THESIS

THE ROLE OF ALTERED NEURODYNAMICS IN PATIENTS WITH CERVICAL RADICULOPATHY

By

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ABSTRACT

Cervical radiculopathy (CR) is a clinical condition associated with symptoms of neck, shoulder, and upper limb pain as well as upper limb paraesthesia and weakness, which are attributed to cervical nerve root irritation. There is a paucity of evidence on the diagnosis and management of patients with CR. This thesis investigated (1) the validity of neurodynamic and other physical tests in diagnosing patients with CR, (2) the effect of neurodynamic mobilisation on longitudinal nerve movement in patients with CR compared to healthy matched controls, (3) the effectiveness of neurodynamic mobilisation in patients with CR and (4) the optimal timing of neurodynamic mobilisation and other conservative treatment modalities for patients with CR considering the evolution of the disorder.

A systematic review of the literature concluded that, when consistent with the patient's history and other physical findings, a combination of a positive Spurling's test and at least one positive upper limb neural tension test (ULNT) in a cluster of all four ULNTs may be used to increase the likelihood of the presence of CR.

A case-controlled study concluded that longitudinal median nerve movement at the wrist and the elbow is significantly less in patients with CR compared to healthy matched volunteers. But after 3 months of multi-modal conservative management, this difference is no longer present. Monitoring of the improvement in median nerve movement using ultrasound imaging has the potential to assist clinical decision making with regards to either continuing or suspending conservative management. This study also reported that an increase in nerve movement is strongly correlated with improvement in functional disability assessed by the Patient Specific Functional Scale, Neck Disability Index and Global Perceived Effect.

A systematic review of the literature concluded that there is low to very low-level evidence that neurodynamic mobilisation is effective on pain, disability and physical function in patients with CR.

Finally, an E-Delphi study was conducted which concluded that some of the previously reported generally effective conservative treatment modalities are more clinically useful than others across the different stages of CR.

The overall conclusions of the research presented in this thesis is that neurodynamics play an important role in both the diagnosis and conservative management of CR.

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LIST OF PAPERS AND CONFERENCE ABSTRACTS

Throughout my PhD, the following papers have either been published, presented in conferences or are in preparation/under review and relate to this thesis directly. A summary will be provided with further detail of the papers and use within this thesis at the start of each Chapter where required. Therefore, sections of this thesis are written verbatim from published work. Sections of the thesis have been developed from published work and in this situation will resemble the published work in terms of structure and content. Permission to reprint the published work in this thesis has been granted by the publishers (**APPENDIX 9**).

Published Articles

Published manuscripts in this thesis

Thoomes E, Ellis R, Dilley A, Falla D, Thoomes-de Graaf M (2021) Excursion of the median nerve during a contra-lateral cervical lateral glide movement in people with and without cervical radiculopathy. Musculoskelet Sci Pract. 2021 Apr;52:102349. doi: 10.1016/j.msksp.2021.102349. Epub 2021 Feb 16.PMID: 33618231

Thoomes E, Thoomes-de Graaf M, Cleland JA, Gallina A, Falla D. Timing of evidence-based nonsurgical interventions as part of multimodal treatment guidelines for the management of cervical radiculopathy: a Delphi study.
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Related published articles which are not included in the thesis

Thoomes EJ, Scholten-Peeters GG, de Boer AJ, Olsthoorn RA, Verkerk K, Lin C, Verhagen AP (2012) Lack of uniform diagnostic criteria for cervical radiculopathy in conservative intervention studies: a systematic review. Eur Spine J. 2012 Aug;21(8):1459-70. doi: 10.1007/s00586-012-2297-9. Epub 2012 Apr 25. PMID: 22531897

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Thoomes E, de Graaf M, Gallina A, Falla D, Stathi A. Comparison between two patient-reported outcome measures for patients with cervical radiculopathy: a think-aloud study. Musculoskelet Sci Pract. 2023 Apr 14;65:102764. doi: 10.1016/j.msksp.2023.102764.

Conference Presentations

Platform presentations

Thoomes EJ, Scholten-Peeters W, Koes B, Falla D, Verhagen AP. The effectiveness of conservative treatment for patients with cervical radiculopathy: A systematic review. IFOMPT2012, September 30th to October 5th 2012, Québec, Canada.

Thoomes EJ, Scholten-Peeters GG, de Boer AJ, Olsthoorn RA, Verkerk K, Lin C, Verhagen AP Lack of uniform diagnostic criteria for cervical radiculopathy in

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Thoomes EJ. "Evidence based evaluation and rehabilitation of the cervical radiculopathy" Belgian Back Society Conference September 5th 2012, Antwerp, Belgium.

Thoomes EJ, Scholten-Peeters W, Koes B, Falla D, Verhagen AP. The effectiveness of conservative treatment for patients with cervical radiculopathy. (Dutch General Practitioners Scientific Annual Conference) NHG Wetenschapsdag, June 14th 2013, Leiden, The Netherlands.

Gross A, Hing W, MacDermid J, **Thoomes EJ**, Pool JJ. Focussed Symposium: "Clinical tracking for cervical radiculopathy: diagnostic classification, management, outcome benchmarking". WCPT 2015, May 1st to 4th Singapore.

Thoomes EJ, WCPT Revisited; Clinical tracking for cervical radiculopathy: diagnostic classification, management, outcome benchmarking''. Dutch KNGF annual physiotherapy conference, November 6th, 2015, Utrecht, The Netherlands.

Thoomes E, Ellis R, Dilley A, Falla D, Thoomes-de Graaf. Excursion of the median nerve during a contra-lateral cervical lateral glide movement in people with and without cervical radiculopathy. WCPT2021. April 8th – 10th 2021, Dubai, United Arab Emirates. (Online)

<u>Poster presentations</u>

Thoomes E, van Geest S, van der Windt DA, Falla D, Verhagen P, Koes BW, Thoomes-de Graaf M, Kuijper B, Scholten-Peeters GGM, Vleggeert-Lankamp CL. Diagnosis and Clinical Management of Patients with Cervical Radiculopathy. WCPT2019, May 10th-13th, Geneva, Switzerland

Thoomes E, Ellis R, Dilley A, Falla D, Thoomes-de Graaf. Excursion of the median nerve during a contra-lateral cervical lateral glide movement in people with and without cervical radiculopathy. Physio UK; VPUK 2020. (Online)

Webinar

EuroSpine Webinar: “Evidenced based diagnosis and rehabilitation of cervical rehabilitation”.
Date: Tuesday 18 April 2023
Presenters:
Erik Thoomes - Evidence based diagnosis of cervical radiculopathy.
Prof. Pierre Côté - Evidence for non-surgical management in the rehabilitation of cervical radiculopathy.
Dr. Patrick Statham - Evidence for surgery in the rehabilitation of cervical radiculopathy.
Prof. Jan Van Zundert - Evidence for pain medication and injections in the rehabilitation of cervical radiculopathy.

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LIST OF ABBREVIATIONS AND DEFINITIONS

APTA: American Physical Therapy Association

CCLG: Contralateral Cervical Lateral Glide

CCT: Controlled Clinical Trial

CR: Cervical Radiculopathy

CREDES: Guidance on Conducting and REporting DElphi Studies

CTS: Carpal Tunnel Syndrome

CT: Computer Tomography

EMG: electromyography

GP: General Practitioner

GPE: Global Perceived Effect

GRADE: Grading of Recommendations, Assessment, Development and Evaluation

GROC: Global Rating of Change

HVLAT High Velocity Low Amplitude Thrust

ICC: Intraclass Coefficient

MRI: Magnetic Resonance Imaging

NASS: North American Spine Association

NDI: Neck Disability Index

NPRS: Numerical Pain Rating Scale

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROM: Patient Related Outcome Measures

PSFS: Patient Specific Functional Scale

QUADAS: Quality Assessment of Diagnostic Accuracy Studies

RCT: Randomised Controlled Trial

ROB: Risk of Bias

ROM: Range of Motion

STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

UI: Uncertainty Interval

ULNT: Upper Limb Neural Tension test

ULTT: Upper Limb Tension Test

VAS: Visual Analogue Scale

CHAPTER 1

1.1 INTRODUCTION

1.1.1 Definition - what is cervical radiculopathy?

Cervical radiculopathy (CR) is a clinical condition whereby motor, reflex and/or sensory changes such as paraesthesia or numbness can present, often provoked by neck posture(s) and/or movement(s) [1]. In general, radiculopathy needs to be differentiated from radicular pain. Radicular pain is pain evoked by ectopic discharges emanating from a dorsal root or its ganglion. Therefore, it is pain not due to a discharge exclusively of nociceptive afferents, but due to a heterospecific discharge in the affected nerve. The evoked sensation is very unpleasant but is not exactly pain, in a classical, nociceptive sense but is often described as “lancinating”, “shocking”, or “electric” [2-4]. In contrast, radiculopathy is a neurological state in which conduction is blocked along a spinal nerve or its roots, resulting in numbness as a symptom or when motor fibres are blocked, weakness ensues. Diminished reflexes occur as a result of a sensory or motor block [2-4].

CR is usually caused by compression of the nerve root due to cervical disc herniation or degenerative spondylotic changes, but radicular symptoms can also occur without evident compression, for instance due to inflammation of the nerve [2].

The aetiology of CR is foraminal compression of the spinal nerve in 70 to 75% of cases. This can be due to several factors, including a reduction of disc height and anterior and posterior degenerative changes of the uncovertebral and zygapophyseal joints [5]. A herniated disc in the cervical spine accounts for only 20 to 25% of the cases of CR [6-8]. The most common level of nerve root compression is C7, followed by C6, and compression of roots C5 and C8 are less frequent [6, 8]. CR as a direct result of cervical trauma or metastases is infrequent [9].

To date, CR is a widely used diagnosis in patients with symptoms of neck, shoulder, and upper limb pain and/or upper limb paraesthesia and weakness, attributed to cervical nerve root irritation [10]. However, for a long time there was no consensus on the definition of CR [11]. Furthermore, there were no generally accepted, well-defined clinical criteria for the diagnosis of CR [6, 12]. This is very relevant however, in order to make sure we are comparing the outcomes of comparable patients in clinical trials and in systematic reviews and meta-analysis [13]. Inclusion of patients with a comparable diagnosis in randomised controlled trials (RCTs) or case-controlled trials is essential and a widely agreed on definition of CR could facilitate this [13]. Furthermore, from a clinical point of view, it is important to be able to differentiate patients with radicular symptoms due to a nerve root compression from those with non-specific neck pain and referred somatic pain or with a thoracic outlet compression syndrome, as the management plan and prognosis could very well be different [14, 15]. In order to assess how patients with CR were selected in RCTs and how they were differentiated from patients with somatic referred pain or with peripheral nerve related arm pain, a systematic review of the literature was performed prior to this thesis, aiming to assess the uniformity of diagnostic criteria and definitions used to select patients with CR in intervention studies (with at least one conservative treatment group) [10]. This review found no uniformity in definitions of CR; the criteria used to select patients with CR in intervention studies vary widely between the different studies. The review found consensus on only one criterion, which was neck and/or arm pain to select patients with CR for randomised clinical trials using conservative therapy as an intervention. The review also concluded that the selection criteria and test method used were poorly described. Therefore, the review determined the need for consensus to be reached on an appropriate definition

for CR and proposed the following definition: "radiating pain into the arm of a neuropathic nature or with an in part neuropathic quality, provoked by neck posture(s) and/or movement(s) with concomitant or concurrent mechanical neck pain".

