom, E., Karlberg, M., Melander, A. and Magnusson, M., 2003. Zebris versus Myrin: A Comparative Study Between a Three-Dimensional Ultrasound Movement Analysis and an Inclinometer/Compass Method. *Spine*, 28 (21), E433-E440.

Manca, A., Epstein, D. M., Torgerson, D. J., Klaber Moffett, J. A., Coulton, S., Farrin, A. J., Hahn, S., Jackson, D. A. and Richmond, S. J., 2006. Randomized trial of a brief physiotherapy intervention compared with usual physiotherapy for neck pain patients: Cost-effectiveness analysis. *International Journal of Technology Assessment in Health Care*, 22 (01), 67-75.

Mann, E., Peterson, C., Hodler, J. and Pfirrmann, C. A., 2014. The evolution of degenerative marrow (Modic) changes in the cervical spine in neck pain patients. *European Spine Journal*, 23 (3), 584-589.

Mannion, A. and Troke, M., 1999. A comparison of two motion analysis devices used in the measurement of lumbar spinal mobility. *Clinical Biomechanics*, 14, 612-619.

Marchiori, D. M. and Henderson, C. N. R., 1996. A cross-sectional study correlating cervical radiographic degenerative findings to pain and disability. *Spine*, 21 (23), 2747-2752.

Maroufi, N., Ahmadi, A. and Mousavi Khatir, S. R., 2013. A comparative investigation of flexion relaxation phenomenon in healthy and chronic neck pain subjects. *European Spine Journal*, 22 (1), 162-168.

Marras, W. S., Ferguson, S. A., Gupta, P., Bose, S., Parnianpour, M., Kim, J.-Y. and Crowell, R. R., 1999. The Quantification of Low Back Disorder Using Motion Measures: Methodology and Validation. *Spine*, 24 (20), 2091-2100.

Marras, W. S., Parnianpour, M., Ferguson, S. A., Kim, J., Crowell, R. R., Bose, S. and Simon, S. R., 1995. The Classification of Anatomic- and Sympton-based Low Back Disorders Using Motion Measure Models. *Spine*, 20 (23), 2531-2546.

Martinez-Segura, R., De-La-Llave-Rincon, A. I., Ortega-Santiago, R., Cleland, J. A. and Fernandez-De-las-Penas, C., 2012. Immediate changes in widespread pressure pain sensitivity, neck pain, and cervical range of motion after cervial or thoracic thrust manipulation in patients with bilateral chronic mechanical neck pain: A randomized clinical trial. *Journal of Orthopaedic & Sports Physical Therapy*, 42 (9), 806-814.

Martinez-Segura, R., Fernandez-de-las-Penas, C., Ruiz-Saez, M., Lopez-Jimenez, C. and Rodriguez-Blanco, C., 2006. Immediate effects of neck pain and active range of motion after a single cervical high-velocity low-amplitude manipulation in subjects presenting with mechanical neck pain: A randomised controlled trial. *Journal of Manipulative & Physiological Therapeutics*, 29 (7), 511-517.

May, S. and Rosedale, R., 2009. Prescriptive Clinical Prediction Rules in Back Pain Research: A Systematic Review. *Journal of Manipulative & Physiological Therapeutics*, 17 (1), 36-45.

McCarthy, P. W., Olsen, J. P. and Smeby, I. H., 1997. Effects of contract-relax stretching procedures on active range of motion of the cervical spine in the transverse plane. *Clinical Biomechanics*, 12 (2), 136-138.

McCormick, J.D., Werner, B.C., Shimer, A.L., 2013. Patient-reported outcome measures in spine surgery. *Journal of the American Academy of Orthopedic Surgery*, 21(2), 99-107.

McDonald, C. P., Bachison, C. C., Chang, V., Bartol, S. W. and Bey, M. J., 2010. Three-dimensional dynamic in vivo motion of the cervical spine: assessment of measurement accuracy and preliminary findings. *The Spine Journal*, 10 (6), 497-504.

McDowell, I., 2006. *Measuring health: a guide to rating scales and questionnaires*. 3rd. Oxford: Oxford University Press.

McGraw, K. O. and Wong, S. P., 1996. Forming inferences about some intraclass correlation coefficients. *Psychological Methods*, 1 (1), 30-46.

McGregor, A. H., Anderton, L. D., Gedroyc, W. M., Johnson, J. and Hughes, S., 2001. Assessment of spinal kinematics using open interventional magnetic resonance imaging. *Clinical Orthopaedics and Related Research*, 392, 341-348.

McNair, P. J., Portero, P., Chiquet, C., Mawston, G. and Lavaste, F., 2007. Acute neck pain: Cervical spine range of motion and position sense prior to and after joint mobilization. *Manual Therapy*, 12, 390-394.

McReynolds, T. M. and Sheridan, B. J., 2005. Intramuscular ketorolac versus osteopathic manipulative treatment in the management of acute neck pain in the emergency department: a randomised clinical trial. *Journal of The American Osteopathic Association*, 105 (2), 57-68.

Meeker, W. C. and Haldeman, S., 2002. Chiropractic: A profession at the crossroads of mainstream and alternative medicine. *Annals of Internal Medicine*, 136 (3), 216-227.

Meier, M. L., Hotz-Boendermaker, S., Boendermaker, B., Luechinger, R. and Humphreys, B. K., 2014. Neural responses of posterior to anterior movement on lumbar vertebrae: a functional magnetic resonance imaging study. *Journal of Manipulative & Physiological Therapeutics*, 37 (1), 32-41.

Mellor, F., Muggleton, J. M., Bagust, J., Mason, W., Thomas, P. W. and Breen, A. C., 2009. Mid-lumbar lateral flexion stability measured in healthy volunteers by in-vivo fluoroscopy. *Spine*, 34 (22), E811-E817.

Mellor, F. E., 2014. *An evaluation of passive recumbent quantitative fluoroscopy to measure mid-lumbar intervertebral motion in patients with chronic non-specific low back pain and healthy volunteers.* Thesis (PhD). Bournemouth University.

Mellor, F. E., Thomas, P. W., Thompson, P. and Breen, A. C., 2014. Proportional lumbar spine inter-vertebral motion patterns: a comparison of patients with chronic, non-specific low back pain and healthy controls. *European Spine Journal* [online], Available from: http://link.springer.com/article/10.1007/s00586-014-3273-3 [Accessed 15/4/2014].

Michaelson, P., Sjölander, P. and Johansson, H., 2004. Factors Predicting Pain Reduction in Chronic Back and Neck Pain After Multimodal Treatment. *The Clinical Journal of Pain*, 20 (6), 447-454.

Mieritz, R. M., Bronfort, G., Kawchuk, G., Breen, A. and Hartvigsen, J., 2012. Reliability and Measurement Error of 3-Dimensional Regional Lumbar Motion Measures: A Systematic Review. *Journal of Manipulative and Physiological Therapeutics*, 35 (8), 645-656.

Miller, J., Gross, A., D'Sylva, J., Burnie, S. J., Goldsmith, C. H., Graham, N., Haines, T., Bronfort, G. and Hoving, J. L., 2010. Manual therapy and exercise for neck pain: A systematic review. *Manual Therapy*, 15 (4), 334-354.

Mimura, M., Panjabi, M. M., Oxland, T. R., Crisco, J. J., Yamamoto, I. and Vasavada, A., 1994. Disc Degeneration Affects the Multidirectional Flexibility of the Lumbar Spine. *Spine*, 19 (12), 1371-1380.

Misterska, E., Jankowski, R. and Glowacki, M., 2011. Cross-cultural adaptation of the Neck Disability Index and Copenhagen Neck Functional Disability Scale for patients with neck pain due to degenerative and discopathic disorders. Psychometric properties of the Polish versions. *BMC Musculoskeletal Disorders*, 12 (84).

Molina Ortega, F., Lomas-Vega, R., Hita-Contreras, F., Plaza Manzano, G., Achalandabaso, A., Ramos-Morcillo, A. J. and Martínez-Amat, A., 2014. Immediate effects of spinal manipulation on nitric oxide, substance P and pain perception. *Manual Therapy* [online], In Press. Available from: http://www.sciencedirect.com/science/article/pii/S1356689X14000290 [Accessed 6/6/2014].

Murphy, D. R., 2010. Current understanding of the relationship between cervical manipulation and stroke: What does it mean for the chiropractic profession? *Chiropractic & Osteopathy*, 18 (22).

Murphy, D. R. and Hurwitz, E. L., 2007. A theoretical model for the development of a diagnosis-based clinical decision rule for the management of patients with spinal pain. *BMC Musculoskeletal Disorders*, 8 (75).

Murphy, D. R. and Hurwitz, E. L., 2011. Application of a Diagnosis-Based Clinical Decision Guide in Patients with Neck Pain. *Chiropractic & Manual Therapies*, 19 (1).

Murray, C. J. and Lopez, A. D., 2013. Measuring the global burden of disease. *New England Journal of Medicine*, 369 (5), 448-457.

Murray, C. J. L., Vos, T., Lazano, R., Naghavi, M., Flaxman, A. D. and Michaud, C., 2012. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *The Lancet*, 380 (9859), 2197-2223.

Myles, P., 2007. Using the Bland-Altman method to measure agreement with repeated measures: Editorial I. *British Journal of Anaesthesia*, 99 (3), 309-311.

Nachemson, A. L., Schultz, A. B. and Berkson, M. H., 1979. Mechanical properties of human lumbar spine motion segments: influences of age, sex, disc level and degeneration. *Spine*, 4, 1-8.

Naderi, S., Andalkar N. and Benzel, E. C., 2007. History of spine biomechanics: part I - the pre-Greco-Roman, Greco-Roman, and medieval roots of spine biomechanics. *Neurosurgery*, 60 (2), 382-390.

Nansel, D., Cremata, E., Carlson, J. and Szlazak, M., 1989a. Effect of unilateral spinal adjustments on goniometrically-assessed cervical lateral-flexion end-range asymmetries in otherwise asymptomatic subjects. *Journal of Manipulative and Physiological Therapeutics*, 12 (6), 419-427.

Nansel, D. D., Peneff, A. L., Jansen, R. D. and Cooperstein, R., 1989b. Interexaminer concordance in detecting joint-play asymmetries in the cervical spines of otherwise asymptomatic subjects. *Journal of Manipulative & Physiological Therapeutics*, 12 (6), 428-433.

Natvig, B., Ihlebaek, C., Grotle, M., Brage, S. and Bruusgaard, D., 2010. Neck Pain Is Often a Part of Widespread Pain and Is Associated With Reduced Functioning. *Spine*, 35 (23), E1285-E1289.

Neziri, A. Y., Scaramozzino, P., Andersen, O. K., Dickenson, A. H., Arendt-Nielsen, L. and Curatolo, M., 2011. Reference values of mechanical and thermal pain tests in a pain-free population. *European Journal of Pain*, 15 (4), 376-383.

NHMRC., 2003. *Evidence-based management of acute musculoskeletal pain: Australian Acute Musculoskeletal Pain Guidelines Group.* Brisbane: University of Queensland and the Commonwealth Department of Health and Ageing. National Health and Medical Research Council.

Nijs, J. and Van Houdenhove, B., 2009. From acute musculoskeletal pain to chronic widespread pain and fibromyalgia: Application of pain neurophysiology in manual therapy practice. *Manual Therapy*, 14, 3-12.

Nilsson, N., Christensen, H. W. and Hartvigsen, J., 1996a. Lasting changes in passive range of motion after spinal manipulation: a randomised, blind, controlled trial. *Journal of Manipulative & Physiological Therapeutics*, 19 (3), 165-168.

Nilsson, N., Hartvigsen, J. and Christensen, H. W., 1996b. Normal ranges of passive cervical motion for women and men 20-60 years old. *Journal of Manipulative & Physiological Therapeutics*, 19, 306-309.

Nordin, M., Carragee, E., Hogg-Johnson, S., Weiner, S., Hurwitz, E., Peloso, P., Guzman, J., van der Velde, G., Carroll, L., Holm, L., Cote, P., Cassidy, J. D. and Haldeman, S., 2008. Assessment of Neck Pain and Its Associated Disorders: Results of the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. *Spine*, 33(4S) Neck Pain Task Force (Supplement), S101-S122.

Ohberg, F., Grip, H., Wiklund, U., Sterner, Y., Karlsson, J. S. and Gerdle, B., 2003. Chronic whiplash associated disorders and neck movement measurements: an instantaneous helical axis approach. *IEEE Transactions on Information Technology in Biomedicine*, 7 (4), 274-282.

Ong, B. N., Hooper, H., Jinks, C., Dunn, K. and Croft, P., 2006. 'I suppose that depends on how I was feeling at the time': perspectives on questionnaires measuring quality of life and musculoskeletal pain. *Journal of Health Service Research Policy*, 11 (2), 81-88.

Ordway, N. R., Seymour, R. J., Donelson, R. G., Hojnowski, L. S. and Edwards, W. T., 1999. Cervical Flexion, Extension, Protrusion, and Retraction: A Radiographic Segmental Analysis. *Spine*, 24 (3), 240-247.

Ostelo, R. W. J. G., Deyo, R. A., Stratford, P., Waddell, G., Croft, P., Von Korff, M., Bouter, L. M. and de Vet, H. C., 2008. Interpreting Change Scores for Pain and Functional Status in Low Back Pain: Towards International Consensus Regarding Minimal Important Change. *Spine*, 33 (1), 90-94.

Padayachy, K., Vawda, G. H. M., Shaik, J. and McCarthy, P. W., 2010. The immediate effect of low back manipulation on serum cortisol levels in adult males with mechanical low back pain. *Clinical Chiropractic*, 13 (4), 246-252.

Palmer, K., T.,, Walker-Bone, K., Griffin, M. J., Syddall, H., Pannett, B., Coggon, D. and Cooper, C., 2001. Prevalence and occupational associations of neck pain in the British population. *Scandinavian Journal of Work Environment & Health*, 27 (1), 49-56.

Panjabi, M. M., 1979. Centres and angles of rotation of body joints: a study of errors and optimization. *Journal of Biomechanics* 12, 911-920.

Panjabi, M., Chang, D. and Dvorak, J., 1992. An analysis of errors in kinematic parameters associated with in vivo functional radiographs. *Spine*, 17 (2), 200-205.

Panjabi, M. M., 1992a. The stabilising system of the spine - Part 1: Function, dysfunction, adaptation and enhancement. *Journal of Spinal Disorders*, 5 (4), 383-389.

Panjabi, M. M., 1992b. The stabilising system of the spine - Part 2: Neutral zone and instability hypothesis. *Journal of Spinal Disorders*, 5 (4), 390-397.