1.1.2 Epidemiological data – prevalence, incidence and related costs.

There is a recognized paucity of evidence on epidemiology, aetiology, diagnosis and management of patients with CR, with 453 clinical trials and review articles indexed on PubMed from 1978-2011, compared to 388 in the period from 2012-2020 [6, 16-19]. Epidemiological data on CR are also sparse [1] and mainly based on one population-based study in Rochester, Minnesota (USA) indicating that CR has an annual incidence rate of 107.3 per 100,000 for men and 63.5 per 100,000 for woman. Age-specific annual incidence rates were reported to reach a peak of 202.9 for the age group 50 to 54 years [6]. Another study reported a prevalence of 3.5 per 1000 people and a peak annual incidence of 2.1 cases per 1000 people, increasing to a peak at age 50-59 years [20]. A recent systematic review, aiming to determine the incidence and/or prevalence of CR in adults, mentioned the need to still rely on these studies for a substantial part [21].

Health care related costs of CR as a subgroup are unclear as they are usually included in the cost of neck pain and/or low back pain. The total cost of neck pain in The Netherlands in 1996 was estimated to be US $686 million. The share of these costs was about 1% of total health care expenditures and 0.1 % of the Gross Domestic Product in 1996. Direct costs were $160 million (23%). Paramedical care accounted for largest proportion of direct costs (84%). The total number of sick days related to neck pain were estimated to be 1.4 million with a total cost of $185.4

million in 1996 [22]. In 2016 in the USA, low back and neck pain generated the highest expenditures at $134.5 billion and was the highest rated in the Health Care Estimated Spending for the 100 most expensive health conditions of the 154 health conditions analysed [23]. In the United Kingdom, the age-standardized point prevalence of neck pain per 100,000 population in 2019 was the third highest in the world (4,501.3, 95% uncertainty interval [UI] 3,591.7 to 5,675.2) [24]. Additionally, the United Kingdom also had the third highest age-standardized years lived with a disability of neck pain per 100,000 population in 2019 (446.9, 95% UI 302.0 to 636.9) [24].

1.1.3 Diagnosis.

There are many other diagnostic labels used to describe CR (e.g. ‘stinger’, ‘burner’, ‘herniated disc’, ‘bulging disc’, ‘discogenic pain’), not always indicating a similar aetiology [16, 17]. The diagnosis of CR is usually based on information received during the subjective (history taking) and physical examination, which is then confirmed via diagnostic imaging (MRI or CT-myelography), electrophysiological tests (electromyogram, EMG) and/or supported by surgical findings [25]. However, there is a growing amount of evidence that diagnostic imaging has a significant amount of false positives [26, 27]. Also, the evidence on the validity of EMG is conflicting and more likely positive only when there is substantial axonal damage or degeneration [28-30]. Moreover, the first point of contact and most of the management of patients with CR will be in primary care facilities (GPs or physiotherapists), and these clinicians usually do not have MRI or EMG readily available to them. The most commonly used physical tests for CR include tendon reflexes, manual muscle testing of key muscles for weakness or atrophy in addition

to testing for sensory deficits. Additionally, provocative tests like the foraminal compression test or Spurling's test [31], shoulder abduction (relief) test [32], Upper Limb Tension Test (ULTT) or Upper Limb Neural Tension test (ULNT) [33], neck traction/distraction test, and Valsalva manoeuvre [34] have been proposed. Previous narrative reviews have summarized results of studies on the diagnostic accuracy of some of these proposed tests for the identification of CR [7, 19, 28]. Since then, new tests [35] or combinations of tests [36] have been described and a commonly used test (i.e. Spurling's test) has been further assessed [37]. Having knowledge of the validity of individual physical tests is important for clinicians to classify patients correctly, thereby ensuring a better understanding of the most effective management strategy and being able to make a better evaluation of the prognosis. The previously mentioned study on the lack of diagnostic criteria also concluded there was a need to assess the validity of clinical tests used to diagnose CR or to differentiate CR from non-specific neck pain with somatic referred pain [10].

In view of the above and continuing on from the conclusion of a systematic review published prior to this thesis on the diagnostic criteria used to identify patients with CR in RCTs [10], I performed a systematic review, aiming to summarize and update the evidence on the diagnostic performance of specific tests carried out during the physical examination for the diagnosis of CR. The original systematic review was published in 2018 [38] and for the purpose of this thesis, I updated this review (see **CHAPTER 2**).

1.1.4 Management

In order to assess the need and the effectiveness of management strategies, knowledge with regard to the natural course of a condition is necessary. Little is

known about the natural course of CR. One study which followed 51 patients with CR over the course of 2 to 19 years, found that 43% of patients had no further symptoms after a few months, 29% had mild or intermittent symptoms and 27% had more disabling pain [39]. Several recent studies support a more favourable natural course of CR at an average of 6 months [40-43]. A recent systematic review reported that patients with CR due to cervical disc herniation substantially improved on levels of pain and activity within the first 4 to 6 months and were able to return to their normal activities after 24 to 36 months [44]. One study reported that patients compensated through a workers' compensation system, demonstrated a significantly worse prognosis [45]. A prospective cohort study identified a subset of four predictor variables (age of <54 years; dominant arm not affected; looking down does not worsen symptoms; and multimodal treatment including manual therapy, cervical traction, and deep neck flexor muscle strengthening for at least 50% of visits) able to identify which patients were likely to experience short-term successful outcomes [46]. In this study “short term success” was defined as surpassing the minimal clinically important change for all four outcome measures: the Neck Disability Index (NDI), the Patient-Specific Functional Scale (PSFS), the Numeric Pain Rating Scale (NPRS) and the Global Rating of Change (GROC) [46].

Research on the effectiveness of conservative treatment of CR is sparse. Few reviews have looked at CR alone; some have added it solely as a subgroup in their review [47-50]. In a best evidence synthesis of the Neck Pain Task Force (NPTF), only one RCT was identified on the effectiveness of surgical versus conservative treatment for patients with CR, therefore concluding that insufficient evidence was available to determine the effectiveness of non-invasive procedures in the short or long term [51]. A systematic review published in 2011, aimed at producing a North

American Spine Society (NASS) clinical guideline, reported that the literature yielded no studies to adequately address the role of physical therapy, exercise, manipulation or chiropractic care in the management of CR from degenerative disorders [28]. Nevertheless, conservative management for CR continues to be preferred to surgery, as surgery is not superior and the risk benefit ratio seemed to be less favourable [52, 53]. However, little is known about the actual effectiveness of conservative care, especially compared to no treatment or surgical care [52-55]. In order for clinicians to best manage patients with CR, knowledge of the effectiveness or ineffectiveness of conservative management is essential. Prior to this thesis, I published two literature reviews on the effectiveness of conservative management of patients with CR [56, 57]. I also reviewed additional literature which confirmed these results and mentioned the paucity of evidence of effectiveness of conservative management of patients with CR [28, 47, 51, 58, 59].

One systematic review aimed to assess the effectiveness of conservative treatments for patients with CR compared to placebo, no treatment, other forms of conservative care or surgery [57]. In this study we concluded that overall, low-level evidence from two studies was found that a collar was no more effective than physiotherapy at a 3 months follow up and that traction was no more effective than placebo traction. The pooled effect sizes for pain and disability from these studies were small, not significant and not clinically relevant. One low risk of bias study indicated that at 3 week follow up, a collar was more effective on neck pain and disability than physiotherapy and a wait & see policy. At the 6 week follow up, both a collar and physiotherapy were more effective on neck and arm pain than a wait and see policy. Small and sometimes temporary effects were found in other studies, but with questionable clinical significance.

Additionally, I published a narrative review aiming to assess the effectiveness of individual spinal manipulative (physical) therapy interventions for patients with CR compared to placebo, no treatment, other forms of conservative care or surgery on patient outcome such as pain, disability, return to work, global perceived effect or quality of life. This study concluded that there was low-level evidence that cervical manipulation as a unimodal intervention is effective on pain directly after treatment but not at longer term follow up. And there was very low-level evidence that cervical mobilisation as a unimodal intervention is more effective at immediate follow up than a placebo or a wait-and-see policy on pain and range of motion (ROM). With regard to neurodynamic mobilisation, there was low-level evidence of the effectiveness of cervical mobilisation with a neurodynamic intent as unimodal intervention. Additionally, there was low-level evidence on the effectiveness of a multimodal intervention with neurodynamic intent on pain activity limitations and global perceived effect (GPE) compared to a wait-and-see policy. Also, there was low-level evidence that a multimodal intervention consisting of spinal and neurodynamic mobilisations and specific exercises is effective on pain in patients with CR. Furthermore, there was low-level evidence that a combination of spinal mobilisation and motor control exercises was more effective on pain and activity limitations than separate interventions or a wait-and-see policy. There was no evidence on the effectiveness of thoracic manipulation or mobilisation as a unimodal intervention. And there was low-level evidence that traction is no more effective than placebo traction, questioning the use of traction as an effective treatment modality.

In the meanwhile, several systematic reviews [57, 58, 60] and contemporary (inter)national treatment guidelines [61-65] suggested effective non-surgical management strategies for patients with CR which include: information and patient

education, advice to stay physically active, manual therapy alone or in combination with different types of supervised exercise, traction, neurodynamic mobilisation and use of a cervical collar.

However, systematic reviews traditionally include outcomes from RCTs (and sometimes controlled clinical trials) and RCTs have a limitation in that the management strategies are often not tailored to the individual. RCTs usually report central tendencies of a cohort, which is not representative for the management of individual patients [66, 67]. The limited external validity is partly related to the inclusion of patients and practitioners in RCTs, which are different from those in routine practice. Additionally, RCTs in general do not relate the management strategy under scrutiny to the different stages of the studied condition [68]. Instead, they manage all participants identically, regardless of the stage of the studied condition being acute, sub-acute or chronic. Rehabilitation programs however, are based on the logical assumption that some treatment modalities might potentially be better suited in the early acute stage of the disorder, while others might be better for the management during the subacute or chronic phases [69, 70]. Current evidence on the effectiveness of non-surgical management of patients with CR report a lack of consensus on the optimal timing and dosage of treatment modalities [56-58].

The Delphi technique is described as “a method used to obtain the most reliable consensus of opinion of a group of experts by a series of intensive questionnaires interspersed with controlled feedback” [71-73]. Considering the above, a Delphi study was performed, with the aim of combining clinical expertise and achieving consensus on what preferred management options should or could be included in the management of patients with CR at varying stages **(CHAPTER 5).**

1.1.5 Neurodynamic tests and neurodynamic mobilisation (NM)

Prior to this thesis, research interest in a potential correlation between neurodynamic tests and neurodynamic treatment in patients with radiculopathy was growing [74-77], identifying a need for further research in both diagnostic validity (**CHAPTER 2**), as well as management effectiveness constructs (**CHAPTER 4 & 5**).

Prior to the start of the research projects undertaken for this thesis, the effectiveness of a neural based manual therapy treatment technique (a contra-lateral cervical lateral glide (CCLG)) was reported [78, 79]. The CCLG neurodynamic mobilisation has been documented as an effective technique or component in the effective conservative management of patients with CR [56, 80-82]. A CCLG mobilisation technique was shown to be effective for improving the range of elbow extension, reducing symptom distribution and reducing pain intensity during neural provocation tests that tension the median nerve in patients with nerve-related neck and arm pain [79, 82]. Hypotheses about the mechanisms of effect of neurodynamic mobilisation have evolved from an original mechanical paradigm of influencing nerve movements and nerve biomechanics [83, 84]. More recent theoretical models indicate that neurodynamic mobilisation may improve neural vascularity, nerve movement and restoration of optimal intraneural homeostasis by reducing intraneural oedema [85-87]. The CCLG technique can be used to mobilise the median nerve in relation to non-neural structures that surround the nerve and nerve root (e.g. muscle, tendon, fascia and bone: i.e. the “mechanical interface”) [88, 89]. Based on our current understanding of how nerves in the upper limb respond to limb movements, movement of the median nerve may be reduced in patients with CR, possibly due to a restriction in sliding of the cervical nerve roots through the intervertebral foramina. To answer this research question, a study was performed using ultrasound imaging

to assess longitudinal excursion of the median nerve during a mechanically induced CCLG movement in asymptomatic subjects and patients with CR.

Building on from the research question above, we monitored the longitudinal nerve excursions at a 12 week follow up measurement. Patients received a personalised treatment plan as suggested by the previously performed systematic and narrative reviews [56, 57], consisting of a combination of manual therapy (manipulation and/or mobilisation), neurodynamic mobilisation, specific motor control exercises, general strengthening and cardio-vascular fitness exercises. Given that it is unclear whether conservative treatments such as neural mobilisation improve nerve excursion, reassessing median nerve excursion at three months following neural mobilisation treatment in patients with CR could increase the body of knowledge on this subject [56, 80-82]. We also assessed if there was a correlation between the hypothesised difference in nerve excursion and patient reported outcome measures (PROMs) such as the PSFS, NDI and GPE **(CHAPTER 3)**.

1.2 Central argument

Patients with neck pain and/ or radiating arm pain usually initially visit first-line practitioners [90-92]. General physicians (GPs), physiotherapists, osteopaths and chiropractors are among those most consulted [92, 93]. The consultation usually consists of history taking and physical examination leading into formulating hypotheses which in turn drives a best-evidence management plan [94-96]. It has been proposed that neurodynamic tests might assist clinical reasoning processes in differentiating somatic referred pain from radicular pain [19].

Clinical evidence as well as clinical practice suggests that management plans for specific non-serious specific cervical disorders should differ from those for non-specific neck pain [97-99]. In clinical practice, the management plans for patients with

specific serious neck pain [100-103] and non-specific neck pain [61-63, 104, 105] are well researched and underpinned with evidence based clinical practice guidelines. Non-surgical or conservative management for patients with non-specific neck pain has been universally established and is a generally accepted preferred treatment option [48, 53, 61-63, 106, 107]. Similarly, in-depth research is ongoing on the diagnostic accuracy of medical tests [108-114] as well as on the effectiveness treatments of specific serious conditions causing neck pain [115-118]. Until the second decade however, there was a paucity of evidence on these areas for CR [1, 28, 58]. Evidence on surgical management for CR suggests it is not a preferred treatment option due to the high recurrence ratio [53, 119]. Evidence on non-surgical management of patients with CR was sparse and mainly anecdotal up until the first decade of this century and even then assessed in mixed populations of patients with non-specific neck pain and with CR [47]. This paucity of evidence led to the need of doing research in this specific population of patients with CR and initiated this thesis [7]. Neurodynamic mobilisation is one of the treatment interventions often mentioned in or suggested in clinical guidelines [56-58, 62, 63]. Combined with neurodynamic tests as mentioned being proposed to assist diagnosing CR, this leads to believe there is a difference in neurodynamics between patients with CR and healthy controls.

An overarching theme of this thesis is the interaction of the patient journey and the clinician's clinical reasoning process, starting with a clinical diagnosis leading to a shared decision making choice of offering a best-evidence non-surgical management plan for patients with CR, especially for first contact practitioners. The research question this thesis has tried to answer is:

What role do altered neurodynamics play in patients with CR?

Figure 1.1 Flow of Themes and Chapters in this Thesis

RESEARCH QUESTION:
WHAT ROLE DO ALTERED NEURODYNAMICS PLAY IN PATIENTS WITH CR?

CHAPTER 2
Diagnostic value of neurodynamic and other physical tests in diagnosing cervical radiculopathy: An updated systematic review.

- The updated results now show a moderate specificity and sensitivity of neurodynamic testing. The next question was; is there a difference in neurodynamics between patients with CR and healthy matched controls?

CHAPTER 3
Excursion of the median nerve during a contra-lateral cervical lateral glide movement in people with and without cervical radiculopathy. *Thoomes E, Ellis R, Dilley A, Falla D, Thoomes-de Graaf M. Published: Musculoskelet Sci Pract. 2021*

- Results show there is indeed a difference in neurodynamics between patients with CR and healthy controls,
- The study also shows that neurodynamics are potentially effective as a treatment technique in patients with CR, so the next questions were:
    - Is there evidence on this effectiveness?
    - Are they effective in each stage of the disorder?

CHAPTER 4
Systematic review of the effectiveness of neurodynamic mobilisations in patients with cervical radiculopathy.

- Results show low to very low-level evidence of effectiveness of neurodynamic mobilisation on pain, function and disability in patients with cervical radiculopathy,
- So the next question was: is that true across the evolution i.e. in all stages of the disorder?

CHAPTER 5
Timing of Evidence-Based Nonsurgical Interventions as Part of Multimodal Treatment Guidelines for the Management of Cervical Radiculopathy: A Delphi Study. *Thoomes E, Thoomes-de Graaf M, Cleland JA, Gallina A, Falla D. Published: Phys Ther. 2022*

- Results show there is a shift of focus in treatment interventions through the evolution of the disorder as the patient improves.

1.3 Thesis aims

Evidence from studies suggests that neurodynamic techniques could be an important part of both the diagnostic triage as well an effective multi-modal management strategy. This leads to five related research questions:

Q1: What is the validity and accuracy of neurodynamic and other physical tests used in clinical practice when diagnosing patients with a CR? (How accurately can clinicians differentiate patients with non-specific neck pain and somatic referred pain from patients with CR?)

Q2: Is there a difference in the longitudinal excursion peripheral nerves at the wrist and elbow during a contralateral cervical glide mobilisation between patients with CR and healthy matched controls?

Q3: Do the diminished longitudinal excursions of the median nerve at the wrist and elbow during a contralateral cervical glide mobilisation increase in patients with CR as their symptoms decrease? And does that correlate with decrease in disability measured with PROMs such as the PSFS, the NDI and the GPE?

Q4: What is the effectiveness of neurodynamic mobilisations in patients with CR?

Q5: Are neurodynamic mobilisations an effective element in each stage of management plans for patients with CR across the evolution of the disorder?

In the next four chapters I aim to answer these research questions.

CHAPTER 2
DIAGNOSTIC VALUE OF NEURODYNAMIC AND OTHER PHYSICAL TESTS IN DIAGNOSING CERVICAL RADICULOPATHY: UPDATE OF A SYSTEMATIC REVIEW.

2.1 INTRODUCTION

Most patients with neck and radiating arm pain will first visit a primary health care practitioner (e.g., a General Practitioner, Physiotherapist, Osteopath or Chiropractor) [62, 120, 121]. After history taking, clinicians will form initial hypotheses concerning the cause of the patient's problem and next they will plan a physical examination in an effort to underpin one (or more) of the initially formed hypotheses [62, 122-124]. In patients presenting with radiating neck and arm pain, it is important to differentiate between somatic referred pain and radicular pain caused by an encroached cervical nerve root, as both the prognosis as well as the management strategies will differ [44, 125]. In patients with a suspected CR, several physical tests have been proposed, aiming to provoke or decrease patient specific signs and symptoms, thereby increasing the likelihood of a CR being the cause [19, 38, 126].

Prior to this thesis, in 2018, we published a systematic review (Thoomes, 2018) of the then current evidence of the diagnostic accuracy and validity of physical tests for patients with CR [38]. Given the time passed, it is likely that new studies assessing the value of physical tests for the diagnosis of CR will have been published. Additionally, most peer-reviewed journals publishing diagnostic accuracy studies, mandatorily require use of the QUADAS and Standards for Reporting Diagnostic Accuracy (STARD) [127] guidelines, which was not used in the previous publication. Therefore, it is likely that the methodological quality of any new studies might be higher than older studied, thereby influencing the strength of the overall evidence.

Given the relevance to this thesis, an update of the original (Thoomes et al., 2018) systematic review was performed to answer the following question: “What is the diagnostic accuracy of physical tests used to assess for the presence of CR?” The methodological quality of the studies was assessed using the QUADAS-2 guidelines. To further increase the rigour and value of this current review with respect to the original review, the strength of the evidence was also assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method approach [128].

2.2 METHODS AND ANALYSIS

This systematic review was registered in the PROSPERO database (CRD42023058465) in November 2023 and is written in compliance with Preferred Reporting System and Meta-Analysis (PRISMA) 2020 guidelines [129].