Pearcy, M. and Bogduk, N., 1988. Instantaneous axes of rotation of the lumbar intervertebral joint. *Spine*, 13 (9), 1033-1041.

Pearcy, M. J. and Whittle, M. W., 1982. Movements of the lumbar spine measured by three-dimensional x-ray analysis. *Journal of Biomedical Engineering*, 4 (April), 107-112.

Peloso, P. and Gross, A., 2003. Further studies are needed to assess the competing therapies for neck pain. *The Journal of Pain*, 4 (8), 442-426.

Pernold, G. M., Mortimer, M. P., Wiktorin, C. P., Tornqvist, E. W. P., Vingard, E. M. D. and the Musculoskeletal Intervention Center -Norrtalje Study, G., 2005. Neck/Shoulder Disorders in a General Population. Natural Course and Influence of Physical Exercise: A 5-Year Follow-up. *Spine*, 30 (13), E363-E368.

Peterson, C., Bolton, J. and Humphreys, B. K., 2012. Predictors of outcome in neck pain patients undergoing chiropractic care: comparisons of acute and chronic patients. *Chiropractic & Manual Therapies*, 20, 27.

Peterson, D. H. and Bergmann, T. F., 2011. *Chiropractic technique: principles and procedures*. 3rd. St Louis, Missouri: Mosby Inc.

Pettersson, K., Hildingsson, C., Toolanen, G., Fagerlund, M. and Bjornebrink, J., 1994. MRI and neurology in acute whiplash trauma. No correlation in prospective examination of 39 cases. *Acta Orthopaedica Scandinavica*, 65 (5), 525-528.

Pickar, J. G. and Bolton, P. S., 2012. Spinal manipulative therapy and somatosensory activation. *Journal of Electromyography and Kinesiology*, 22, 785-794.

Pietrobon, R., Coeytaux, R. R., Carey, T. S., Richardson, W. J. and DeVellis, R. F., 2002. Standard scales for measurement of functional outcome for cervical pain or dysfunction: a systematic review. *Spine*, 27 (5), 515-522.

Pincus, T., Kent, P., Bronfort, G., Loisel, P., Pransky, G. and Hartvigsen, J., 2013. Twenty-five years with the biopsychosocial model of low back pain-is it time to celebrate? A report from the twelfth international forum for primary care research on low back pain. *Spine*, 38 (24), 2118-2123.

Piva, S. R., Erhard, R. E., Childs, J. D. and Browder, D. A., 2006. Inter-tester reliability of passive intervertebral and active movements of the cervical spine. *Manual Therapy*, 11 (4), 321-330.

Pool, J. J. M., Ostelo, R. W. J. G., Hoving, J. L., Bouter, L. M. and de Vet, H. C. W., 2007. Minimal Clinically Important Change of the Neck Disability Index and the Numerical Rating Scale for Patients With Neck Pain. *Spine*, 32 (26), 3047-3051.

Posadzki, P. and Ernst, E., 2011. Spinal manipulation: an update of a systematic review of systematic reviews. *New Zealand Medical Journal*, 124 (1340), 55-71.

Puentedura, E. J., Cleland, J. A., Landers, M. R., Mintken, P. E., Louw, A. and Fernandez-de-Las-Penas, C., 2012a. Development of a clinical prediction rule to identify patients with neck pain likely to benefit from thrust joint manipulation to the cervical spine. *Journal of Orthopaedic & Sports Physical Therapy*, 42 (7), 577-592.

Puentedura, E. J., Landers, M. R., Cleland, J. A., Mintken, P., Huijbregts, P. and Fernandez-de-las-Penas, C., 2011. Thoracic Spine Thrust Manipulation versus Cervical Spine Thrust Manipualtion in Patients with Acute Neck Pain: A Randomized Clinical Trial. *Journal of Orthopaedic & Sports Physical Therapy*, 41 (4), 208-220.

Puentedura, E. J., March, J., Anders, J., Perez, A., Landers, M. R., Wallmann, H. W. and Cleland, J. A., 2012b. Safety of cervical spine manipulation: are adverse events preventable and are manipulations being performed appropriately? A review of 134 case reports. *Journal of Manual & Manipulative Therapy*, 20 (2), 66-74.

Puglisi, F., Ridi, R., Cecchi, F., Bonelli, A. and Ferrari, R., 2004. Segmental vertebral motion in the assessment of neck range of motion in whiplash patients. *International Journal of Legal Medicine*, 118, 235-239.

Puglisi, F., Strimpakos, N., Papathanasiou, M., Kapreli, E., Bonelli, A., Sgambetterra, S. and Ferrari, R., 2007. Cervical spine segmental vertebral motion in healthy volunteers feigning restriction of neck flexion and extension. *International Journal of Legal Medicine*, 121, 337-340.

Rabin, R. and de Charro, F., 2001. EQ-5D: a measure of health status from the EuroQol Group. *Annals of Medicine*, 33, 337-343.

Rasmussen-Barr, E., Bohman, T., Hallqvist, J., Holm, L. W. and Skillgate, E., 2013. Do physical activity level and body mass index predict recovery from persistent neck pain in men and women of working age? A population-based cohort study. *European Spine Journal*, 22 (9), 2077-2083.

Reinartz, R., Platel, B., van Mameren, H., van Santbrink, H. and Romeny, B. H., 2009. Cervical vertebrae tracking in video-fluoroscopy using the normalized gradient field. *Medical Image Computing and Computer-Assisted Intervention*, 12 (Pt 1), 524-531.

Reitman, C. A., Hipp, J. A., Nguyen, L. and Esses, S. I., 2004a. Changes in segmental intervertebral motion adjacent to cervical arthrodesis: A prospective study. *Spine*, 29 (11), E221-E226.

Reitman, C. A., Mauro, K. M., Nguyen, L., Ziegler, J. M. and Hipp, J. A., 2004b. Intervertebral Motion Between Flexion and Extension in Asymptomatic Individuals. *Spine*, 29 (24), 2832-2843.

Revel, M., Andre-Deshays, C. and Minguet, M., 1991. Cervicocephalic kinesthetic sensibility in patients with cervical pain. *Archives of Physical Medicine and Rehabilitation*, 72 (5), 288-291.

Reynolds, J., Marsh, D., Koller, H., Zenenr, J. and Bannister, G., 2009. Cervical range of movement in relation to neck dimension. *European Spine Journal*, 18, 863-868.

Robinson, R., Robinson, H. S., Bjorke, G. and Kvale, A., 2009. Reliability and validity of a palpation technique for identifying the spinous processes of C7 and L5. *Manual Therapy*, 14 (4), 409-414.

Ross, J. K., Bereznick, D. E. and McGill, S. M., 2004. Determining cavitation location during lumbar and thoracic spinal manipulation. Is spinal manipulation accurate and specific? *Spine*, 29 (13), 1452-1457.

Rothwell, D. M., Bondy, S. J. and Williams, J. I., 2001. Chiropractic manipulation and stroke: a population-based case-control study. *Stroke*, 32 (10), 1054-1060.

Rubinstein, S. M., Leboeuf-Yde, C., Knol, D. L., de Koekkoek, T. E., Pfeifle, C. E. and van Tulder, M. W., 2007. The benefits outweigh the risks for patients undergoing chiropractic care for neck pain: a prospective, multicentre cohort study. *Journal of Manipulative & Physiological Therapeutics*, 30 (6), 408-418.

Rubinstein, S. M., Peerdeman, S. M., van Tulder, M. W., Riphagen, I. and Haldeman, S., 2005. A systematic review of the risk factors for cervical artery dissection. *Stroke*, 36, 1575-1580.

Rudolfsson, T., Bjorklund, M. and Djupsjobacka, M., 2012. Range of motion in the upper and lower cervical spine in people with chronic neck pain. *Manual Therapy*, 17 (1), 53-59.

Rushton, A., Rivett, D., Carlesso, L., Flynn, T., Hing, W. and Kerry, R., 2014. International framework for examination of the cervical region for potential of Cervical Arterial Dysfunction prior to Orthopaedic Manual Therapy intervention. *Manual Therapy*, 19 (3), 222-228.

Ryd, L., Yuan, X. and Lofgren, H., 2000. Methods for determining the accuracy of radiostereometric analysis (RSA). *Acta Orthopaedica Scandinavica*, 71 (4), 403-408.

Saavedra-Hernandez, M., Arroyo-Morales, M., Cantarero-Villanueva, I., Fernandez-Lao, C., Castro-Sanchez, A. M., Puentedura, E. J. and Ferandez-de-las-Penas, 2012. Short-term effects of spinal thrust joint manipulation in patients with chronic neck pain: a randomized clinical trial. *Clinical Rehabilitation*, 11, 1-9.

Sahrmann, S. A., 2002. *Diagnosis and treatment of movement impairment syndromes* St. Louis, Missouri: Mosby.

Schafer, R. C. and Faye, L. J., 1989. *Motion palpation and chiropractic technic: principles of dynamic chiropractic*. 2nd. California: Motion Palpation Institute.

Schalimtzek, M., 1954. Funtional roentgen examination of degenerated and normal intervertebral disks of the lumbar spine. *Acta Radiologica Supplement*, 116, 300-306.

Schellingerhout, J. M., Verhagen, A. P., Heymans, M. W., Pool, J. J., Vonk, F., Koes, B. W. and Wilhelmina de Vet, H. C., 2008. Which subgroups of patients with non-specific neck pain are more likely to benefit from spinal manipulation therapy, physiotherapy, or usual care? *Pain*, 139 (3), 670-680.

Seaman, D. R., 1997. Joint complex dysfunction, a novel term to replace subluxation/subluxation complex: Etiological and treatment considerations. *Journal of Manipulative & Physiological Therapeutics*, 20 (9), 634-644.

Selvik, G., 1990. Roentgen stereophotogrammetric analysis. *Acta Radiologica*, 31, 113-126.

Shahidi, B., Johnson, C., L.,, Curran-Everett, D. and Maluf, K., S., 2012. Reliability and group differences in quantitative cervicothoracic measures among individuals with and without chronic neck pain. *BMC Musculoskeletal Disorders*, 13 (215).

Shekelle, P. G., 1994. Spine update: Spinal manipulation. *Spine*, 19 (7), 858-861.

Sherman, K. J., Cook, A. J., Wellman, R. D., Hawkes, R. J., Kahn, J. R., Deyo, R. A. and Cherkin, D. C., 2014. Five-week outcomes from a dosing trial of therapeutic massage for chronic neck pain. *Annals of Family Medicine*, 12 (2), 112-120.

Shilton, M., 2014. *Cervical lordosis in patients with non-specific neck pain receiving spinal manipulative therapy and healthy volunteers - a prospective longitudinal study.* Thesis (MChiro). Bournemouth University.

Shrout, P. E., 1998. Measurement reliability and agreement in psychiatry. *Statistical Methods in Medical Research*, 7 (3), 301-317.

Shrout, P. E. and Fleiss, J. L., 1979. Intraclass correlations: uses in assessing rater reliability. *Psychological Bulletin*, 86 (2), 420-428.

Shum, G. L., Tsung, B. Y. and Lee, R. Y., 2013. The Immediate Effect of Posteroanterior Mobilization on Reducing Back Pain and the Stiffness of the Lumbar Spine. *Archives of Physical Medicine and Rehabilitation*, 94, 673-679.

Sim, J. and Wright, C. C., 2005. The Kappa Statistic in Reliability Studies: Use, Interpretation, and Sample Size Requirements. *Physical Therapy*, 85 (3), 257-268.

Simmonds, N., Miller, P. and Gemmell, H., 2012. A theoretical framework for the role of fascia in manual therapy. *Journal of Bodywork and Movement Therapies*, 16, 83-93.

Simpson, A., Biswas, D., Emerson, J., Lawrence, B. and Grauer, J., 2008. Quantifying the Effects of Age, Gender, Degeneration, and Adjacent Level Degeneration on Cervical Spine Range of Motion Using Multivariate Analyses. *Spine*, 33 (2), 183-186.

Sjolander, P., Michaelson, P., Jaric, S. and Djupsjobacka, M., 2008. Sensorimotor disturbances in chronic neck pain - Range of motion, peak velocity, smoothness of movement, and repositioning acuity. *Manual Therapy*, 13, 122-131.

Skillgate, E., Vingård, E. and Alfredsson, L., 2007. Naprapathic Manual Therapy or Evidence-based Care for Back and Neck Pain: A Randomized, Controlled Trial. *The Clinical Journal of Pain*, 23 (5), 431-439

Slater, S. L., Ford, J. J., Richards, M. C., Taylor, N. F., Surkitt, L. D. and Hahne, A. J., 2012. The effectiveness of sub-group specific manual therapy for low back pain: a systematic review. *Manual Therapy*, 17 (3), 201-212.

Smith, A. D., Jull, G., Schneider, G., Frizzell, B., Hooper, R. A. and Sterling, M., 2014. Cervical radiofrequency neurotomy reduces central hyperexcitability and improves neck movement in individuals with chronic whiplash. *Pain Medicine*, 15, 128-141.

Smith, O. G., Langworthy, S. M. and Paxson, M. C., 1906. *A Text Book, Modernized Chiropractic*. Laurance Press Company.

Smith, W. S., Johnston, S. C., Skalabrin, E. J., Weaver, M., Azari, P., Albers, G. W. and Gress, D. R., 2003. Spinal manipulative therapy is an independent risk factor for vertebral artery dissection. *Neurology*, 60 (May), 1424-1428.

Solomonow, M., Zhou, B. H., Harris, M., Lu, Y. and Baratta, R. V., 1998. The ligamento-muscular stabilizing system of the spine. *Spine*, 23 (23), 2552-2562.

Song, X. J., Gan, Q., Cao, J. L., Wang, Z. B. and Rupert, R. L., 2006. Spinal manipulation reduces pain and hyperalgesia after lumbar intervertebral foramen inflammation in the rat. *Journal of Manipulative & Physiological Therapeutics*, 29 (1), 5-13.

Souvlis, T., Vincenzino, B. and Wright, A., 2004. Neurophysiological effects of spinal manual therapy. *In:* Boyling, J. D., G.A.Jull Eds, ed. *Grieve's Modern Manual Therapy 3rd Edition.* Edinburgh: Churchill-Livingstone, 367-379.

Stanton, T. R., Latimer, J., Caher, C. G. and Hancock, M., 2009. Definitions of Recurrence of an Episode of Low Back Pain. *Spine*, 34 (9), E316-E322.

Stanton, W. R. and Jull, G. A., 2003. Cervicogenic Headache: Locus of Control and Success of Treatment. *Headache: The Journal of Head & Face Pain*, 43 (9), 956.

Sterling, M., 2004. Invited Commentary: Proposal of a classification system for patients with neck pain by Childs et al (2004). *Journal of Orthopaedic & Sports Physical Therapy*, 34, 697-699.