2.2.1 Inclusion criteria

The PICOS tool as endorsed by the Cochrane Collaboration was used the develop a search strategy [130]. Using the PICO format for questions about medical tests has been advocated by many [131-133] and then the acronym stands for: Population, Index test, Comparator test and test accuracy as Outcome. Studies were included where they assessed (P) patients who were suspected of having CR. The aim of each study (I) had to be to assess the diagnostic accuracy of physical tests during physical examination for identifying CR (i.e., how well a test, or a series of tests, was able to correctly identify patients with CR). Studies carried out in primary as well as secondary care were eligible. The results of the index test(s) had to be at least (C) compared to a reference standard consisting of either (1) diagnostic imaging such as

magnetic resonance imaging (MRI), computed tomography (CT) or myelography, or (2) findings during surgery [60, 134]. The outcome (O) of studies had to be presented as values of sensitivity, positive predictive value, specificity or negative predictive value.

2.2.2 Exclusion criteria

Abstracts for which full reports were not available or studies without the outcome of interest or not written in English were excluded.

2.2.3 Search methods

The search strategy of the initial systematic review (Thoomes, 2018) performed a search through CENTRAL (The Cochrane Library Central Register of Controlled Trials), PubMed (including MEDLINE), Embase, CINAHL (Cumulative Index to Nursing and Allied Health Literature), Web of Science (WoS), and Google Scholar for eligible diagnostic studies from their inception to March 2016. This search strategy was developed in collaboration with a librarian according to guidelines set by the Cochrane Diagnostic Test Accuracy group. For the current study, the original search was adapted to fit the different search engines of Medline (via OVID) and Embase (via Embase.com) and ran with help of an information specialist. All the databases of the original review were searched from March 2016 to March 2023. Outcomes of both searches were pooled. The detailed search strategy for Medline (via OVID) and Embase (via Embase.com) are listed as an Appendix (**APPENDIX 1**).

2.2.4 Data collection and analysis

Selection of studies

Retrieved studies were uploaded in EndNote 20 (Clarivate Analytics, Philadelphia , PA) to assist review authors (ET and MdG) to screen titles of abstracts and assess the full texts of potentially relevant articles for eligibility. Disagreements on inclusion were resolved first by discussion and if necessary, through arbitration by a third review author (DF).

Data extraction

Characteristics of participants, the index tests and reference standard, and aspects of study methods for each included study were extracted by two review authors (ET, MdG) using a standardised form identical to the form used in the original review. Diagnostic two-by-two tables (true positive [TP], false positive [FP], true negative [TN], and false negative [FN] positive predictive values [PPV] and negative predictive values [NPV]) for each study were also extracted. Two-by-two tables and also PPV and NPV were reconstructed if they were not available, using information on relevant parameters (e.g., sensitivity and specificity).

Statistical analysis

Two-by-two tables were constructed for each index test evaluated in each study based on the extracted number of TPs, FNs, TNs, and FPs. Results in terms of sensitivity, specificity PPV, NPV, accuracy and 95% confidence interval (CI) for each individual studied test are presented. When pooling of studies of individual tests was possible, two-by-two tables were also constructed and results presented separately. The range of sensitivity and specificity for each index test are presented in cases where no pooled estimate could be calculated. Values for sensitivity, specificity, PPV

and NPV ≥ 0.80 were defined as “high”; 0.60–0.79 as “moderate” and <0.60 as “low” [135].

Assessment of methodological quality

In the original review, four different authors assessed the methodological quality of the included studies using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool [136]. For the current review, two authors (ET, MdG) assessed the methodological quality of each newly added study, also using the QUADAS-2 tool. Similar guidelines for the assessment of the four bias domains as in the original review [38] were made available to the review authors (**APPENDIX 2**). With respect to the QUADAS-2 risk of bias domain related to the reference standard, the identical tiered scoring system of the original review was used; a combination of history taking, physical examination including neurological assessment and MRI or CT-myelography imaging (or surgical findings) was considered to be a true diagnostic gold standard, resulting in a “yes”, whereas a reference standard of only assessing MRI of CT-myelography imaging should result in “unclear” due to the inappropriate high number of false positives [137-139]. Potential incorporation bias was avoided by the index test never being part of the reference test set. The intraclass coefficient (ICC) assessing the initial agreement between multiple raters on the overall score per domain in the original review had already been assessed. For the three newly added studies, an ICC would not be the correct statistic to use, so Cohen’s kappa *k* was calculated for the agreement between the two raters [140]. Disagreements were resolved by consensus and, if necessary, through arbitration by a third review author (DF). Both a tabular as well as a graphical display was used to summarize the QUADAS-2 assessments.

Strength of the evidence

The strength of the evidence was graded using the GRADE method approach [128]. According to this approach, the quality of the evidence was based upon five principal factors: (1) limitations in study design (downgraded when >25% of the participants were from studies with a high risk of bias), (2) inconsistency of results [downgraded when there was statistical heterogeneity (I^2 >40%) or inconsistent findings (defined as ≤75% of the participants reporting findings in the same direction)], (3) indirectness (e.g., generalizability of the findings), (4) imprecision (downgraded when the total number of participants across studies were <300 for each outcome) and (5) other considerations, such as reporting bias. The quality of the evidence was downgraded by one level when one of the factors described above was met. Single studies were considered inconsistent and imprecise (i.e., sparse data) and providing ‘‘low quality evidence’’, which could be further downgraded to ‘‘very low quality evidence’’ if there were also limitations in design or indirectness. In line with the GRADE approach, the following grading of quality of the evidence was applied:

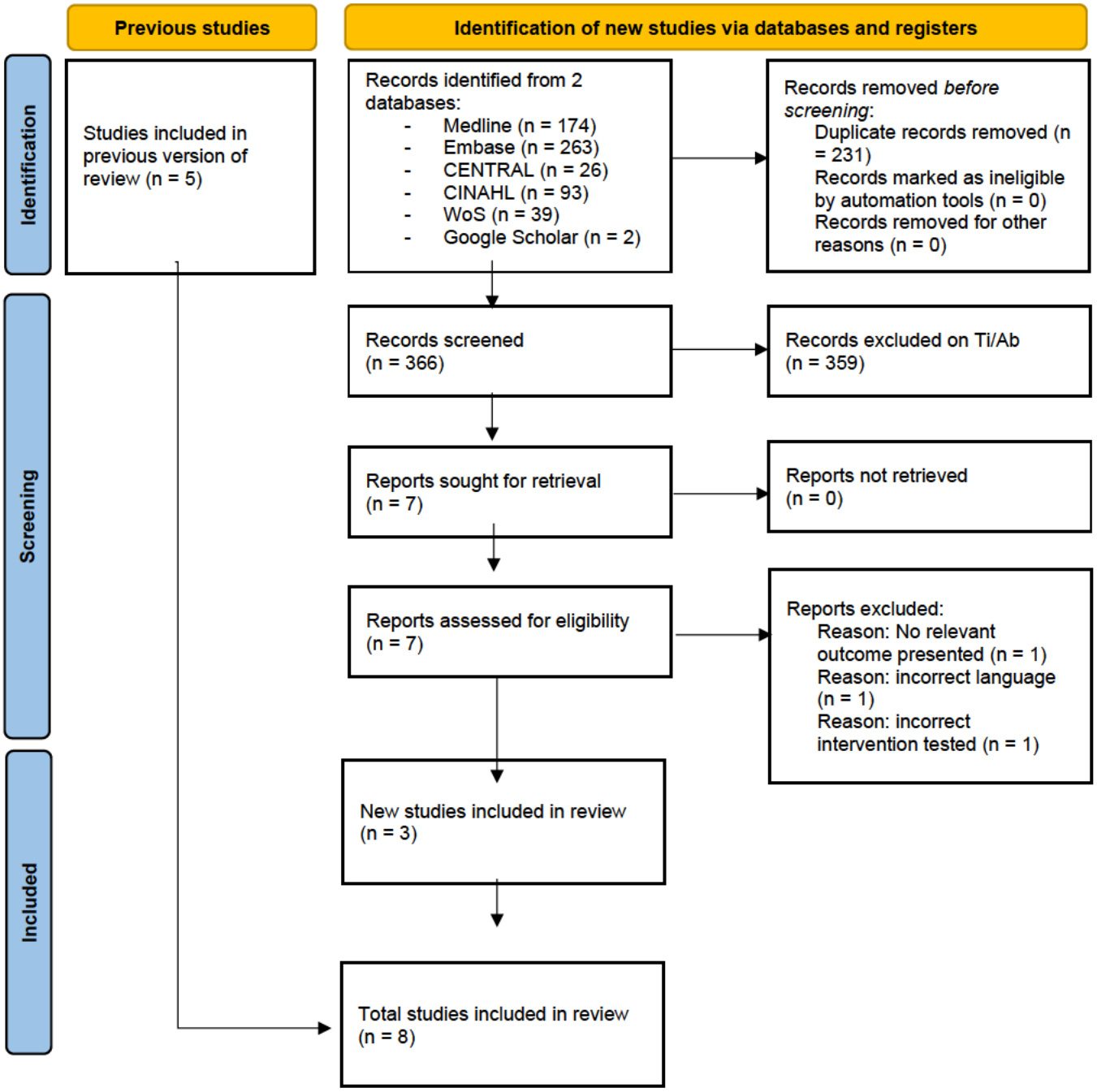
- High quality: further research is very unlikely to change our confidence in the estimate of effect.
- Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low quality: we are very uncertain about the estimate.
- No evidence: no evidence from any RCTs.

2.3 RESULTS

2.3.1 Search results

The search identified 366 unique citations. Seven additional studies to the original review (Thoomes, 2018) were then selected for full text assessment based on title and abstract screening (FIGURE 2.1, PRISMA Flow chart) [129]. After reading the full text, three diagnostic accuracy studies (not reported in the Thoomes, 2018 review) matching the predefined PICO eligibility criteria were included in the assessment [135, 141, 142]. These three studies are summarized below: The prospective cohort study by Grondin (2021) tested diagnostic accuracy of single and combined upper limb neurodynamic tests (ULNTs) and included 85 patients between September 2017 and September 2019 [141]. The retrospective study by Park (2017), reviewed records of 135 patients who were referred to a pain clinic between September 2014 and August 2015 and assessed the diagnostic accuracy of the Spurling test and the newly introduced ‘neck tornado test’ (NTT or ‘Choi’s test’) [142]. The prospective cohort study by Sleijser-Koehorst (2021) assessed the diagnostic accuracy of the Spurling test, ULNT1 test and the shoulder abduction relief test in 134 patients in an unspecified time frame [135]. The characteristics of all eight included studies are described in Table 2.1.

Figure 2.1. PRISMA flow chart of included studies.



2.3.2 Methodological quality of included studies

The methodological quality of the three new studies was higher than most of the studies originally included (see Table 2.2 and Figure 2.2). The initial agreement between multiple raters on the score per domain in the original Thoomes et al (2018) review was good (ICC two-way random agreement=0.92% [95% CI: 0.78–0.98]); initial agreement between both raters on the score per domain on the newly added studies was “substantial” ($k = 0.78$, $p < 0.001$) and arbitration through the third author was not necessary.

The study by Grondin et al., (2021) [141] was the only study which overall was considered to be of high methodological quality. For the patient selection domain, three studies had a high risk of bias: one study [143] strongly resembled a case control study, one study [144] had inappropriate exclusion criteria and one study [142] was a retrospective study. One study had an ‘unclear’ risk of bias in the patient selection domain as patients were referred to a multidisciplinary clinic for conservative management where one would expect that consideration for surgery would be the reason for referral [135]. Regarding the applicability to the review question, one study [144] raised serious concerns due to an unclear process for excluding patients or what tests had been conducted prior to inclusion in the study as exclusions seemed likely to have taken place after history taking and the physical examination. This does not reflect the intended use of the index test. Two studies [143, 145] were unclear in this domain.

For the index test domain, no studies had a high risk of bias, two studies [37, 146] were “unclear” in that it was not clear if the index test results were interpreted without knowledge of the results of the reference standard. Six studies [36, 135, 141, 143-

145] specified a positivity threshold (interpretation of “positive” results). There were no concerns regarding the applicability for any of the studies.

With respect to the reference standard, four studies [36, 135, 141, 142] were considered to have an appropriate reference test (low risk of bias) and one study assessed the root canal diameter on MRI for all patients, and for a portion of patients, the results at surgery [147]. The remaining studies did not include information on the type of physical examination with the information in their (MRI or CT-myelography) reference standard conclusion, or were unclear with respect to blinding of assessors, resulting in an unclear score [35, 37, 146, 148].

The most common methodological concerns were with respect to the patient flow and timing. Two studies used different reference tests for some patients [145, 147]. One study [144] had too many missing patients and not all included patients received the same reference standard or index test, while another study [36] reported an inappropriate time between reference and index test. One study was a retrospective study [142] and it was not clear if the index test results were interpreted without knowledge of the results of the reference standard. Other studies did not report on time between the reference and index test.

Table 2.1 Characteristics of included studies

Study	Characteristics		Diagnostics			Study design
	Setting	Population	Indextest	Comparator test	Reference test (cut-off)	
Thoomes (2018)						
Apelby-Albrecht (2013)	Center for Spinal surgery Country: Sweden Prevalence: 0.69 (95% CI 0.54 to 0.81)	Mean age: NR Female (%): NR Duration of pain: NR	ULNT1 (median), ULNT2a (median), ULNT2b (radial) and ULNT3 (ulnar)	-	1: Clinical examination, medical history and; 2: MRI-scan and; 3 history	Diagnostic cohort study
Gumina (2013)	Shoulder Clinical Office and Orthopedic Spine Ambulatory Country: Italy Prevalence: 0.20 (95% CI 0.18 to 0.22)	Median age: NR Female (%): NR Duration of pain: NR	Arm squeeze test	-	1: Clinical examination and; 2: MRI-scan and; 3 history	Cohort study
Shabat (2012)	Spine Surgery Unit Country: Israel Prevalence: 0.68 (95% CI 0.71 to 0.75)	Median age: NR Female (%): NR Duration of pain: NR	Spurling (Ext+Rot+Ax compression)	-	Complete physical examination and MRI/CT imaging	Cohort study
Shah (2004)	Neurosurgical Unit Country: India Prevalence: 0.86 (95% CI 0.72 to 0.82)	Mean age: NR Female (%): NR Duration of pain: NR	Spurling (Ext+LF+Ax pressure)	-	T-2 weighted axial MRI	Prospective cohort study
Viikari-Juntura (1989)	Neurosurgery department Country: Finland Prevalence:	Mean age: NR Female (%): NR Duration of pain: NR	Spurling (LF+Rot+Ax compression)	-	1: conventional neurological examination and; 2: Cervical myelography	Prospective cohort study
Grondin (2021)	Neurosurgery department Country: France Prevalence: 0.317	Mean age (SD): 44 (CR+) and 45 (CR-) Female (%): NR Duration of pain, months (SD): 93 (98) for CR+ and 71 (62) for CR-	ULNT1 (median), ULNT2a (median), ULNT2b (radial) and ULNT3 (ulnar)	-	1: diagnosis based on clinical presentation by neurosurgeon and; 2: MRI-scan	Prospective cohort study
Park (2017)	Pain clinic in hospital Country: Korea Prevalence: 0.50 (95% CI 0.41 to 0.58)	Mean age: 53.4 (13.1) Female (%): 57 (42) Duration of pain: NR	Spurling (Ext+Rot+Ax pressure)		1 diagnosis based on clinical presentation by neurosurgeon and; 2: MRI-scan	Retrospective study
Sleijser-Koehorst (2021)	Multidisciplinary clinic Country: the Netherlands Prevalence: 0.37 (0.27 to 0.48)	Mean age (SD): 49.9 (10.7) Female (%): 65 (48.5) Median duration of pain, weeks (IQR): 26 (13- 104)	Spurling (Ext+Rot+LF)	ULNT1, Shoulder abduction relief test, and cervical distraction test	1: diagnosis based on clinical presentation by neurosurgeon and; 2: MRI-scan	Prospective cohort study

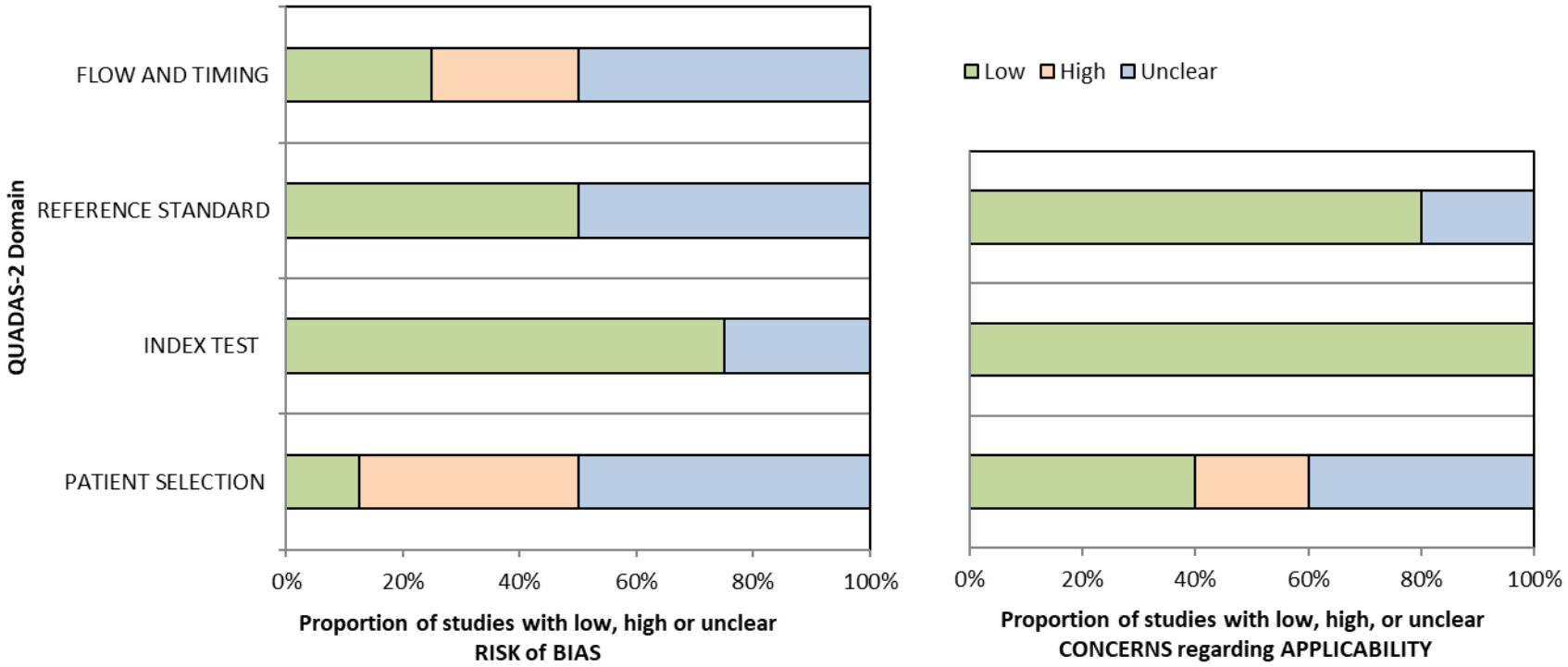
Abbreviations: Ax: axial compression/pressure; CR+: subjects with cervical radiculopathy; CR- subjects without cervical radiculopathy; Ext: extension; LF: lateral flexion; NR: not reported; Rot: rotation; SD: standard deviation; ULNT: Upper Limb Neurodynamic Tests.

Table 2.2 Tabular presentation for QUADAS-2 results

Study	RISK OF BIAS				APPLICABILITY CONCERNS		
	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD
Apelby-Albrecht, 2013	?	+	+	-	+	+	+
Gumina, 2013	-	+	?	?	?	+	+
Shabat, 2012	?	?	?	?	?	+	?
Shah, 2004	?	?	?	-	+	+	+
Viikari-Juntura, 1989	-	+	?	-	-	+	+
Park 2017	-	+	+	?	+	+	+
Grondin, 2021	+	+	+	+	+	+	+
Sleijser-Koehorst, 2021	?	+	+	+	+	+	+

+Low Risk -High Risk ? Unclear Risk

Figure 2.2 QUADAS-2. Proportion of studies with low, high or unclear risk of bias



2.3.3 Diagnostic accuracy

Diagnostic accuracy was assessed for the following physical tests: Spurling's test, upper limb neural tension tests (ULNT's), shoulder abduction (relief) test, arm squeeze test, axial traction test and neck tornado test. The reported or re-calculated diagnostic values of the individual studies are presented in Table 2.3.

Spurling's test

Spurling's test has been the subject of five studies to date, but all studies have used slightly different ways of executing the test or interpreting the results (see Table 2.3) [37, 135, 142, 146, 148]. It is therefore difficult to compare the different outcomes. The reported specificity was high across all studies and ranged from 0.84 to 1.00 (95% CI range: 0.56 – 1.00). Sensitivity ranged from "low" to "high" with values ranging from 0.38 – 0.98 (95%CI range: 0.22 – 0.99).