Sterling, M., 2009. Neck Pain: Much more than a Psychosocial Condition. *Journal of Orthopaedic & Sports Physical Therapy*, 39 (6), 309-311.

Sterling, M., Jull, G. and Wright, A., 2001. Cervical mobilisation: concurrent effects on pain, sympathetic nervous system activity and motor activity. *Manual Therapy*, 6 (2), 72-81.

Stokes, I. A. F., Wilder, D. G., Frymoyer, J. W. and Pope, M. H., 1981. Assessment of patients with low back pain by biplanar radiographic measurement of intervertebral motion (1980 Volvo Award in Clinical Sciences). *Spine*, 6 (3), 233-240.

Strimpakos, N., Sakellari, V., Gioftsos, G., Papathanasiou, M., Brountzos, E., Kelekis, D., Kapreli, E. and Oldham, J., 2005. Cervical spine ROM measurements: optimizing the testing protocol by using a 3D ultrasound-based motion analysis system. *Cephalalgia*, 25, 1133-1145.

Takasaki, H., Hall, T., Kaneko, S., Ikemoto, Y. and Jull, G., 2011. A radiographic analysis of the influence of initial neck posture on cervical segmental movement at end-range extension in asymptomatic subjects. *Manual Therapy*, 16, 74-79.

Taylor, A. J. and Kerry, R., 2010. A 'system based' approach to risk assessment of the cervical spine prior to manual therapy. *International Journal of Osteopathic Medicine*, 13 (3), 85-93.

Teodorczyk-Injeyan, J. A., Injeyan, H. S. and Ruegg, R., 2006. Spinal manipulative therapy reduces inflammatory cytokines but not substance P production in normal subjects. *Journal of Manipulative & Physiological Therapeutics*, 29 (1), 14-21.

Teodorczyk-Injeyan, J. A., Triano, J. J., McGregor, M., Woodhouse, L. and Injeyan, H. S., 2011. Elevated production of inflammatory mediators including nociceptive chemokines in patients with neck pain: a cross-sectional evaluation. *Journal of Manipulative & Physiological Therapeutics*, 34 (8), 498-505.

Teyhen, D. S., Flynn, T. W., Bovik, A. C. and Abraham, L. D., 2005. A new technique for digital fluoroscopic video assessment of sagittal plane lumbar spine motion. *Spine*, 30 (14), E406-E413.

Teyhen, D. S., Flynn, T.W., Childs, J.D., Kuklo, T.R., Rosner, M.K., Polly, D.W., Abraham, L.D., 2007. Fluoroscopic Video to Identify Aberrant Lumbar Motion. . *Spine*, 32 (7), E220-E229.

Thiel, H. and Rix, G., 2005. Is it time to stop functional pre-manipulation testing of the cervical spine? *Manual Therapy*, 10 (2), 154-158.

Thiel, H. W., Bolton, J. E., Docherty, S. and Portlock, J. C., 2007. Safety of chiropractic manipulation of the cervical spine; A prospective national survey. *Spine*, 32 (21), 2375-2378.

Tousignant, M., Boucher, N., Bourbonnais, J., Gravelle, T., Quesnel, M. and Brosseau, L., 2001. Intratester and intertester reliability of the Cybex electronic digital inclinometer (EDI-320) for measurement of active neck flexion and extension in healthy subjects. *Manual Therapy*, 6 (4), 235-241.

Treleaven, J. and Takasaki, H., 2014. Characteristics of visual disturbances reported by patients with neck pain. *Manual Therapy*, 19 (3), 204-207.

Triano, J. J., 1984, 3-5th October. *Accurate determination of motion from plain films.* Paper presented at the 8th Annual Meeting of the American Society of Biomechanics, University of Arizona, Tucson.

Triano, J. J., Budgell, B., Bagnulo, A., Roffey, B., Bergmann, T., Cooperstein, R., Gleberzon, B., Good, C., Perron, J. and Tepe, R., 2013. Review of methods used by chiropractors to determine the site for applying manipulation. *Chiropractic & Manual Therapies*, 21 (36).

Trouli, M. N., Vernon, H. T., Kakavelakis, K. N., Antonopoulou, M. D., Paganas, A. N. and Lionis, C. D., 2008. Translation of the Neck Disability Index and validation of the Greek version in a sample of neck pain patients. *BMC Musculoskeletal Disorders*, 9 (106).

Tsang, S. M., Szeto, G. P. and Lee, R. Y., 2014. Altered spinal kinematics and muscle recruitment pattern of the cervical and thoracic spine in people with chronic neck pain during functional task. *Journal of Electromyography and Kinesiology*, 24 (1), 104-113.

Tsang, S. M. H., Szeto, G. P. Y. and Lee, R. Y. W., 2013. Normal kinematics of the neck: The interplay between the cervical and thoracic spines. *Manual Therapy*, 18, 431-437.

Tseng, Y.-L., Wang, W. T. J., Chen, W.-Y., Hou, T.-J., Chen, T.-C. and Lieu, F.-K., 2006. Predictors for the immediate responders to cervical manipulation in patients with neck pain. *Manual Therapy*, 11 (4), 306-315.

Tuchin, P. J., 1998. The effect of chiropractic spinal manipulative therapy on salivary cortisol levels. *Journal of Australasian Chiropractic and Osteopathy*, 7, 86-92.

Turk, D. C., Dworkin, R. H., Allen, R. R., Bellamy, N., Brandenburg, N., Carr, D. B., Cleeland, C., Dionne, R., Farrar, J. T., Galer, B. S., Hewitt, D. J., Jadad, A. R., Katz, N. P., Kramer, L. D., Manning, D. C., McCormick, C. G., McDermott, M. P., McGrath, P., Quessy, S., Rappaport, B. A., Robinson, J. P., Royal, M. A., Simon, L., Stauffer, J. W., Stein, W., Tollett, J. and Witter, J., 2003. Core outcomes domains for chronic pain clinical trials: IMMPACT recommendations. *Pain*, 106, 337-345.

UK BEAM, 2004. United Kingdom back pain exercise and manipulation (UK BEAM) randomised trial: effectiveness of physical treatments for back pain in primary care. *British Medical Journal*, 329 (7479), 1377-1384.

van der Velde, G., Hogg-Johnson, S., Bayoumi, A., Cassidy, J. D., Cote, P., Boyle, E., Llewellyn-Thomas, H., Chan, S., Subrata, P., Hoving, J. L., Hurwitz, E., Bombardier, C. and Krahn, M., 2008. Identifying the Best Treatment Among Common Nonsurgical Neck Pain Treatments: A Decision Analysis. *Spine*, 33(4S) Neck Pain Task Force (Supplement), S184-S191.

van Loon, I. H. M., Mellor, F. E. and Breen, A., 2012. Accuracy and repeatability of sagittal translation of lumbar vertebrae in vitro and in vivo using quantitative fluoroscopy. *Clinical Chiropractic*, 15 (3–4), 135-146.

van Mameren, H., Drukker, J., Sances, H. and Beursgens, J., 1990. Cervical spine motion in the sagittal plane (1): range of motion of actually performed movements, an x-ray cinematographic study. *European Journal of Morphology*, 28 (1), 47-68.

van Mameren, H., Sanches, H., Beursgens, J. and Drukker, J., 1992. Cervical spine motion in the sagittal plane II: position of segmental averaged instantaneous centres of rotation - a cineradiographic study. *Spine*, 17 (5), 467-474.

Vernon, H. T. and Mior, S., 1991. The neck disability index: a study of reliability and validity. *Journal of Manipulative & Physiological Therapeutics*, 14 (7), 409-415.

Vernon, H. T., Humphreys, B. K. and Hagino, C., 2006. The outcome of control groups in clinical trials of conservative treatments for chronic mechanical neck pain: a systematic review. *BMC Musculoskeletal Disorders*, 7 (58).

Vernon, H. T., Proctor, D., Bakalovski, D. and Moreton, J., 2010. Simulation tests for cervical nonorganic signs: a study of face validity. *Journal of Manipulative & Physiological Therapeutics*, 33 (1), 20-28.

Vernon, H. T., Triano, J. T., Ross, J. K., Tran, S. K., Soave, D. M. and Dinulos, M. D., 2012. Validation of a novel sham cervical manipulation procedure. *The Spine Journal*, 12 (11), 1021-1028.

Vernon, H. T., Triano, J. T., Soave, D. M., Dinulos, M. D., Ross, J. K. and Tran, S., 2013. Retention of blinding at follow-up in a randomized clinical study using a sham-control cervical manipulation procedure for neck pain: secondary analyses from a randomized clinical study. *Journal of Manipulative & Physiological Therapeutics*, 36(8), 522-526.

Vincent, K., Maigne, J.-Y., Fischhoff, C., Lanlo, O. and Dagenais, S., 2013. Systematic review of manual therapies for nonspectific neck pain. *Joint Bone Spine*, 80 (5), 508-515.

Vogt, L., Segieth, C., Banzer, W. and Himmelreich, H., 2007. Movement behaviour in patients with chronic neck pain. *Physiotherapy Research International*, 12 (4), 206-121.

Vos, C., Verhagen, A., Passchier, J. and Koes, B., 2007. Management of acute neck pain in general practice: a prospective study. *British Journal of General Practice*, 57, 23-28.

Waddell, G., 2004. *The Back Pain Revolution. 2nd edition*. London: Churchill Livingstone.

Wagennaar, J. P., 2000. *A Survey of presenting complaints at the AECC outpatient clinic with an evaluation of the AECC patient demographic/morbidity database.* Thesis (BSc(Hons)). Bournemouth University.

Walker, B. F. and French, S. D., 2012. Pain in the Neck: Many (Marginaly Different) Treatment Choices. *Annals of Internal Medicine*, 156, 52-53.

Walter, S. D., Eliasziw, M. and Donner, A., 1998. Sample size and optimal designs for reliability studies. *Statistics in Medicine*, 17, 101-110.

Walters, S. J. and Brazier, J. E., 2005. Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. *Quality of Life Research*, 14 (6), 1523-1532.

Walton, D. M., Carroll, L. J., Kasch, H., Sterling, M., Verhagen, A. P., MacDermid, J. C., Gross, A., Santaguida, P. L., Carlesso, L. and ICON, 2013. An Overview of Systematic Reviews on Prognostic Factors in Neck Pain: Results from the International Collaboration on Neck Pain (ICON) Project. *The Open Orthopaedics Journal*, 7 (Suppl 4), 494-505.

Wand, B. M., Heine, P. J. and O'Connell, N. E., 2012. Should we abandon cervical spine manipulation for mechanical neck pain? Yes. *British Medical Journal*, 344.

Wang, L. and Weber, 2005. *MRI and X-ray Visualization.* United States 2005/0215874 A1.

Webb, A. L., Collins, P., Rassoulian, H. and Mitchell, B. S., 2011. Synovial folds - a pain in the neck? *Manual Therapy*, 16 (2), 118-124.

Weir, J. P., 2005. Quantifying Test-Retest Reliability Using the Intraclass Correlation Coefficient and the *SEM*. *Journal of Strength and Conditioning Research*, 19 (1), 231-240.

Weishaupt, D., Schweitzer, M. E., DiCuccio, M. N. and P.E., W., 2001. Relationships of cervical, thoracic and lumbar bone mineral density by quantitative CT. *Journal of Computer Assisted Tomography*, 25 (1), 146-150.

Wermeling, M., Scherer, M. and Himmel, W., 2011. GPs' experiences of managing non-specific neck pain - a qualitative study. *Family Practice*, 28 (3), 300-306.

Whelan, T. L., Dishman, J. D., Burke, J., Levine, S. and Sciotti, V., 2002. The effect of chiropractic manipulation on salivary cortisol levels. *Journal of Manipulative and Physiological Therapeutics*, 25 (3), 149-153.

White, A. A. and Panjabi, M. M., 1990. *Clinical Biomechanics of the Spine*. 2nd. Philadelphia: JB Lippincott.

Whittingham, W. and Nilsson, N., 2001. Active range of motion in the cervical spine increases after spinal manipulation (toggle recoil). *Journal of Manipulative and Physiological Therapeutics*, 24 (9), 552-555.

Williams, M. A., McCarthy, C. J., Chorti, A., Cooke, M. W. and Gates, S., 2010. A systematic review of reliability and validity studies of methods for measuring active and passive cervical range of motion. *Journal of Manipulative & Physiological Therapeutics*, 33 (2), 138-155.

Williams, M. A., Williamson, E., Gates, S. and Cooke, M. W., 2012. Reproducibility of the cervical range of motion (CROM) device for individuals with sub-acute whiplash associated disorders. *European Spine Journal*, 21, 872-878.

Wirth, B., Amstalden, M., Perk, M., Boutellier, U. and Humphreys, B. K., 2014. Respiratory dysfunction in patients with chronic neck pain – influence of thoracic spine and chest mobility. *Manual Therapy* [online], In Press. Available from: http://www.manualtherapyjournal.com/article/S1356-689X(14)00076-9/abstract [Accessed 25/5/2014].

Woesner, M. E. and Mitts, M. G., 1972. The evaluation of cervical spine motion below C2: a comparison of cineroentgenographic and conventional roentgenographic methods. *American Journal of Roentgenology*, 115 (1), 148-154.

Wolsko, P. M., Eisenberg, D. M., Davis, R. B., Kessler, R. and Phillips, R. S., 2003. Patterns and perceptions of care for treatment of back and neck pain. *Spine*, 28 (3), 292-298.

Wong, K., Luk, K., Leong, J., Wong, S. and Wong, K., 2006. Continuous dynamic spinal motion analysis. *Spine*, 31 (4), 414-419.

Wong, K. W. N., Leong, J. C. Y., Chan, M.-K. and Lu, W. W., 2004. The flexion-extension profile of lumbar spine in 100 healthy volunteers. *Spine*, 29 (15), 1636-1641.

Wood, T. G., Colloca, C. J. and Matthews, R., 2001. A pilot randomized clinical trial on the relative effect of instrumental (MFMA) versus manual (HVLA) manipulation in the treatment of cervical spine dysfunction. *Journal of Manipulative and Physiological Therapeutics*, 24 (4), 260-271.

Woodhouse, A. and Vasseljen, O., 2008. Altered motor control patterns in whiplash and chronic neck pain. *BMC Musculoskeletal Disorders*, 9, 90.

Wu, S., Kuo, L., Lan, H., Tsai, S., Chen, C. and Su, F., 2007. The quantitative measurements of the intervertebral angulation and translation during cervical flexion and extension. *European Spine Journal*, 16, 1435-1444.

Wu, S., Kuo, L., Lan, H., Tsai, S., Chen, C. and Su, F., 2010. Segmental Percentage Contributions of Cervical Spine During Difference Motion Ranges of Flexion and Extension. *Journal of Spinal Disorders*, 23 (4), 278-284.

Wynd, S., Westaway, M., Vohra, S. and Kawchuk, G., 2013. The quality of reports on cervical arterial dissection following cervical spinal manipulation. *PLOS ONE*, 8 (3), e59170.

Yeomans, S. G., 1992. The assessment of cervical intersegmental mobility before and after spinal manipulative therapy. *Journal of Manipulative & Physiological Therapeutics*, 15 (2), 106-114.

Yochum, T. R. and Rowe, L. J., 2004. *Essentials of Skeletal Radiology*. 3rd. Vol. 1. London: Lippincott Williams & Wilkins.

Yoganandan, N., Kumaresan, S. and Pintar, F. A., 2001. Biomechanics of the cervical spine Part 2: Cervical spine soft tissue responses and biomechanical modeling. *Clinical Biomechanics*, 16 (1), 1-27.

Yoganandan, N., Pintar, F. A., Stemper, B. D., Baisden, J. L., Aktay, R., Shender, B. S. and Paskoff, G., 2006a. Bone Mineral Density of Human Female Cervical and Lumbar Spines From Quantitative Computed Tomography. *Spine*, 31 (1), 73-76.

Yoganandan, N., Pintar, F. A., Stemper, B. D., Baisden, J. L., Aktay, R., Shender, B. S., Paskoff, G. and Laud, P., 2006b. Trabecular bone density of male human cervical and lumbar vertebrae. *Bone*, 39, 336-344.

Zhu, Y., Haldeman, S., Hsieh, C.-Y. J., Wu, P. and Starr, A., 2000. Do cerebral Potentials to Magnetic Stimulation of Paraspinal Muscles Reflect Changes in Palpable Muscul Spasm, Low Back Pain and Acitivity Scores? *Journal of Manipulative & Physiological Therapeutics*, 23 (7), 458-464.

Zusman, M., 1986. Spinal Manipulative Therapy: Review of some proposed mechanisms, and a new hypothesis. *The Austrailian Journal of Physiotherapy*, 32 (2), 89-99.

Appendices

Appendix 1: MDCs reported in the literature for regional cervical ROM measurement

Study	Participants	Measurement device	Time between measures	Observers	MDC*	
(Hoving et al. 2005)	32 patients with NP	EDI-320 (Cybex)	5mins (intra)	1	11.1° (Flex-ext)	
			10mins (inter)	2	Not reported	
(Piva et al. 2006)	30 patients with NP	Gravity inclinometer	≤ 20mins (inter)	2	16° (Flex); 16° (Ext)	
(Cleland et al. 2008)	22 patients with NP	Universal goniometer	5mins	2	18.8° (Flex);13.0 (Ext)	
(Dunleavy and Goldberg 2013)	36 patients with NP	CROM	0mins	1 (5 in different locations)	Habitual posture	12.2° (Flex) 9.7° (Ext)
					Position-ed	9.7° (Flex) 7.5° (Ext)
(Fletcher and Bandy 2008)*	22 patients with NP	CROM	30secs	1	9.6° (Flex); 7.0° (Ext)	
	25 healthy volunteers		30secs	1	6.5°(Flex); 9.3° (Ext)	
(Audette et al. 2010)*	20 healthy volunteers	CROM	48hrs	1	6.5°(Flex); 5.1°(Ext)	
(Shahidi et al. 2012)	19 patients with NP	Gravity inclinometer	3-14 days	2	16° (Flex); 16° (Ext)	
	20 healthy volunteers		3-14 days	2	14° (Flex); 15° (Ext)	

*MDCs reported by Fletcher and Bandy (2008) and Audette et al (2010) are MDC_{90}, all others MDC_{95}

Appendix 2: Number of inter-vertebral levels successfully tracked by two observers and those that measured at least 5° sagittal rotation (for IAR calculations)

	No. of inter-vertebral levels successfully tracked by two observers		No. of inter-vertebral levels ≥ 5° sagittal rotation	
Inter-vertebral level	Flexion	Extension	Flexion	Extension
C1/2	9	9	6	1
C2/3	10	9	3	4
C3/4	10	9	8	6
C4/5	10	10	5	8
C5/6	9	9	3	5
Total	48	46	25	24
Percentage of total levels	96%	92%	50%	48%

The two observers disagreed in their judgements of successful tracking for three inter-vertebral levels (one each of C1/2 in flexion and extension and C5/6 in flexion) so data were not available for analysis in these three instances.

Appendix 3: *Inter-observer* repeatability (agreement and reliability) for angular range

Inter-vertebral level	Standard error of measurement (°)		Intra-class correlation coefficient (95% confidence interval)	
	Flexion	Extension	Flexion	Extension
C1/2	0.8	0.4	0.96 (0.822 to 0.990)	0.97 (0.875 to 0.993)
C2/3	0.4	0.7	0.97 (0.900 to 0.993)	0.95 (0.806 to 0.988)
C3/4	0.3	1.0	0.99 (0.978 to 0.999)	0.92 (0.711 to 0.981)
C4/5	0.5	0.8	0.97 (0.891 to 0.993)	0.97 (0.886 to 0.992)
C5/6	0.3	1.0	0.99 (0.974 to 0.999)	0.97 (0.854 to 0.992)
All levels pooled	0.5	0.9	0.98 (0.960 to 0.987)	0.97 (0.943 to 0.982)

Intra-class correlation coefficient: ICC(2C,1), two-way single measure mixed effects model (consistency)

Standard error of measurement and intra-class correlation coefficients for *intra-observer* repeatability: angular range

Appendix 4: *Intra-observer* agreement for IAR - 5° sagittal rotation

Inter-vertebral level	No. of inter-vertebral levels ≥ 5° sagittal rotation		Standard error of measurement (mm)			
			Flexion		Extension	
	Flexion	Extension	X	Y	X	Y
C1/2	8	2	2.1	1.5	-	-
C2/3	3	4	2.8	3.6	2.4	1.7
C3/4	8	6	1.9	1.4	1.7	2.9
C4/5	5	9	1.8	1.8	1.5	2.4
C5/6	5	5	1.1	2.1	1.4	0.1
All levels pooled	29	26	1.8	1.8	1.7	2.1

mm, equivalent millimetres (1 VBU = 15mm)

Standard error of measurement for *intra-observer* repeatability: IAR x, y co-ordinate locations (distance in mm from posterior-inferior corner of inferior vertebra) calculated from levels that rotated at least five degrees

Appendix 5: *Inter-observer* agreement for IAR - 5° sagittal rotation

Inter-vertebral level	No. of inter-vertebral levels ≥ 5° sagittal rotation		No. of inter-vertebral levels ≥ 5° sagittal rotation			
			Flexion		Extension	
	Flexion	Extension	X	Y	X	Y
C1/2	6	1	3.1	7.7	-	-
C2/3	3	4	2.3	2.9	0.9	0.6
C3/4	8	6	1.3	1.5	0.5	0.7
C4/5	5	8	1.2	0.8	1.9	1.2
C5/6	3	5	0.8	1.1	0.1	1.0
All levels pooled	25	24	2.0	3.5	1.4	0.9

mm, equivalent millimetres (1 VBU = 15mm)

Standard error of measurement for *inter-observer* repeatability: IAR x, y co-ordinate locations (distance in mm from posterior-inferior corner of inferior vertebra) calculated from levels that rotated at least five degrees

Appendix 6: *Intra-observer* reliability for IAR - 5° sagittal rotation

Inter-vertebral level	Intra-class correlation coefficient (95% confidence interval)			
	Flexion		Extension	
	X	Y	X	Y
C1/2	0.655 (0.112 to 0.900)	0.985 (0.935 to 0.996)	-	-
C2/3	0.360 (-1.727 to 0.979)	-0.138 (-2.494 to 0.958)	-0.040 (-0.726 to 0.937)	0.330 (-1.745 to 0.978)
C3/4	-0.165 (-1.020 to 0.664)	0.615 (-0.079 to 0.919)	0.437 (-0.749 to 0.925)	0.456 (-0.546 to 0.925)
C4/5	0.530 (-0.186 to 0.931)	-0.045 (-1.112 to 0.821)	0.613 (-0.406 to 0.937)	0.029 (-0.852 to 0.779)
C5/6	0.823 (0.022 to 0.987)	-0.184 (-1.548 to 0.872)	0.308 (-0.577 to 0.971)	0.997 (0.510 to 1.000)
All levels pooled	0.805 (0.621 to 0.904)	0.961 (0.919 to 0.982)	0.405 (-0.101 to 0.738)	0.517 (0.076 to 0.792)

Intra-class correlation coefficient: ICC(3C,1), two-way single measure mixed effects model (consistency)

Intra-class correlation coefficients for *intra-observer* repeatability: IAR x, y co-ordinate locations (distance in mm from posterior-inferior corner of inferior vertebra) calculated from levels that rotated at least five degrees

Appendix 7: *Inter-observer* reliability for IAR - 5° sagittal rotation

Inter-vertebral level	Intra-class correlation coefficient (95% confidence interval)			
	Flexion		Extension	
	X	Y	X	Y
C1/2	0.57 (-0.236 to 0.911)	0.15 (-0.719 to 0.785)	-	-
C2/3	0.32 (-2.532 to 0.979)	0.13 (-0.564 to 0.953)	0.87 (0.176 to 0.990)	0.94 (0.397 to 0.996)
C3/4	0.15 (-0.415 to 0.717)	0.42 (-0.412 to 0.853)	0.89 (0.083 to 0.992)	0.96 (0.463 to 0.997)
C4/5	0.79 (-0.165 to 0.977)	0.74 (-0.331 to 0.970)	0.22 (-0.598 to 0.832)	0.25 (-0.870 to 0.858)
C5/6	0.74 (-0.385 to 0.992)	-0.08 (-0.866 to 0.937)	0.19 (-0.003 to 0.899)	0.92 (-0.172 to 0.998)
All levels pooled	0.80 (0.599 to 0.904)	0.78 (0.574 to 0.896)	0.55 (0.112 to 0.809)	0.91 (0.774 to 0.967)

Intra-class correlation coefficient: ICC(2C,1), two-way single measure mixed effects model (consistency)

Intra-class correlation coefficients for *inter-observer* repeatability: IAR x, y co-ordinate locations (distance in mm from posterior-inferior corner of inferior vertebra) calculated from levels that rotated at least five degrees

Appendix 8: Pre-study form for healthy volunteers

ANGLO-EUROPEAN COLLEGE OF CHIROPRACTIC

Bournemouth University

IMRCI Institute for Musculoskeletal Research & Clinical Implementation

Pre-study healthy volunteer form V3: 6/11/12

Office use only:

Participant ID_____ Eligibility_____

Your name_____
Last First

Telephone (Home)_____(Mobile)_____Email_____

Address_____

Date of Birth_____ Age_____ Sex(M/F)_____
Day/month/year

Q1.	Have you had neck pain that prevented normal activity for at least one day in the past year?	☐ Yes	☐ No
Q2.	Have you ever had neck surgery?	☐ Yes	☐ No
Q3.	Have you had a CT scan of your chest, abdomen,or pelvis or interventional procedures under radiological control (such as angiography) in the past two years?	☐ Yes	☐ No
Q4.	Are you participating in any other research study at the moment?	☐ Yes	☐ No
Q5.	Have you received any manipulation to your neck or upper back in the past week?	☐ Yes	☐ No
Q6.	Would you like to be contacted when your spinal motion has been analysed to view the motion graphs produced?	☐ Yes	☐ No

Spinal manipulation and cervical intervertebral motion

Appendix 9: Pre-study form for patients

ANGLO-EUROPEAN COLLEGE OF CHIROPRACTIC

Bournemouth University

IMRCI

Pre-study patient form V2: 17/08/12

Office use only:

Participant ID_____ Eligibility_____

Your name_____

Q1. Do you have pain within the area shown on either diagram below? ☐ Yes ☐ No

Q2. Have you had this pain for at least two weeks? ☐ Yes ☐ No

Q3. Have you received *any* manual therapy, such as chiropractic, osteopathy, physiotherapy, massage or similar for the neck pain you have now? ☐ Yes ☐ No

Q4. Is the neck pain you have now related to an accident or trauma e.g. a car accident? ☐ Yes ☐ No

Q5. Are you currently involved in a claim for compensation associated with the neck pain you have now? ☐ Yes ☐ No

Q6. Have you been diagnosed with depression within the last year? ☐ Yes ☐ No

Q7. Have you been diagnosed with fibromyalgia? ☐ Yes ☐ No

Q8. Have you previously had surgery to your neck? ☐ Yes ☐ No

Q9. Is your *main problem* arm pain rather than neck pain? ☐ Yes ☐ No

Q10. Are you currently involved in any other research study? ☐ Yes ☐ No

Spinal manipulation and cervical intervertebral motion

Appendix 10: Consent Form

ANGLO-EUROPEAN COLLEGE OF CHIROPRACTIC

Bournemouth University

IMRCI Institute for Musculoskeletal Research & Clinical Implementation

CONSENT FORM

Title of project: A study of changes in motion of bones in the neck after spinal manipulative therapy

Name of Researcher: Jonathan Branney

Office use only:

Participant ID_____

Please tick

1. I confirm that I have read and understood the information sheet dated 26/4/11 (version 2) for the above study. I have had the opportunity to consider the information, to ask questions and have 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 all data will be anonymised and may be used in future studies. ☐
4. I agree to my GP being informed of my participation in the study. ☐

GP's Details: Name.....

Surgery Address.....

.....

.....

5. I agree to take part in the above study. ☐

Name of participant	Date	Signature
.....	.....	.....

Name of person taking consent	Date	Signature
.....	.....	.....

Spinal manipulation and cervical intervertebral motion
V1: 22/3/11 (healthy volunteers)

Appendix 11: Patient Information Sheet

18. Further information and contact details

Mr Jonathan Branney
Research Fellow, IMRCI
01202 436277
jbranney@aecc.ac.uk

Institute of Musculoskeletal Research and Clinical Implementation (IMRCI)
Anglo-European College of Chiropractic
13-15 Parkwood Road
Bournemouth
BH5 2DF

Professor Alan Breen
Director of IMRCI
01202 436275
imrci.abreen@aecc.ac.uk

ANGLO-EUROPEAN COLLEGE OF CHIROPRACTIC

BU Bournemouth University

IMRCI Institute for Musculoskeletal Research & Clinical Implementation

Patient Information Sheet

A study of changes in motion of bones in the neck after spinal manipulative therapy

I would like to invite you to take part in my PhD study. Before you decide I would like you to understand why the research is being done and what it would involve for you. **I will go through the information sheet with you and answer any questions you have.** I suggest this should take around 5 minutes. Please feel free to talk to others about the study if you wish. Ask me if there is anything that is not clear.