Upper limb Neural tension tests

Three recent studies assessed the diagnostic value of the ULNT 1 (with a median nerve bias) [74, 135, 141]. These studies reported a sensitivity of the ULNT1 ranging from "moderate" (0.59) to high" (0.83) (95%Cis ranging from 0.39 – 0.93). The specificity was reported as "moderate", ranging from 0.67 – 0.76 (95%Cis ranging from 0.48 – 0.93). As both the execution and the cut-off point of the ULNT1 in these studies were similar, we decided to pool the data from these three studies, resulting in a moderate specificity of 0.71 (85%CI 0.63 – 0.79) and sensitivity of 0.69 (95%CI 0.61 – 0.78) (see Table 2.4). Recently, two studies also reported on the diagnostic accuracy of using a combination of four ULNTs [74, 141]. Both studies reported comparable high sensitivity (0.96 [95%CI 0.81 – 0.99]) [141] and (0.97 85%CI [0.85 –

1.00]) [74] and low (0.47 [95%CI 0.33 – 0.60]) [141] to moderate (0.69 [95%CI 0.41 – 0.89) [74] specificity for having one of the ULNTs positive in a cluster of four ULNTs. Pooled values confirm a high sensitivity 0.97 (95%CI 0.89 – 1.00) and low specificity 0.51 (95%CI 0.39 – 0.63) (see Table 2.4).

Shoulder abduction test

Two studies reported on the Shoulder abduction (relief) test [135, 148]. The pooled data analysis showed a moderate specificity of 0.72 (95%CI 0.61 – 0.81) and low sensitivity of 0.49 (95%CI 0.38 – 0.61) (see Table 2.4).

Arm squeeze test, traction test and neck tornado test

The arm squeeze test, axial traction test and neck tornado test were all assessed in one single study only [35, 142, 148]. The arm Squeeze test showed a high sensitivity of 0.97 (95%CI 0.93 – 0.98) and high specificity of 0.97 (95%CI 0.95 – 0.98) [35]. The axial traction test showed a low sensitivity of 0.33 (95%CI 0.13 – 0.61) and high specificity of 0.97 (95%CI 0.83 – 0.99) [148]. The neck tornado test showed high sensitivity of 0.85 (0.74 – 0.93) and high specificity of 0.87 (0.76 – 0.94) [142].

Table 2.3. Diagnostic accuracy of included studies.

Author, year, N	Index Test(s)	TP	FP	FN	TN	Sensitivity (95%CI)	Specificity (95%CI)	PPV	NPV
Ape by-Albrecht (2013), n = 51	ULNT1 median nerve	29	4	6	12	0.83 (0.66-0.93)	0.75 (0.48-0.93)	0.88 (0.71-0.96)	0.67 (0.41-0.86)
	ULNT2a median nerve	23	4	12	12	0.66 (0.48-0.80)	0.75 (0.47-0.92)	0.85 (0.65-0.95)	0.50 (0.29-0.71)
	ULNT2b radial nerve	15	4	20	12	0.43 (0.27-0.60)	0.75 (0.47-0.92)	0.79 (0.54-0.93)	0.38 (0.22-0.56)
	ULNT3 ulnar nerve	25	2	10	14	0.71 (0.54-0.85)	0.88 (0.60-0.98)	0.93 (0.74-0.99)	0.58 (0.37-0.77)
	Combined 4 ULNTs	34	5	1	11	0.97 (0.83-1.00)	0.69 (0.41-0.88)	0.87 (0.72-0.95)	0.92 (0.59-1.00)
Gumina (2013), n = 1567	Arm Squeeze test	295	43	10	1219	0.97 (0.93-0.98)	0.97 (0.95-0.98)	0.87 (0.83-0.91)	0.99 (0.98-0.99)
Shabat (2012), n = 257	Spurling's test (Ext+Rot): radicular pain	115	6	3	49	0.98 (0.92-0.99)	0.89 (0.77-0.96)	0.95 (0.89-0.98)	0.94 (0.83-0.99)
	Spurling's test: radiating pain	196	9	3	49	0.99 (0.95-1.00)	0.85 (0.72-0.92)	0.96 (0.92-0.98)	0.94 (0.83-0.99)
Shah (2004), n = 50	Spurling's test (Ext+LF)	28	0	15	7	0.65 (0.49-0.79)	1.00 (0.56-1.00)	1.00 (0.85-1.00)	0.32 (0.15-0.55)
Vi kari-Juntura (1989), n = 43	Spurling's test (LF+Rot), n=43:	12	3	20	51	0.38 (0.22-0.56)	0.94 (0.83-0.99)	0.86 (0.56-0.98)	0.80 (0.51-0.95)
	Axial traction test, n=24:	5	1	10	32	0.33 (0.13-0.61)	0.97 (0.83-0.99)	0.83 (0.37-0.99)	0.76 (0.60-0.87)
	Shoulder Abduction test, n=13:	7	2	8	11	0.47 (0.22-0.73)	0.85 (0.54-0.97)	0.78 (0.40-0.96)	0.58 (0.34-0.79)
Grondin (2021), n = 85	ULNT1 median nerve	16	14	11	44	0.59 (0.39-0.78)	0.76 (0.63-0.86)	0.53 (0.34-0.72)	0.80 (0.67-0.90)
	Combined 4 ULNTs	26	31	1	27	0.96 (0.81-1.00)	0.47 (0.33-0.60)	0.57 (0.44-0.73)	1.00 (0.99-1.00)
Park (2017), n = 135	Spurling;s test (Ext+Rot)	37	1	30	67	0.55 (0.43-0.67)	0.99 (0.92-1.00)	0.97 (0.85-1.00)	0.59 (0.59-0.78)
	Neck Torsion test	57	9	10	59	0.85 (0.74-0.93)	0.87 (0.76-0.94)	0.86 (0.76-0.94)	0.86 (0.75-0.93)
Sleijser-Koehorst (2021), n = 134	Spurling's test (Ext+Rot+LF)	38	11	27	57	0.59 (0.46-0.70)	0.84 (0.72-0.91)	0.78 (0.63-0.88)	0.68 (0.57-0.78)
	ULNT1 median nerve	43	22	21	44	0.67 (0.54-0.78)	0.67 (0.54-0.78)	0.66 (0.53-0.77)	0.68 (0.55-0.79)
	Shoulder Abduction test,	32	17	32	50	0.50 (0.37-0.63)	0.75 (0.62-0.84)	0.65 (0.50-0.78)	0.61 (0.50-0.72)

TP: true positive, FP: false positive, TN: true negative, FN: false negative, PPV: positive predictive value, NPV; negative predictive value, ULNT: upper limb neural test, Ext: Extension, Rot: rotation, LF: lateral flexion

Table 2.4. Pooled data results of diagnostic value.

Index Test	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)	Accuracy (95%CI)
ULNT1 alone	0.69 (0.71 – 0.78)	0.71 (0.63 – 0.79)	0.69 (0.62 – 0.75)	0.72 (0.66 – 0.78)	71% (65 – 76%)
Combined ULNTs; 1 positive	0.96 (0.88 – 1.00)	0.51 (0.39 – 0.63)	0.63 (0.50 – 0.80)	1.00 (1.00 – 1.00)	52% (43 – 60%)
Shoulder Abduction test	0.49 (0.38 – 0.61)	0.72 (0.61 – 0.81)	0.62 (0.52 – 0.71)	0.60 (0.54 – 0.66)	61% (53 – 68%)
PPV: positive predictive value, NPV; negative predictive value, ULNT: upper limb neural test.					

2.3.4 Level of evidence

The justification for downgrading the level of evidence for the different comparisons is presented in **APPENDIX 3.**

Four combined Upper limb Neural tension tests

There is low-level evidence that the sensitivity of having one out of four combined ULNT's positive is likely high (>0.80) for diagnosing CR [74, 141]. There is very low-level evidence about the moderate specificity of four combined ULNTs for diagnosing CR [74, 141], and there is low-level evidence that the PPV and NPV of four combined ULNT's is high for diagnosing CR [74, 141].

ULNT1

There is very low-level evidence of moderate to high sensitivity and moderate PPV and NPV of the ULNT1 used alone for diagnosing CR [74, 135, 141]. There is very low-level evidence of moderate specificity for diagnosing CR [74, 135, 141].

Arm squeeze test

There is low-level evidence of high diagnostic accuracy (sensitivity, specificity, PPV and NPV) for the arm squeeze test for diagnosing CR [35].

Spurling's test

There is very low-level evidence of low to moderate sensitivity, PPV and NPV of Spurling's test for diagnosing CR [37, 135, 142, 146, 148]. There is low-level evidence of high specificity of Spurling's test for diagnosing CR [37, 135, 142, 146, 148]

Axial traction test

There is very low-level evidence of low sensitivity, moderate NPV and high specificity and PPV supporting the use of the axial traction test for diagnosing CR [148].

Shoulder abduction test

There is low-level evidence of low sensitivity and moderate NPV for the shoulder abduction test for diagnosing CR [135, 148]. There is very low-level evidence of moderate specificity and PPV for the shoulder abduction test for diagnosing CR [135, 148].

Neck tornado test (Choi's test)

There is very low-level evidence of high sensitivity, specificity, PPV and NPV supporting the use of the Neck tornado test (Choi's test) in diagnosing CR [142].

2.4 DISCUSSION

This study aimed to assess the value of physical tests used to diagnose CR and did so by updating a systematic review [38]. Three additional studies were added to the original review and the GRADE method approach was used to grade the strength of the evidence across all included studies [128]. Compared to the original review, more support on the level of evidence on the diagnostic accuracy of Spurling's test, the ULNTs and the shoulder abduction test was added. Information on one more newly proposed test, the Neck Torsion test, was also added [142].

A previous study concluded that (when consistent with the history and other physical findings), a positive Spurling's, traction test and Valsalva's manoeuvre might be indicative of CR, but that a negative ULNT might be used to rule it out [19]. With respect to Spurling's test, the present review confirmed this high specificity, which was also mentioned in the original systematic review [38]. The current review also showed that the sensitivity of the ULNT1 ranged from moderate to high, confirming that a negative UNLT 1 might assist in a decision of ruling a CR out. In addition, the present study showed the high sensitivity of having one test positive in performing a cluster of four ULNTs. One study on the diagnostic value of Valsalva's manoeuvre [126] was not added to the present review, as that study used a different reference test (i.e., EMG) to the reference test proposed in the inclusion criteria.