1. What is the purpose of the study?

The purpose of this study is to find out if motion of the bones in the neck changes after a course of spinal manipulation, a therapy commonly used by chiropractors. Neck pain can be a real problem for people but we are still unable to find out the cause of the pain in most cases, which makes it difficult to ensure patients are getting the best treatment option. It is thought that abnormal motion of the

spinal bones in the neck can cause pain, and that spinal manipulation can change this motion, thus reducing pain.
We now have available the necessary technology to explore this, quantitative fluoroscopy (video x-rays). Using video x-rays we can observe the movement of the bones in the neck as the patient moves. By taking a video x-ray before and after a course of spinal manipulation, we can see if the motion has changed. Most importantly, we want to see if any motion changes are related to patients improving.

2. Why have I been invited?

You have been invited as your chiropractor has diagnosed you with mechanical (non-specific) neck pain, your pain has been present for at least four weeks, and you are 18-60 years of age.

3. Do I have to take part?

It is up to you to decide to join the study. I will describe the study and go through this information sheet. If you agree to take part, I will then ask you to sign a consent form. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive.

16. Who is organising and funding the research?

This study is being funded by a research fellowship awarded from the European Academy of Chiropractic: www.eacacademy.com and is supported and sponsored by AECC.

17. Who has reviewed the study?

This study has been reviewed by my PhD supervisors; Professor Alan Breen, Professor Jenni Bolton and Dr Sarah Hean. Additionally this study has been reviewed and given a favourable opinion by the NRES (National Research Ethics Service) Committee South West - Cornwall & Plymouth.

due to someone's negligence, you may have grounds for legal action for compensation against the AECC, but you may have to pay your own legal costs.

14. Will my taking part in this study be kept confidential?

Your information will be kept confidential as you would expect in any healthcare encounter. With your consent your GP will be informed of your participation and you will be asked to provide your GP's name and address on the consent form. Following review of your video x-rays all your data will have information that identifies you removed which means I will not be able to identify you from your x-rays or questionnaires.

15. What will happen to the results of the research study?

The results from this study will be presented in my PhD thesis and submitted to Bournemouth University. They will also be presented at academic conferences, published in international journals and listed on the AECC website: www.aecc.ac.uk. You may wish to occasionally check the progress of the study by looking at the website. Feel free to contact me any time [contact information at end of this document].

4. What will happen to me if I take part?

Before you are due to return to the clinic for your scheduled 'report of findings' visit where your chiropractor/intern discusses your diagnosis and treatment plan, I will speak to you on the telephone to see if you would like to take part. If you say yes, I will invite you to the AECC clinic where I will meet you. We will discuss this information sheet and if you wish to proceed I will ask you to sign three consent forms, one of which is for you to keep. I will ask you to complete a questionnaire and I will take video x-rays of your neck. Please allow around one hour for the whole procedure.

The video x-ray assessment

You will receive a video x-ray assessment, which is called OSMIA (Objective Spinal Motion Imaging Assessment), on the first day and again after four weeks of treatment. This will allow me to see if the movement of your neck bones has changed after treatment. This assessment is not currently offered as a routine test for everyone with neck pain. In the x-ray department of AECC clinic you will be shown to the changing room to change into a gown. Using a device that fits comfortably on your head I will measure your neck range of motion, forwards and backwards.

As a warm-up you will be asked to bend your head/neck forwards then backwards five times at a speed comfortable to you. You will then be invited to sit on a stool and a face-piece will be comfortably positioned against your forehead. The face-piece is attached to a motor and you will be asked to bend your neck forwards then backwards, following the movement of the face-piece.
You will be given a button which you may press at any time to stop the motor, or you can simply move away from the face-piece at any time. The purpose of the face-piece is to keep the speed at which all patients move the same, while measuring the angles you move through. Once you are happy with the set-up I will x-ray your neck as you move using the fluoroscope (x-ray machine). This procedure should take no longer than 30 minutes. Please visit http://www.aecc.ac.uk/research/imrci/osmia.aspx if you would like to observe a video of the neck procedure taking place.

Treatment

You will be invited to attend twice per week for four weeks, a total of eight treatment sessions. These will last up to 30 minutes and are provided free-of-charge. It is important that you realise the treatment options available to you will be restricted to spinal manipulation, trigger point therapy (a way of reducing tension in muscles) and light massage only.

11. What if relevant new information becomes available?

Sometimes we get new information about the treatment being studied. If this happens, I will tell you and discuss whether you should continue in the study.

12. What will happen if I don't want to carry on with the study?

You may withdraw from the study at any time, without giving a reason. However, you will not be able to withdraw data from the study once it has been collected as it will have been anonymised. Any collected data will be retained indefinitely for use in further studies. Should you still require chiropractic care you will need to pay for this as normal.

13. What if there is a problem?

If you have a concern about any aspect of the study please speak to me in the first instance and I will do my best to address your concerns [contact information at end of this document]. If you remain unhappy and wish to complain formally you can do this by contacting Professor Breen at the AECC. In the event that something does go wrong and you are harmed during the research

9. What are the side effects of any treatment received when taking part?

Around 50% of people treated with any manual therapy e.g. spinal manipulation, joint mobilisation, massage, can expect mainly minor to moderate temporary increased discomfort after treatment.
This might also include mild bruising from trigger point muscle therapy. Please inform your chiropractor/intern of any symptoms you think may be treatment side effects.
A possible link of spinal manipulation with one rare type of stroke has been investigated and the conclusion is that there is no evidence of spinal manipulation causing this. Rather the link is thought to be that patients with this rare disorder may seek care from a chiropractor or GP for relief of neck symptoms that result from the undetected stroke.

10. What happens when the research study stops?

If you require treatment beyond the four week study period you will be required to pay for this as normal. Treatment options will no longer be restricted.

Other therapy which might normally be part of the treatment plan for neck pain will not be offered. This is important so that any changes in the movement of the bones in your neck can be related to spinal manipulation alone. Manipulation will be delivered by an experienced chiropractor while any muscle treatment will be performed by your intern.

5. What will I have to do?

You will be required to attend treatment appointments twice per week for four weeks. It is important that you do so, even if you are feeling much better. The chiropractor will not treat you with manipulation if it is not needed at that particular visit. You are also asked to avoid doing any stretching or strengthening exercises for your neck at home and not to receive other neck pain treatment for four weeks. After your second video x-ray assessment you will be asked to complete some questionnaires which will take around 10 minutes and this will signify the end of your participation in the study.

6. What are the alternatives for treatment?

An effective treatment approach for mechanical neck pain is thought to be the combination of spinal manipulation or mobilisation and exercise, although the specific type of exercise that is best remains

unknown. Exercise therapy is thought to be beneficial in the long-term. If treatment is required beyond the short study period your chiropractor may discuss other options with you.

7. What are the risks of taking part?

This study involves the exposure to radiation from x-rays.
The dose involved from two video x-rays examinations of the neck is 0.02mSv, the same as two detailed x-rays of your teeth, and much less than a normal x-ray of your neck (0.08mSv). This dose is considered to be very low and equivalent to 3 day's natural background radiation in the UK. ***Females please note, x-rays may harm an unborn child. It is therefore vital that you inform me beforehand if you are pregnant or suspect you might be.*** At such low doses of radiation experts agree that it is difficult to determine what the risk is of inducing cancer, however, it is estimated that this dose results in a **1 in 1 million** increased chance over a lifetime of inducing a fatal cancer in addition to the 1 in 3 natural lifetime risk. To help you put this risk into context, the risk of being killed by lightening is 1 in 300,000 and the risk of having an accident on the road in 1 in 500.

There is a risk of an 'incidental' finding being observed on your x-ray which is not related to your neck pain. To date six patients have undergone this examination with no significant incidental findings.

As a chiropractor I am trained to interpret these examinations and if necessary they will also be reviewed by a chiropractor with specialised training in interpreting x-rays. You will be informed of any incidental findings and, with your permission, so will your GP. Such detection has the benefit of starting treatment early but in a small number of cases may have implications for future employment and insurance.

8. What are the benefits of taking part?

Spinal manipulation for neck pain has been shown to be effective for short-term pain relief. Trigger point muscle therapy and light massage are included, where necessary, to provide relief from tight, sore muscles. There may not be any direct benefit from the video x-rays examinations but I expect the information we get from this study will help improve the treatment of people with neck pain in the future. After the examination you will be invited to watch the movement of your neck bones on a television screen which many patients find fascinating.

Appendix 12: Healthy Volunteer Information Sheet

13. Who has reviewed the study?

This study has been reviewed by my PhD supervisors; Professor Alan Breen, Professor Jenni Bolton and Dr Sarah Hean. Additionally this study has been reviewed and given a favourable opinion by the NRES (National Research Ethics Service) Committee South West - Cornwall & Plymouth.

14. Further information and contact details

Mr Jonathan Branney
Research Fellow, IMRCI
01202 436277
jbranney@aecc.ac.uk

Professor Alan Breen
Director of IMRCI
01202 436275
imrci.abreen@aecc.ac.uk

Institute of Musculoskeletal Research and Clinical Implementation (IMRCI)
Anglo-European College of Chiropractic
13-15 Parkwood Road
Bournemouth
BH5 2DF

ANGLO-EUROPEAN COLLEGE OF CHIROPRACTIC

BU Bournemouth University

IMRCI Institute for Musculoskeletal Research & Clinical Implementation

Healthy Volunteer Information Sheet

A study of changes in motion of bones in the neck after spinal manipulative therapy

I would like to invite you to take part in my PhD study. Before you decide I would like you to understand why the research is being done and what it would involve for you. **I will go through the information sheet with you and answer any questions you have.** I suggest this should take around 5 minutes. Please feel free to talk to others about the study if you wish. Ask me if there is anything that is not clear.

1. What is the purpose of the study?

The purpose of this study is to find out if motion of the bones in the neck changes after a course of spinal manipulation, a therapy commonly used by chiropractors. Neck pain can be a real problem for people but we are still unable to find out the cause of the pain in most cases, which makes it difficult to ensure patients are getting the best treatment option. It is thought that abnormal motion of the spinal bones in the neck can cause pain, and that spinal manipulation can change this motion, thus reducing pain. We now have available the necessary technology to explore this, quantitative fluoroscopy (video x-rays). Using video x-rays we can observe the movement of the bones in the neck as the patient moves.

I wish to find out about this motion, and how it changes after manipulation, in patients with neck pain, compared to people without neck pain who have no manipulation. By taking a video x-ray before and after a course of spinal manipulation, we can see if the motion has changed. Most importantly, we want to see if any motion changes are related to patients improving, compared with untreated people without neck pain.

2. Why have I been invited?

You have been invited as you are 18-60 years of age and you replied to an advert, email, Facebook page or talk at AECC or Bournemouth University asking for healthy volunteers who fit the inclusion criteria and who would like to take part in this research study to be in the comparison group. This information sheet will provide you with more details about the study.

3. Do I have to take part?

It is up to you to decide to join the study. You will have at least one week to consider taking part before I contact you. I will describe the study and go through this information sheet. If you agree to take part, I will then ask you to sign two consent forms. You are free to withdraw at any time, without giving a reason, at any time prior to the taking of the video x-rays.

4. What will happen to me if I take part?

Your name, sex, age, email, address, and telephone number will be stored on a password-protected database.

10. Will my taking part in this study be kept confidential?

Your information will be kept confidential as you would expect in any healthcare encounter. Your details will be kept on a password-protected database until 36 matched healthy volunteers have been recruited. With your consent your GP will be informed of your participation and you will be asked to provide your GP's name and address on the consent form. Following review of your video x-rays all your data will have information that identifies you removed which means I will not be able to identify you from your x-rays.

11. What will happen to the results of the research study?

The results from this study will be presented in my PhD thesis and submitted to Bournemouth University. They will also be presented at academic conferences, published in international journals and listed on the AECC website: www.aecc.ac.uk. You may wish to occasionally check the progress of the study by looking at the website. Feel free to contact me any time [contact information at end of this document].

12. Who is organising and funding the research?

This study is being funded by a research fellowship awarded from the European Academy of Chiropractic: www.eacacademy.com and is supported and sponsored by AECC.

Spinal manipulation and cervical intervertebral motion V2: 26/4/11

neck pain. After the examination you will be invited to watch the movement of your neck bones on a television screen which many patients find fascinating. If you are a chiropractic student or faculty member you will probably find the experience educational.

8. What will happen if I don't want to carry on with the study?

You may withdraw from the study at any time, without giving a reason. This will not have a detrimental effect on your education if you are a student or your employment if you are a staff member. However, you will not be able to withdraw data from the study once it has been collected as it will have been anonymised. Any collected data will be retained indefinitely for use in further studies.

9. What if there is a problem?

If you have a concern about any aspect of the study please speak to me in the first instance and I will do my best to address your concerns [contact information at end of this document]. If you remain unhappy and wish to complain formally you can do this by contacting Professor Breen at the AECC. In the event that something does go wrong and you are harmed during the research due to someone's negligence, you may have grounds for legal action for compensation against the AECC, but you may have to pay your own legal costs.

For every patient with neck pain who takes part in the research I will match one healthy volunteer based on age and sex.

It may be that you are NOT matched to a patient, in which case your contact details will be destroyed after 36 patients have been recruited – I will inform you by email if this is the case after the 12 month recruitment period. If you are matched you will be invited to attend the x-ray department at the AECC clinic at a time convenient to you. I will meet with you, go through this information sheet, and explain the video x-ray assessment. If you wish to proceed you will be asked to sign three consent forms, one of which is for you to keep. You will receive two video x-ray assessments, called OSMIA (Objective Spinal Motion Imaging Assessment). This will allow me to see the movement of your neck bones. The reason for the second video x-ray, four weeks after the first, is to see if neck bone motion changes over time or not.

<u>The video x-ray assessment</u>

In the x-ray department of AECC clinic you will be shown to the changing room to change into a gown. Using a device that fits comfortably on your head I will measure your neck range of motion, forwards and backwards. As a warm-up you will be asked to bend your head/neck forwards then backwards five times at a speed comfortable to you. You will then be invited to sit on a stool and a face-piece will be comfortably positioned against your forehead. The face-piece is attached to a motor and you will be asked to bend your neck forwards then backwards, following the movement of the face-piece.

Spinal manipulation and cervical intervertebral motion V2: 26/4/11

You will be given a button which you may press at any time to stop the motor, or you can simply move away from the face-piece at any time. The purpose of the face-piece is for you to follow to keep the speed at which all participants move the same, while measuring the angles you move through. Once you are happy with the set-up I will x-ray your neck as you move using the fluoroscope (x-ray machine). This procedure should take no longer than 30 minutes. Please visit http://www.aecc.ac.uk/research/imrci/osmia.aspx if you would like to observe a video of the neck procedure taking place.

5. What will I have to do?

You will be required to attend the x-ray department at the AECC clinic on two occasions, four weeks apart, where you will receive a video x-ray assessment of your neck. You will be asked to report any activity-limiting neck pain, or neck pain experienced for 24 hours or more, during the four week interval between video x-rays. If you have experienced neck pain during this time and/or you have received neck or upper back manipulation, you will not receive a second video x-ray. The data from the first video x-ray will remain important and will be used in the study.

6. What are the risks of taking part?

This study involves the exposure to radiation from x-rays.

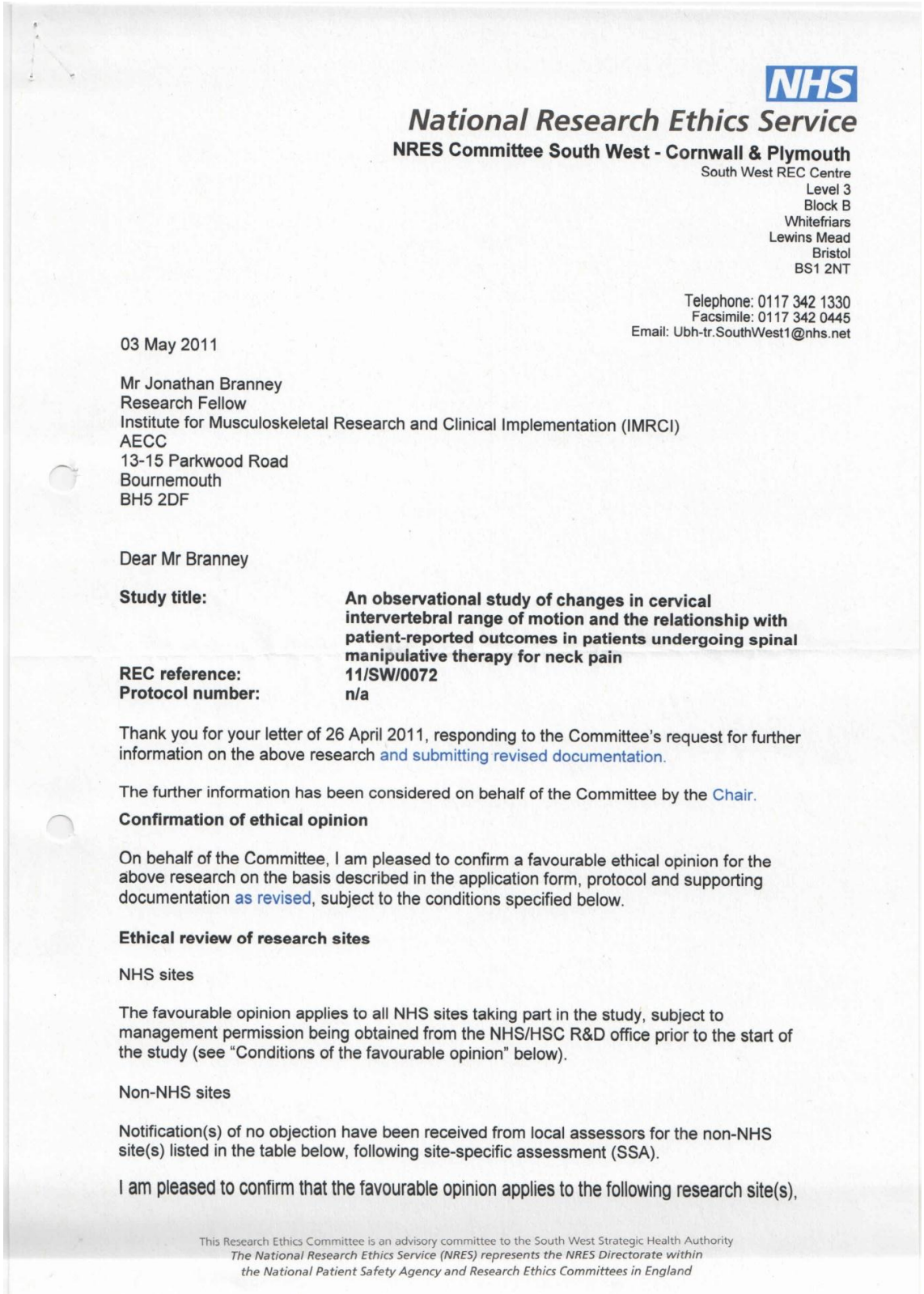
The dose involved from two video x-rays examinations of the neck is around 0.02mSv, the same as two detailed x-rays of your teeth, and much less than a normal x-ray of your neck (0.08mSv). This dose is considered to be very low and equivalent to 3 day's natural background radiation in the UK. ***Females please note, x-rays may harm an unborn child. It is therefore vital that you inform me beforehand if you are pregnant or suspect you might be.*** At such low doses of radiation experts agree that it is difficult to determine what the risk is of inducing cancer, however, it is estimated that this dose results in a **1 in 1 million** increased chance over a lifetime of inducing a fatal cancer in addition to the 1 in 3 natural lifetime risk. To help you put this risk into context, the risk of being killed by lightning is 1 in 300,000 and the risk of having an accident on the road is 1 in 500. There is a risk of an 'incidental' finding being observed on your x-ray. To date six patients have undergone this examination with no significant incidental findings. As a chiropractor I am trained to interpret these examinations and if necessary they will also be reviewed by a chiropractor with specialised training in interpreting x-rays. You will be informed of any incidental findings and, with your permission, so will your GP. Such detection has the benefit of starting treatment early but in a small number of cases may have implications for future employment and insurance.

7. What are the benefits of taking part?

There are no specific educational or employment advantages to be gained by taking part. There may be no overall benefit to you from this study but the information I receive might help improve the treatment of patients with

Spinal manipulation and cervical intervertebral motion V2: 26/4/11

Appendix 13: Ethical approval from National Research Ethics Service



NHS

National Research Ethics Service

NRES Committee South West - Cornwall & Plymouth

South West REC Centre
Level 3
Block B
Whitefriars
Lewins Mead
Bristol
BS1 2NT

Telephone: 0117 342 1330
Facsimile: 0117 342 0445
Email: Ubh-tr.SouthWest1@nhs.net

03 May 2011

Mr Jonathan Branney
Research Fellow
Institute for Musculoskeletal Research and Clinical Implementation (IMRCI)
AECC
13-15 Parkwood Road
Bournemouth
BH5 2DF

Dear Mr Branney

Study title: **An observational study of changes in cervical intervertebral range of motion and the relationship with patient-reported outcomes in patients undergoing spinal manipulative therapy for neck pain**

REC reference: **11/SW/0072**

Protocol number: **n/a**

Thank you for your letter of 26 April 2011, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

Notification(s) of no objection have been received from local assessors for the non-NHS site(s) listed in the table below, following site-specific assessment (SSA).

I am pleased to confirm that the favourable opinion applies to the following research site(s),

This Research Ethics Committee is an advisory committee to the South West 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 14: Comparison of mean (SD) healthy volunteer group combined flexion-extension angular range data (°) with previous studies

	Plain film x-ray [1] n = 241	Plain film x-ray [2] n = 128	Plain film x-ray n = 126	Plain film x-ray n = 26	Cineradiography [3] n = 10	Fluoroscopy [4] n = 140	Quantitative fluoroscopy [5] n = 30
Age range	12 – 79yrs	16 – 58yrs	Not published	Not published	19 – 22yrs	18 – 64+yrs	19 – 67yrs
Mean (SD) age	See below [6]	33	31.9 (7.2)	28.7 (7.7)	Not published	Not published	40.9 (13.1)
Male: female ratio	1:2 [7]	1:2.5	1:0.8	1:1.7	1:0	1:1	1:2.5
C1/2	-	11.3 (4.7)	-	-	15.9	-	9.2 (5.1)
C2/3	9.3 (3.8)	8.2 (3.3)	10.0 (3.0)	9.6 (3.2)	13.4	9.9 (3.7)	10.1 (3.9)
C3/4	14.3 (5.1)	14.2 (4.7)	15.7 (3.5)	15.6 (4.8)	17.6	15.2 (3.2)	14.5 (6.2)
C4/5	16.9 (5.5)	16.3 (5.3)	17.9 (4.0)	18.6 (4.7)	20.4	16.9 (3.8)	16.5 (5.4)
C5/6	17.3 (7.4)	16.6 (6.7)	18.9 (4.6)	18.3 (4.9)	22.6	15.8 (4.2)	13.7 (7.1)
Totals	57.8	66.6	62.5	62.1	89.8	57.8	64.0
Study	(Deitz et al. 2011)	(Frobin et al. 2002)	(Puglisi et al. 2004)	(Puglisi et al. 2007)	(Van Mameren et al. 1990)	(Reitman et al. 2004)	This study

1. Deitz et al. (2011) aggregated the findings of the four flexion-extension plain film x-ray studies they found to have the most sound methodology and reporting (Aho et al. 1955; Dvorak et al. 1988; Frobin et al. 2002; Lind et al. 1989)
2. Frobin et al (2002) was the only plain-film x-ray study of the four identified by Dietz et al. (2011) to measure C1/2. The data above are the means of the means published by sex. SD of age not published.
3. Standard deviations not published. Data represent the mean of the mean values published from a starting position of full flexion, and starting position of full extension
4. Standard deviations calculated from the published lower and upper limits either side of the mean
5. Data from this study, baseline flexion and extension combined – assumed that neutral position was identical prior to flexion and extension motion commencing
6. Mean(SD) age and range of separate study samples as follows: 25.3yrs (4.8) (calculated from published raw data), range 16-30yrs (Aho et al. 1955); 30yrs (standard deviation not published), range 22-47yrs (Dvorak et al. 1988); mean not published, range 12-79 (Lind et al. 1989); 33yrs (standard deviation not published), range 16-58yrs (Frobin et al. 2002)
7. Calculated by combining the following separate male: female ratios: 1:1.1 (Aho et al. 1955); 1:2.5 (Dvorak et al. 1988); 1:1 (Lind et al. 1989); 1:2.5 (Frobin et al. 2002)

Appendix 15: Comparison of mean (SD) healthy volunteer group flexion and extension angular range data (°) with previous fluoroscopy studies

	Fluoroscopy n = 56		**Fluoroscopy n = 48**		**Quantitative Fluoroscopy n = 30**	
Age range	20 – 30yrs		20 – 30yrs		19 -67yrs	
Age, mean (SD)	25.8 (2.7)		25.2 (3.4)		40.9 (13.1)	
Male: female ratio	1:1		1:1		1:2.5	
Direction	Flexion	Extension	Flexion	Extension	Flexion	Extension
C1/2	-	-	-	-	7.4 (3.5)	2.9 (2.5)
C2/3	5.8 (2.8)	7.7 (3.7)	5.5 (2.5)	7.6 (3.9)	5.9 (2.8)	4.7 (3.7)
C3/4	7.3 (3.8)	10.0 (5.6)	7.8 (3.3)	9.8 (5.1)	6.6 (2.8)	8.2 (5.5)
C4/5	10.0 (6.4)	12.6 (5.2)	10.0 (3.4)	12.3 (4.0)	6.1 (3.4)	11.0 (5.8)
C5/6	9.6 (6.1)	9.4 (6.7)	9.8 (4.8)	9.4 (4.5)	5.8 (3.9)	8.4 (4.9)
Total	32.7	39.7	33.1	39.1	31.7	35.1
Study	(Wu et al. 2007)		(Wu et al. 2010)		This study	

Appendix 16: Baseline mean (SD) flexion inter-vertebral angular ranges in patients and healthy volunteers

	Number of levels tracked		Healthy volunteers n = 30	Patients n = 29		
	HV	P	Mean (SD)	Mean (SD)	Difference (95%CI)	p value†
C1/2	28	29	7.4 (3.5)	7.7 (3.7)	-0.4 (-2.3 to 1.6)	0.72
C2/3	29	29	5.9 (2.8)*	5.6 (3.1)	0.2 (-1.3 to 1.9)	0.73
C3/4	29	29	6.6 (2.8)	6.9 (3.8)	-0.3 (-2.1 to 1.4)	0.71
C4/5	30	29	6.1 (3.4)*	5.8 (2.8)	0.3 (-1.5 to 1.8)	0.91
C5/6	30	28	5.8 (3.8)	4.9 (2.9)*	0.9 (-1.2 to 2.8)	0.46
C1/2-C5/6	146	144	32.2 (11.3)	30.7 (8.9)	1.5 (-3.9 to 6.9)	0.58

SD, standard deviation; *HV*, healthy volunteers; *P*, patients; *95% CI*, 95% Confidence Interval; p-values are 2-sided; †, (unpaired) *t* test; *, data from a non-normal distribution

Appendix 17: Baseline median (interquartile range) flexion inter-vertebral angular ranges in patients and healthy volunteers

	Healthy volunteers n = 30	Patients n = 29		
	Median (25, 75)	Median (25, 75)	Difference (95%CI)	P value‡
C1/2	7.4 (5.9, 10.0)	7.4 (5.4, 9.8)	-0.1 (-2.16 to 1.69)	0.96
C2/3	5.2 (4.3, 6.9)	5.6 (3.4, 6.8)	0.2 (-1.21 to 1.70)	0.80
C3/4	6.2 (5.0, 8.1)	6.6 (3.6, 10.2)	-0.2 (-2.28 to 1.61)	0.81
C4/5	5.8 (3.1, 7.5)	5.1 (3.5, 7.8)	0.1 (-1.48 to 1.84)	0.91
C5/6	5.3 (2.8, 8.2)	4.5 (3.0, 6.5)	0.8 (-1.18 to 2.80)	0.46
C1/2-C5/6	32.2 (24.4, 38.2)	29.5 (24.8, 35.8)	1.2 (-4.76 to 7.18)	0.69

‡, Mann-Whitney *U* test

Appendix 18: Baseline mean (SD) extension inter-vertebral angular ranges in patients and healthy volunteers

	Number of levels tracked		Healthy volunteers n = 30	Patients n = 29		
	HV	P	Mean (SD)	Mean (SD)	Difference (95%CI)	p value†
C1/2	30	29	2.9 (2.5)*	2.7 (2.1)*	0.2 (-0.7 to 0.8)	0.94
C2/3	30	29	4.7 (3.7)*	4.1 (3.2)*	0.6 (-0.8 to 2.0)	0.57
C3/4	29	29	8.2 (5.5)	6.5 (3.7)	1.7 (-1.3 to 4.0)	0.32
C4/5	29	29	11.0 (5.8)*	8.3 (4.7)	2.6 (-0.4 to 5.71)	0.10
C5/6	29	27	8.4 (4.9)*	8.5 (4.9)	-0.03 (-2.9 to 2.6)	0.86
C1/2-C5/6	147	143	35.2 (16.0)	29.6 (12.5)	5.7 (-1.9 to 13.2)	0.14