The moderate specificity of 0.71 (95% CI 0.63 - 0.79) and moderate sensitivity of 0.67 (95% CI 0.54 - 0.78), reported in the present review are in line with results of a recent systematic review reporting on the diagnostic accuracy of

the ULNT1 alone, showing a pooled specificity of 0.54 (95% CI 0.36 - 0.71) and sensitivity 0.69 (95% CI 0.50 - 0.83) and a summary receiver operating characteristic curve area of 0.65 (95% CI 0.61 - 0.69) [149].As expected, the condition of having one out of four ULNT tests positive was the most sensitive combination and as such, has the ability to “rule out” CR as shown in the study by Grondin et al., [141] which reported a negative LR of 0.08 (or strong evidence [150, 151]). Additionally, the condition of having four out of four ULNT tests positive was the most specific and has been reported to have an infinite LR + in the study by Grondin et al., [141]. But it should be noted that in that study there were only three cases in which all four tests were positive. The condition of having three of four tests positive was reported to have a positive LR of 12.89 (‘strong evidence’ [150, 151]).

2.4.1 Strengths and limitations

The present review has several strengths in that it followed the guidelines set by the Cochrane Diagnostic Test Accuracy group, assessed the methodological quality of all studies using the QUADAS-2 guidelines and assessed the strength of the evidence using the GRADE method approach. Nevertheless, the evidence on the measurement properties of physical tests diagnosing CR is sparse. Additionally, the strength of the evidence of the tests was low to very low. This was mainly due to methodological shortcomings (risk of bias) and broad confidence intervals, often combined with small study populations (imprecision) and clinical heterogeneity. Therefore, based on the literature, no solid conclusions can be drawn.

2.4.2 Clinical implications

A best evidence synthesis based on the results from this study suggest that, when consistent with the history and other physical findings, a positive outcome of a combination of Spurling's test and using the outcome of a cluster of four ULNTs are able to increase the likelihood of a diagnosis of CR. Adding the outcome of the Arm Squeeze test (due to the large cohort it was studied in) and the Shoulder Abduction Relief test (as it was assessed in > 1 study) might be used to further increase this likelihood. Negative outcomes of the Spurling's test and also the outcome of a cluster of four ULNTs can increase the likelihood of ruling out CR.

CR is usually proposed as a clinical diagnosis [7, 12, 19, 38, 60]. As such the use of the ULNT for CR are similar to the use of the Straight Leg Raise or Lasègue's test in lumbo-sacral radiculopathy [152], where the Straight Leg Raise also is a test of high sensitivity used mainly to rule the condition out [153, 154].

A complete patient history taking leading to the hypothesis of CR is one of the most important diagnostic tools for any clinician [155, 156]. Augmenting the diagnostic probability from that hypothesis with physical tests is a cost-effective way when compared to diagnostic imaging such as MRI or CT. Additionally, these tests have been proposed to only be used in patients failing conservative management and being potential candidates for surgery [12, 60, 157].

2.4.3 Implications for future research

Future research should focus on the validity and diagnostic accuracy of the neurological examination (myotendon reflexes, sensibility testing and key muscle strength testing) often used by both General Practitioners and medical specialists (neurologists, neurosurgeons) when assessing patients with radiating arm pain. Additionally, evaluating the most effective way of executing Spurling's test needs to be assessed, as there are many inconsistencies and variations in its execution [158]. Assessing the diagnostic accuracy of patient interview items is another subject worth further study [159].

The diagnostic value of neurodynamic testing raises the question if there is a difference in neurodynamic mobility between patients with a CR and healthy controls and this led to the research question posed in the next chapter **(CHAPTER 3)**.

2.5 CONCLUSION

When consistent with the history and other physical findings, clinicians can use the outcome of Spurling's test and the outcome of a cluster of four ULNTs to assist their clinical reasoning in diagnosing CR. However, evidence on the measurement properties of all physical tests diagnosing CR is sparse and the strength of the evidence was low to very low for all outcomes of all tests, implying that new studies of high methodological value are required to strengthen these results. If the outcome of neurodynamic tests differ between patients with a CR and healthy controls, this may imply that nerves move

differently in their tract during ULNTs in patients with a CR and this is explored in the following chapter.

CHAPTER 3
EXCURSION OF THE MEDIAN NERVE DURING A CONTRA-LATERAL CERVICAL LATERAL GLIDE MOVEMENT IN PEOPLE WITH AND WITHOUT CERVICAL RADICULOPATHY

This chapter reports in full a manuscript which has been published previously (Thoomes et al., 2021) [160]. Changes have been made in the text of this chapter for the purposes of a thesis, specifically;
- The introduction has been edited to reflect the content of previous chapters in this thesis and avoid repetition
- The discussion and conclusion have been edited to increase cohesion between linked studies in later chapters.
However, the majority of the text in this chapter reflects the published manuscript verbatim and has been reprinted with permission from Elsevier / Musculoskeletal Science and Practice.

3.1 INTRODUCTION

In the previous chapter, we showed that neurodynamic testing by executing four ULNTs has high sensitivity and moderate specificity for diagnosing a patient with a CR. Additionally, in the management of patients with CR, there is low-level evidence for the effectiveness of multimodal interventions with a neurodynamic intent (including neurodynamic mobilisation) combined with joint and muscle mobilisations [56, 80-82].

A segmental contralateral cervical lateral glide (CCLG) mobilisation technique is effective for improving the range of elbow extension, reducing symptom distribution and reducing pain intensity during neural provocation tests that tension the median nerve in patients with nerve-related neck and arm pain [79, 82]. The CCLG technique can be used to mobilise the median nerve in relation to non-neural structures that surround the nerve and nerve root (e.g. muscle, tendon, fascia and bone: i.e. the “mechanical interface”) [88, 89]. As such, the CCLG mobilisation technique is often included as part of a conservative treatment regime for patients with CR [56, 57, 63, 161, 162].

Hypotheses about the mechanisms of effect of neurodynamic mobilisation have evolved from an original mechanical paradigm of influencing nerve movements and nerve biomechanics [83, 84]. More recent theoretical models, based on fundamental research, indicate that neurodynamic mobilisation may improve neural vascularity, nerve movement and restoration of optimal intraneural homeostasis by reducing intraneural oedema [85-87]. Ultrasound imaging has demonstrated sliding of the median nerve at the wrist and the elbow during the CCLG technique in healthy individuals [163]. However, nerve movement in response to the CCLG has not been assessed in patients with CR. Based on our current understanding of how nerves in the upper limb respond to limb movements, movement of the median nerve may be reduced in patients with CR, possibly due to a restriction in sliding of the cervical nerve roots through the intervertebral foramina. Therefore, an initial aim of this study was to assess longitudinal excursion of the median nerve using ultrasound imaging in patients with CR with radicular pain and asymptomatic participants during a CCLG movement. Given that it is unclear whether conservative treatments such as neural mobilisation improve nerve excursion, a further aim of this study was to reassess median nerve excursion at three months following neural mobilisation treatment in patients with CR. A final aim was to correlate changes in nerve excursions with changes in clinical signs and symptoms.

3.2 METHODS

3.2.1 Study design

This was a case-controlled study registered at the NTR trial register (NTR7458) and approved by the Medical Ethical Committee of the Erasmus Medical Centre under NL66281.078.18. (MEC-2018-139, **APPENDIX 4**). Both study and research design conform to the STROBE statement [164]. All measurements were performed between October 2018 and September 2019 in an outpatient physiotherapy clinic by two clinical researchers (ET, MTdG).

3.2.2 Sample size

A sample size calculation performed using G*Power [165] on the differences and the variability of longitudinal nerve excursion (SEM ± 0.2 mm) reported in other studies [163, 166, 167] confirmed that 18 subjects per group was necessary to detect a 0.1 mm difference in the excursion of the median nerve with a power of 90% an α of 0.01 [168]. In order to compensate for a potential loss to follow-up, 20 participants were recruited into each group.

3.2.3 Participants

Twenty patients, aged 18 years and over, with clinical signs of CR, which included motor and/or sensory changes (paraesthesia or hypoesthesia) and evidence of radicular pain (i.e. radiating pain in the arm and/or peri-scapular region), were recruited through general practice and neurology clinics. Radicular pain was confirmed by a positive Spurling's test (reproducing patient specific symptoms) and/or positive ULNT (either median, ulnar or radial nerve biased) [38, 126].

A recent review reported high specificity (ranging from 0.89-1.00; 95%CI: 0.59-1.00) and moderate sensitivity (ranging from 0.38-0.97; 95%CI: .021-0.99) [38]. A positive ULNT test was defined as: reproducing patient-specific neurogenic pain (burning or lightninglike pain, tingling sensation, according to dermatome pattern in neck and/or arm; and an increase /decrease of symptoms with structural differentiation; and a notable difference in painful radiation between right and left sides [38, 74]. The combined use of four ULNTs has a reported sensitivity of 0.97 (95% CI: 0.83–1.00) and a specificity of 0.69 (95% CI: 0.41–0.88) [38, 74]. Nerve root encroachment was confirmed via magnetic resonance imaging [38, 126, 137].

Twenty asymptomatic volunteers were recruited and screened to exclude a history of CR and/or radicular referred arm or neck pain in the previous 12 months. All asymptomatic participants had negative findings for the Spurling's Test and ULNTs.

General exclusion criteria for both groups included the presence of chronic diseases, inability to understand and/or adhere to the research protocol, organ failure and other serious medical conditions (systemic inflammations or disorders e.g. diabetes, tumours, etc.). Participants were also excluded if they had a neurological condition or other systemic disorders (e.g. diabetes) that might alter the function of the nervous system or if they had a history of major trauma or surgery to the cervico-thoracic region. Informed written consent was obtained for all participants.

3.2.4 Study protocol

Patients underwent a clinical assessment by one of the investigators (ET or MTdG), which included recording the duration of their symptoms, a detailed medical history and specific physical tests, including Spurling's, Arm Squeeze, Davidson's, traction-distraction and ULNT (median, ulnar and radial nerve biased) tests [38]. Muscle stretch reflexes of the biceps, triceps and brachioradialis muscles were also assessed for relevant side-to-side differences, together with nerve root specific myotomal muscle strength testing using a hand-held dynamometer and a 'patient-initiated break testing' protocol (MicroFET2™, Hoggan Health Industries Inc., USA). Changes in sensory perception threshold over the C5-C8 dermatomes were assessed using five pre-selected Semmes-Weinstein filaments of decreasing evaluator size (6.65, 4.56, 4.31, 3.61 and 2.83 respectively) and target force grams (300.0, 4.0, 2.0, 0.4 and 0.07 respectively) (Baseline® Tactile™ Monofilament) [126]. The monofilament was kept perpendicular to the skin and increasing amounts of pressure were applied until the monofilament bent into a C shape; patients were asked to report if they felt the pressure while whilst the pressure was held for 1 second. A side-to-side difference of one step was considered a relevant change.