SD, standard deviation; *HV*, healthy volunteers; *P*, patients; *95% CI*, 95% Confidence Interval; p-values are 2-sided; †, (unpaired) *t* test; *, data from a non-normal distribution

Appendix 19: Baseline median (interquartile range) extension inter-vertebral angular ranges in patients and healthy volunteers

	Healthy volunteers n = 30	**Patients n = 29**		
	Median (25, 75)	Median (25, 75)	Difference (95%CI)	P value‡
C1/2	2.2 (1.2, 3.3)	2.2 (1.2, 3.1)	0 (-0.72 to 0.83)	0.94
C2/3	3.8 (2.1, 6.0)	2.8 (2.4, 5.5)	0.6 (-0.79 to 2.0)	0.57
C3/4	7.5 (3.9, 11.1)	6.1 (3.8, 8.5)	1.3 (-1.31 to 3.96)	0.32
C4/5	9.7 (6.0, 16.6)	8.0 (4.8, 10.5)	2.4 (-0.4 to 5.7)	0.10
C5/6	7.6 (5.5, 10.1)	8.2 (4.1, 12.1)	-0.3 (-2.89 to 2.61)	0.86
C1/2-C5/6	36.1 (22.0, 43.0)	28.0 (24.6, 35.9)	5.2 (-2.91 to 12.26)	0.20

‡ Mann-Whitney *U* test; *95% CI*, 95% Confidence Interval; *(25, 75)*, interquartile range

Appendix 20: The prevalence of hypo-mobile and paradoxical inter-vertebral levels in each group at baseline by direction

	Hypo-mobile levels				Paradoxical levels			
	HV		Pt		HV		Pt	
	Flex	Ext	Flex	Ext	Flex	Ext	Flex	Ext
C1/2	2	7	1	6	10	1	4	2
C2/3	0	2	1	2	0	2	0	1
C3/4	0	4	3	3	2	3	0	2
C4/5	2	2	2	5	0	3	2	3
C5/6	3	0	2	0	1	3	1	2
Total	**7**	**15**	**9**	**16**	**13**	**12**	**7**	**10**

HV, Healthy volunteers; *P*, patients

Appendix 21: Baseline and follow-up mean (SD) flexion inter-vertebral angular ranges in healthy volunteers (n=30)

Inter-vertebral level	Levels tracked ‡	Baseline	Follow-up	Difference (95%CI)	Sig. (p) †
C1/2	28	7.4 (3.5)	8.0 (3.9)	-0.6 (-1.7 to 0.4)	0.22
C2/3	29	5.9 (2.8)*	5.7 (2.6)*	0.2 (-0.7 to 1.0)	0.72
C3/4	29	6.6 (2.8)	7.1 (2.9)	-0.5 (-1.4 to 0.5)	0.32
C4/5	30	6.1 (3.4)*	6.2 (3.1)*	-0.1 (-0.8 to 0.6)	0.80
C5/6	30	5.8 (3.8)	5.8 (3.2)	0.02 (-0.7 to 0.8)	0.95
C1/2-C5/6	146	32.2 (11.3)	33.3 (9.6)	-1.0 (-3.8 to 1.7)	0.45

SD, standard deviation; *95% CI*, 95% Confidence Interval; p-values are 2-sided; †, (paired) *t* test; *, data from a non-normal distribution; ‡, number of segments tracked at each level unchanged at follow-up

Appendix 22: Baseline and follow-up mean (SD) extension inter-vertebral angular ranges in healthy volunteers (n=30)

Inter-vertebral level	Levels tracked ‡	Baseline	Follow-up	Difference (95%CI)	Sig. (p) †
C1/2	30	2.9 (2.5)*	3.6 (2.8)*	-0.7 (-1.5 to 0.1)	0.08
C2/3	30	4.7 (3.7)*	4.2 (2.9)*	0.6 (-0.3 to 1.5)	0.16
C3/4	29	8.2 (5.5)	7.7 (5.0)	0.5 (-0.8 to 1.7)	0.45
C4/5	29	11.0 (5.8)*	10.7 (6.0)	0.3 (-0.7 to 1.2)	0.57
C5/6	29	8.4 (4.9)*	8.9 (5.5)	-0.4 (-1.4 to 0.5)	0.38
C1/2-C5/6	147	35.2 (16.0)	35.0 (15.5)	0.3 (-2.8 to 3.4)	0.85

SD, standard deviation; *95% CI*, 95% Confidence Interval; p-values are 2-sided; †, (paired) *t* test; *, data from a non-normal distribution; ‡, total number of segments tracked at each level at follow-up = 146 (C2/3 tracked in 29 participants)

Appendix 23: Assessment of the independence of the within-subject deviation from the size of the measurement in healthy volunteers

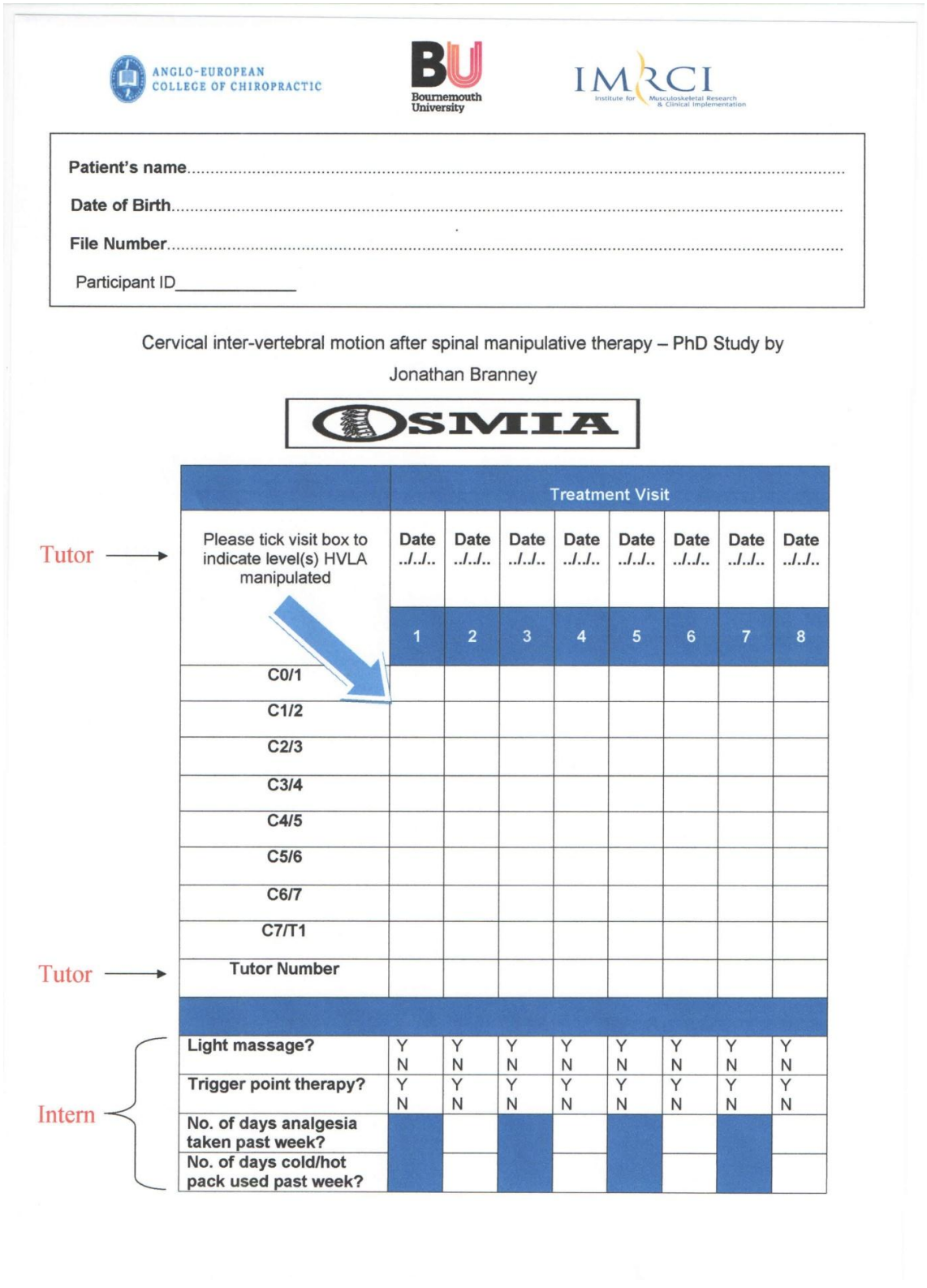
Inter-vertebral level	Kendall's tau	Sig. (p)	Kendall's tau	Sig. (p)
	Flexion	p-value	Extension	p-value
C1/2	0.21	0.156	0.34	0.008*
C2/3	0.12	0.377	0.48	0.0003*
C3/4	0.13	0.363	0.20	0.139
C4/5	0.08	0.548	-0.14	0.285
C5/6	0.23	0.078	0.11	0.423

Kendall's tau, Kendall's tau rank correlation coefficient; *, p-value significant at the 0.05 level

Appendix 24: The prevalence of hypo-mobility and paradoxical segments at baseline and follow-up in healthy volunteers

	Hypo-mobile levels				Paradoxical levels			
	Baseline		Follow-up		Baseline		Follow-up	
	Flex	Ext	Flex	Ext	Flex	Ext	Flex	Ext
C1/2	2	7	0	2	10	1	8	3
C2/3	0	2	0	2	0	2	0	0
C3/4	0	4	0	3	2	3	0	1
C4/5	2	2	1	3	0	3	0	0
C5/6	3	0	1	0	1	3	0	0
Total	**7**	**15**	**2**	**10**	**13**	**12**	**8**	**4**

Appendix 25: Form for chiropractors/interns to document treatment delivered, number of days taking pain medication and cold/hot packs used over the past week



ANGLO-EUROPEAN COLLEGE OF CHIROPRACTIC

Bournemouth University

IMRCI Institute for Musculoskeletal Research & Clinical Implementation

Patient's name.....

Date of Birth.....

File Number.....

Participant ID_____

Cervical inter-vertebral motion after spinal manipulative therapy – PhD Study by Jonathan Branney

SMIA

	Treatment Visit							
Please tick visit box to indicate level(s) HVLA manipulated	Date ../../..	Date ../../..	Date ../../..	Date ../../..	Date ../../..	Date ../../..	Date ../../..	Date ../../..
	1	2	3	4	5	6	7	8
C0/1								
C1/2								
C2/3								
C3/4								
C4/5								
C5/6								
C6/7								
C7/T1								
Tutor Number								
Light massage?	Y N	Y N	Y N	Y N	Y N	Y N	Y N	Y N
Trigger point therapy?	Y N	Y N	Y N	Y N	Y N	Y N	Y N	Y N
No. of days analgesia taken past week?								
No. of days cold/hot pack used past week?								

Tutor →

Tutor →

Intern

Appendix 26: Form for patient file to remind chiropractors/interns of the treatment protocol

ANGLO-EUROPEAN COLLEGE OF CHIROPRACTIC

Bournemouth University

IMRCI Institute for Musculoskeletal Research & Clinical Implementation

Cervical inter-vertebral motion after spinal manipulative therapy – PhD Study by Jonathan Branney

SMIA

Permitted		Not Permitted	
Cervical SMT	✓	**No other mobilization**	×
Trigger point therapy	✓	**No passive or active muscle stretching techniques**	×
Light massage	✓	**No home stretches**	×
Advice: cold/hot pack and/or analgesia if required, avoidance of aggravating activity	✓	**No rehabilitation exercises**	×

Appendix 27: Baseline questionnaire

ANGLO-EUROPEAN COLLEGE OF CHIROPRACTIC

Bournemouth University

IMRCI Institute for Musculoskeletal Research & Clinical Implementation

BASELINE QUESTIONNAIRE V1: 10/3/11

Your name_____ Office use only: Participant ID_____NRS____

This first part of the questionnaire is designed to help me better understand how your **neck pain** affects your ability to manage everyday-life activities. Please mark in each section the **one box** that applies to you. Although you may consider that two of the statements in any one section relate to you, please mark the box that **most closely** describes your situation over the past few days.

SECTION 1 - PAIN INTENSITY

- ❑ I have no neck pain at the moment.
- ❑ The pain is very mild at the moment.
- ❑ The pain is moderate at the moment.
- ❑ The pain is fairly severe at the moment.
- ❑ The pain is very severe at the moment.
- ❑ The pain is the worst imaginable at the moment.

SECTION 2 - PERSONAL CARE

- ❑ I can look after myself normally without causing extra neck pain.
- ❑ I can look after myself normally, but it causes extra neck pain.
- ❑ It is painful to look after myself, and I am slow and careful.
- ❑ I need some help but manage most of my personal care.
- ❑ I need help every day in most aspects of self -care.
- ❑ I do not get dressed. I wash with difficulty and stay in bed.

SECTION 3 – LIFTING

- ❑ I can lift heavy weights without causing extra neck pain.
- ❑ I can lift heavy weights, but it gives me extra neck pain.
- ❑ Neck pain prevents me from lifting heavy weights off the floor but I can manage if items are conveniently positioned, i.e. on a table.
- ❑ Neck pain prevents me from lifting heavy weights, but I can manage light weights if they are conveniently placed on the floor.
- ❑ I can lift only very light weights.
- ❑ I cannot lift or carry anything at all.

SECTION 4 – READING

- ❑ I can read as much as I want with no neck pain.
- ❑ I can read as much as I want with slight neck pain.
- ❑ I can read as much as I want with moderate neck pain.
- ❑ I can't read as much as I want because of moderate neck pain.
- ❑ I can't read as much as I want because of severe neck pain.
- ❑ I can't read at all.

SECTION 5 – HEADACHES

- ❑ I have no headaches at all.
- ❑ I have slight headaches that come infrequently.
- ❑ I have moderate headaches that come infrequently.
- ❑ I have moderate headaches that come frequently.
- ❑ I have severe headaches that come frequently.
- ❑ I have headaches almost all the time.

SECTION 6 – CONCENTRATION

- ❑ I can concentrate fully without difficulty.
- ❑ I can concentrate fully with slight difficulty.
- ❑ I have a fair degree of difficulty concentrating.
- ❑ I have a lot of difficulty concentrating.
- ❑ I have a great deal of difficulty concentrating.
- ❑ I can't concentrate at all.

SECTION 7 – WORK

- ❑ I can do as much work as I want.
- ❑ I can only do my usual work, but no more.
- ❑ I can do most of my usual work, but no more.
- ❑ I can't do my usual work.
- ❑ I can hardly do any work at all.
- ❑ I can't do any work at all.

SECTION 8 – DRIVING

- ❑ I can drive my car without neck pain.
- ❑ I can drive my car with only slight neck pain.
- ❑ I can drive as long as I want with moderate neck pain.
- ❑ I can't drive as long as I want because of moderate neck pain.
- ❑ I can hardly drive at all because of severe neck pain.
- ❑ I can't drive my car at all because of neck pain.

SECTION 9 – SLEEPING

- ❑ I have no trouble sleeping.
- ❑ My sleep is slightly disturbed for less than 1 hour.
- ❑ My sleep is mildly disturbed for up to 1-2 hours.
- ❑ My sleep is moderately disturbed for up to 2-3 hours.
- ❑ My sleep is greatly disturbed for up to 3-5 hours.
- ❑ My sleep is completely disturbed for up to 5-7 hours.

SECTION 10 – RECREATION

- ❑ I am able to engage in all my recreational activities with no neck pain at all.
- ❑ I am able to engage in all my recreational activities with some neck pain.
- ❑ I am able to engage in most, but not all of my recreational activities because of pain in my neck.
- ❑ I am able to engage in only a few of my recreational activities because of neck pain.
- ❑ I can hardly do recreational activities due to neck pain.
- ❑ I can't do any recreational activities due to neck pain.

ANGLO-EUROPEAN COLLEGE OF CHIROPRACTIC

Bournemouth University

IMRCI Institute for Musculoskeletal Research & Clinical Implementation

This second part of the questionnaire is to give me some understanding of your health in general. Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about	❑
I have slight problems in walking about	❑
I have moderate problems in walking about	❑
I have severe problems in walking about	❑
I am unable to walk about	❑

SELF-CARE

I have no problems washing or dressing myself	❑
I have slight problems washing or dressing myself	❑
I have moderate problems washing or dressing myself	❑
I have severe problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

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

I have no problems doing my usual activities	❑
I have slight problems doing my usual activities	❑
I have moderate problems doing my usual activities	❑
I have severe problems doing my usual activities	❑
I am unable to do my usual activities	❑

PAIN / DISCOMFORT

I have no pain or discomfort	❑
I have slight pain or discomfort	❑
I have moderate pain or discomfort	❑
I have severe pain or discomfort	❑
I have extreme pain or discomfort	❑

ANXIETY / DEPRESSION

I am not anxious or depressed	❑
I am slightly anxious or depressed	❑
I am moderately anxious or depressed	❑
I am severely anxious or depressed	❑
I am extremely anxious or depressed	❑

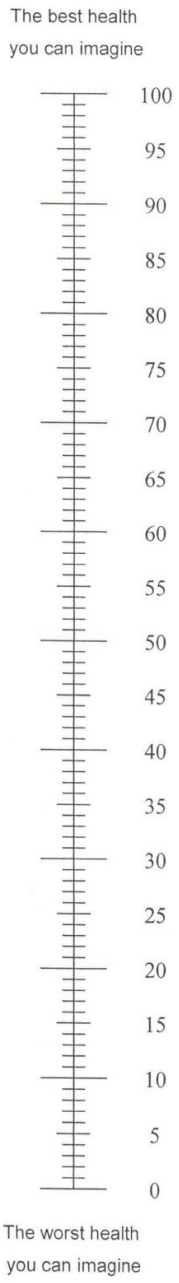
ANGLO-EUROPEAN COLLEGE OF CHIROPRACTIC

Bournemouth University

IMRCI Institute for Musculoskeletal Research & Clinical Implementation

- I would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH = ☐



Appendix 28: Four-week follow-up questionnaire

ANGLO-EUROPEAN COLLEGE OF CHIROPRACTIC

Bournemouth University

IMRCI Institute for Musculoskeletal Research & Clinical Implementation

FOLLOW-UP QUESTIONNAIRE V1: 10/3/11

Your name_____ Office use only: Participant ID_____

This first part of the questionnaire is designed to help me better understand how your **neck pain** affects your ability to manage everyday-life activities. Please mark in each section the **one box** that applies to you. Although you may consider that two of the statements in any one section relate to you, please mark the box that **most closely** describes your situation over the past few days.

SECTION 1 - PAIN INTENSITY

- ❑ I have no neck pain at the moment.
- ❑ The pain is very mild at the moment.
- ❑ The pain is moderate at the moment.
- ❑ The pain is fairly severe at the moment.
- ❑ The pain is very severe at the moment.
- ❑ The pain is the worst imaginable at the moment.

SECTION 2 - PERSONAL CARE

- ❑ I can look after myself normally without causing extra neck pain.
- ❑ I can look after myself normally, but it causes extra neck pain.
- ❑ It is painful to look after myself, and I am slow and careful.
- ❑ I need some help but manage most of my personal care.
- ❑ I need help every day in most aspects of self -care.
- ❑ I do not get dressed. I wash with difficulty and stay in bed.

SECTION 3 – LIFTING

- ❑ I can lift heavy weights without causing extra neck pain.
- ❑ I can lift heavy weights, but it gives me extra neck pain.
- ❑ Neck pain prevents me from lifting heavy weights off the floor but I can manage if items are conveniently positioned, i.e. on a table.
- ❑ Neck pain prevents me from lifting heavy weights, but I can manage light weights if they are conveniently placed on the floor.
- ❑ I can lift only very light weights.
- ❑ I cannot lift or carry anything at all.

SECTION 4 – READING

- ❑ I can read as much as I want with no neck pain.
- ❑ I can read as much as I want with slight neck pain.
- ❑ I can read as much as I want with moderate neck pain.
- ❑ I can't read as much as I want because of moderate neck pain.
- ❑ I can't read as much as I want because of severe neck pain.
- ❑ I can't read at all.

SECTION 5 – HEADACHES

- ❑ I have no headaches at all.
- ❑ I have slight headaches that come infrequently.
- ❑ I have moderate headaches that come infrequently.
- ❑ I have moderate headaches that come frequently.
- ❑ I have severe headaches that come frequently.
- ❑ I have headaches almost all the time.

SECTION 6 – CONCENTRATION

- ❑ I can concentrate fully without difficulty.
- ❑ I can concentrate fully with slight difficulty.
- ❑ I have a fair degree of difficulty concentrating.
- ❑ I have a lot of difficulty concentrating.
- ❑ I have a great deal of difficulty concentrating.
- ❑ I can't concentrate at all.

SECTION 7 – WORK

- ❑ I can do as much work as I want.
- ❑ I can only do my usual work, but no more.
- ❑ I can do most of my usual work, but no more.
- ❑ I can't do my usual work.
- ❑ I can hardly do any work at all.
- ❑ I can't do any work at all.

SECTION 8 – DRIVING

- ❑ I can drive my car without neck pain.
- ❑ I can drive my car with only slight neck pain.
- ❑ I can drive as long as I want with moderate neck pain.
- ❑ I can't drive as long as I want because of moderate neck pain.
- ❑ I can hardly drive at all because of severe neck pain.
- ❑ I can't drive my car at all because of neck pain.

SECTION 9 – SLEEPING

- ❑ I have no trouble sleeping.
- ❑ My sleep is slightly disturbed for less than 1 hour.
- ❑ My sleep is mildly disturbed for up to 1-2 hours.
- ❑ My sleep is moderately disturbed for up to 2-3 hours.
- ❑ My sleep is greatly disturbed for up to 3-5 hours.
- ❑ My sleep is completely disturbed for up to 5-7 hours.

SECTION 10 – RECREATION

- ❑ I am able to engage in all my recreational activities with no neck pain at all.
- ❑ I am able to engage in all my recreational activities with some neck pain.
- ❑ I am able to engage in most, but not all of my recreational activities because of pain in my neck.
- ❑ I am able to engage in only a few of my recreational activities because of neck pain.
- ❑ I can hardly do recreational activities due to neck pain.
- ❑ I can't do any recreational activities due to neck pain.

This second part of the questionnaire is to give me some understanding of your health in general. Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems in walking about ❑
- I have slight problems in walking about ❑
- I have moderate problems in walking about ❑
- I have severe problems in walking about ❑
- I am unable to walk about ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

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

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

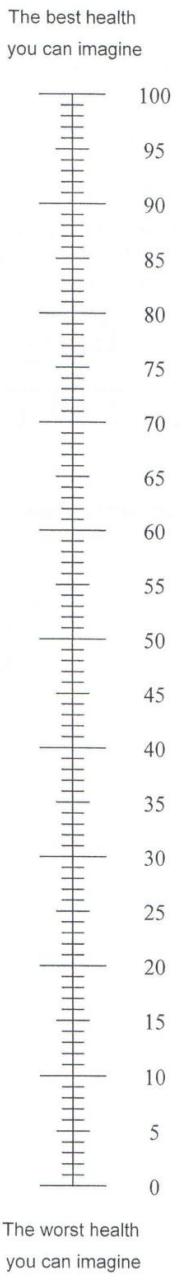
ANGLO-EUROPEAN COLLEGE OF CHIROPRACTIC

Bournemouth University

IMRCI Institute for Musculoskeletal Research & Clinical Implementation

- I would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH = ☐



ANGLO-EUROPEAN COLLEGE OF CHIROPRACTIC

Bournemouth University

IMRCI Institute for Musculoskeletal Research & Clinical Implementation

• Over the last few days, on average, how would you rate your pain on a scale where "0" is "no pain" and "10" is the "worst pain possible"?

	0	1	2	3	4	5	6	7	8	9	10
No pain	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

• Please indicate on the scale below the amount of improvement or deterioration you have experienced so far as a result of treatment and the impact of the treatment results on your daily activities and general well-being. Please put a cross in the applicable box.

DETERIORATION NO CHANGE IMPROVEMENT

Maximum Deterioration	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1	0	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10	Maximum Improvement

• All things considered, how satisfied are you with the results of your treatment for neck pain?

Extremely satisfied	❑
Very satisfied	❑
Somewhat satisfied	❑
Mixed [approximately equal satisfaction and dissatisfaction]	❑
Somewhat dissatisfied	❑
Very dissatisfied	❑
Extremely dissatisfied	❑

THANK YOU

Appendix 29: Baseline and follow-up mean (SD) inter-vertebral angular ranges in patients with neck pain (n=29)

	Flexion				Extension			
	Baseline	4-weeks	Difference (95% CI)	p value	Baseline	4-weeks	Difference (95% CI)	p value
C1/2	7.7 (3.7)	6.8 (3.3)	-0.9 (-1.9 to 0.1)	0.07	2.7 (2.1)	3.4 (2.0)	0.7 (-0.1 to 1.7)	0.07
C2/3	5.6 (3.1)	6.2 (2.7)	0.6 (-0.4 to 1.5)	0.24	4.1 (3.2)	3.5 (2.9)	-0.6 (-1.7 to 0.8)	0.37
C3/4	6.9 (3.8)	8.1 (3.3)	1.2 (0.2 to 2.2)	0.01	6.5 (3.7)	6.6 (4.5)	0.03 (-2.4 to 1.8)	0.74
C4/5	5.8 (2.8)	6.7 (3.2)	0.9 (-0.1 to 1.9)	0.07	8.3 (4.7)	8.8 (4.5)	0.5 (-0.6 to 1.5)	0.34
C5/6*	4.9 (2.9)	5.6 (2.6)	0.7 (-0.6 to 2.2)	0.32	8.5 (4.9)	8.6 (5.1)	0.1 (-3.0 to 2.8)	0.90
C1-6	30.7 (8.9)	33.2 (9.3)	2.4 (-0.3 to 5.2)	0.08	29.6 (12.5)	30.3 (13.2)	0.7 (-2.3 to 3.7)	0.61

*There were four tracking failures at baseline in three patients: C5/6 in flexion (n=1 patient), C5/6 in extension (n=1 patient), and C5/6 in flexion and extension (n=1 patient); and three failures in two of the same patients at follow-up: C5/6 in flexion and extension (n=1 patient), C5/6 in extension (n=1 patient).

Appendix 30: Prognostic factors for neck pain in the general population as identified by the Neck Pain Task Force (Carroll et al. 2008b)

Negative Prognostic Factor	Positive Prognostic Factor
Pain > 6 months[1]	
Previous neck pain[1,3]	
**Older age[1,2,3]	Younger age[5]
Female[2]	Male[6]
*Comorbid LBP[3]	Fewer other symptoms[5]
Poorer quality of life[1]	Better general health[1,4]
Worrying as coping strategy[1]	Self-assurance as coping strategy[4]
Fear avoidance[1]	
Greater baseline pain and disability[1]	
	Lower need to be social[5] ;Social support network[4]
Getting angry or frustrated[4]	Higher external locus of control[7]

References:[1](Bot et al. 2005); [2](Cote et al. 2004); [3](Hill et al. 2004); [4](Hurwitz et al. 2006); [5](Michaelson et al. 2004); [6](Pernold et al. 2005);[7](Stanton and Jull 2003); *Moderate or **high risk according to a more recent overview of systematic reviews (Walton et al. 2013)

Glossary

Accuracy	Accuracy refers to the ‘trueness’ of a measurement and the degree of accuracy is determined by the closeness of a measurement to a reference standard measurement. This is determined by the standard deviation of the measurement differences.
Agreement	This quantifies how close two measurements made on the same subject are and is measured on the same scale as the measurements themselves. Agreement statistical parameters estimate the measurement error.
Precision	In the absence of a reference standard, precision may be calculated from the standard deviation of measurement differences when one measurement method is compared to another or from repeat measurements with one method.
Reliability	Reliability relates the magnitude of the measurement error in observed measurements to the inherent variability in the ‘true’ or underlying level of the quantity between subjects. Statistically, reliability is expressed as a coefficient which is a ratio of variances, and so expresses how well subjects can be differentiated from each other, despite measurement error. In this case the measurement error is related to the variability between subjects.
Repeatability	Repeatability means the degree to which repeated measurements by the same observer or two or more observers produce similar results. This may be considered to encompass both agreement and reliability. In contrast to reproducibility, *repeatability* refers to the variation in repeat measurements made on the same subject under *identical conditions*.
Reproducibility	Reproducibility means the degree to which repeated measurements by the same observer or two or more observers produce similar results. This may be considered to encompass both agreement and reliability.

	In contrast to repeatability, *reproducibility* refers to the variation in repeat measurements made on the same subject under *changing conditions*.
Validity	This refers to the quality of being logically or factually sound. The validity of a measurement method is determined by demonstrating that it measures what is claimed it can measure, the measurement is accurate and repeatable/reproducible.

Publication of main research findings