Each patient was asked to indicate the area where they experienced the most pain. Additionally, an 11-point NPRS (ranging from '0' representing "no pain" to '10' representing "worst pain imaginable") [169] was used to quantify the average pain intensity experienced in that region throughout the day. The level of disability was assessed using the validated NDI [169-171] and functional limitations were recorded using the PSFS [172, 173].

The Occiflex™ (Enraf Nonius BV, Rotterdam The Netherlands) was used to record the degrees of active cervical range of movement (ROM) in flexion/extension, rotation and lateral flexion in a standardised manner and to record and perform the individual passive pain-free range of CCLG movement (see Figure 3.1). The Occiflex™ is a treatment plinth with a computer-controlled headrest that can perform accurate 3-dimensional movements of the cervical spine [174]. The patient's head is not restrained, and the patient can sit up at any time [175, 176]. The range of CCLG was determined by the therapist performing a passive CCLG which was recorded by the Occiflex software; the therapist assessed non-provocative passive CCLG movement up to the point of "taking up the slack" and this was defined as the patient's available 'resistance free' movement. Participants were positioned in a standardised manner with 45° of shoulder abduction, elbow extension, forearm supination and neutral wrist position. (see Figure 3.2) to maximize potential nerve excursions and allow easy scanning access to the median nerve [163, 177].

Figure 3.1 Measuring Active ROM with the Occiflex™.

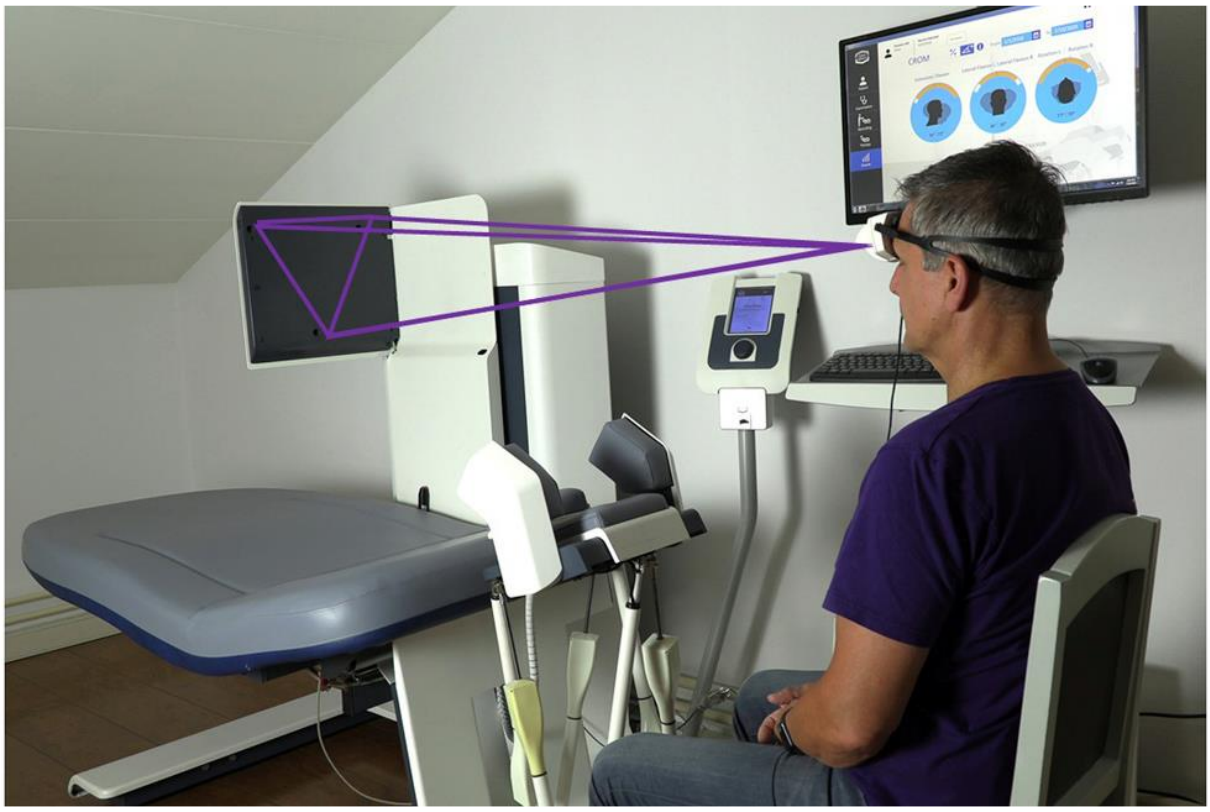
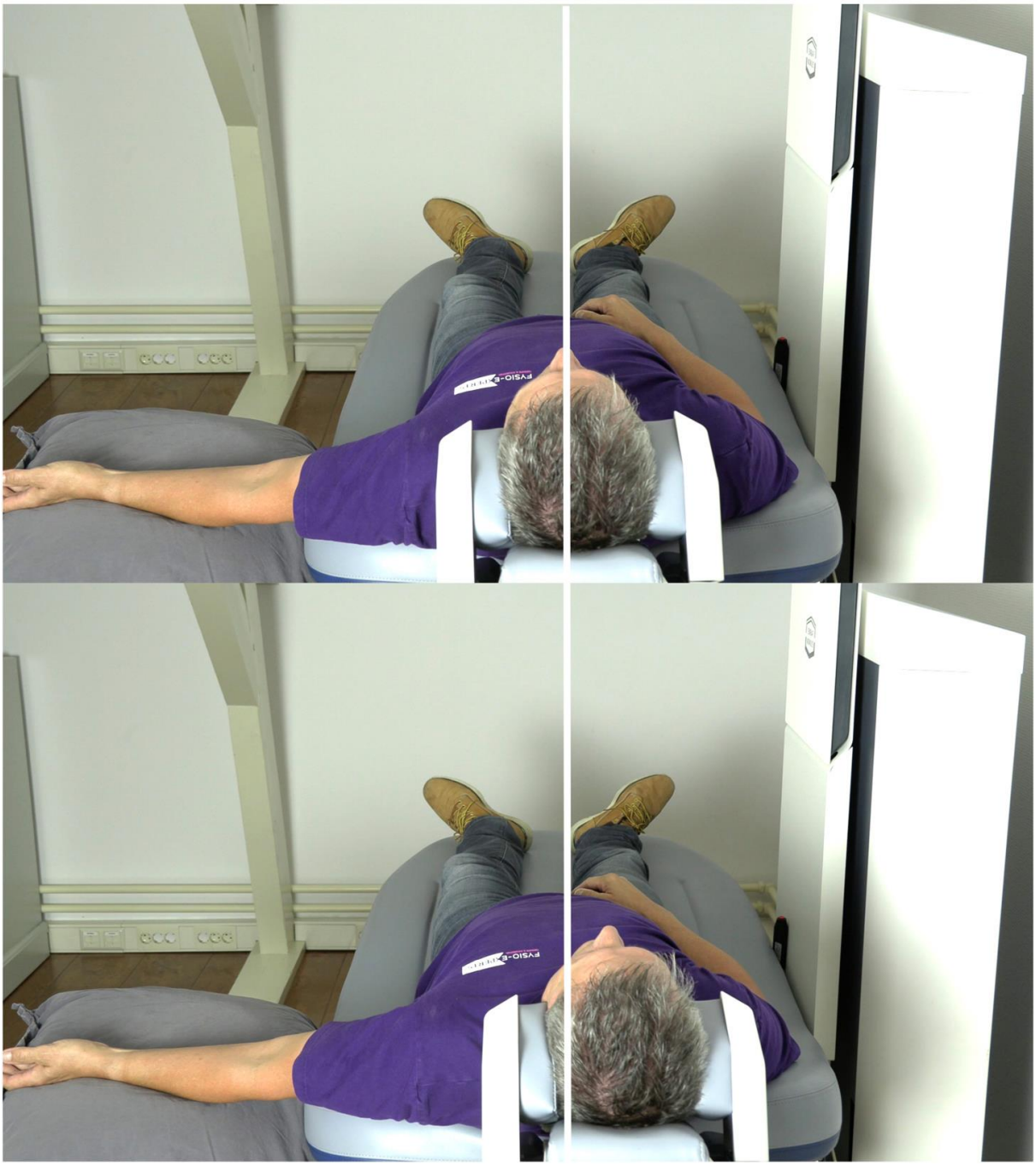


Figure 3.2 Contralateral Cervical Lateral Glide (CCLG) performed by the Occiflex™.



All participants were familiarised with the equipment and conditions during which five repeat CCLG movements were performed. After the familiarisation trials, repeated CCLG movements with a speed of 1.5°/second were performed within the individual participant's available pain free and resistance free range of motion for 3 minutes. The 3 minutes were based on the time needed for ultrasound scanning, clinical experience and treatment time used in previous studies [175, 176].The CCLG movement sequence was stored so that the same parameters could be applied during the follow-up measurements (patients only). During the CCLG movement, the median nerve was imaged longitudinally by a single investigator (ET) using a 53 mm linear array transducer (3-13 MHz; Esaote MyLabFive, Esaote SpA, Italy). Two scanning sites were used: immediately proximal to the wrist and at the elbow (over the joint). Three repeat cine-loops were obtained at each location and each cine-loop consisted of a sequence of approximately 104 images obtained at 16 frames/second. The order that each location was imaged was randomised. Cine-loops were stored offline in an AVI format and longitudinal movements of the median nerve were analysed using frame-by-frame cross correlation algorithm software designed in Matlab (MathWorks, Inc, Natick, MA) [167, 177, 178]. Assessing nerve excursions this way is accurate and reliable [179].

For three months following the initial examination, the patients received personalised conservative physiotherapy treatments once a week from one of two investigators (ET or MTdG), each with more than 15 years of clinical experience. Treatments consisted of cervico-thoracic joint mobilisation, neurodynamic mobilisations (mainly 'openers' and 'sliders') and specific

(home) exercises focused on neurodynamic mobilisation and endurance of the deep neck flexor and extensor muscles [56, 57, 180]. Patients were also prescribed oral analgesics, which included NSAIDs and/or opioids (e.g. Tramadol®, Lyrica® or Oxycodon®).

At three months, the patients were reassessed, which included a repeat of the initial neurological and provocative tests performed during the initial assessment and completion of the NDI and PSFS questionnaires.

Additionally, a GPE questionnaire was used to assess health transition [181]. Patients were considered as responding to therapy if they reported a GPE of "completely recovered", "much improved", or "slightly improved"; achieved a relevant difference in PFPS score of more than 2 points [170]; and reported a decrease in NPRS score of at least 3 points [169]. Patients who did not reach all three of these criteria were designated as "not responding to therapy".

The CCLG movement protocol was repeated and ultrasound images of the median nerve were obtained (by ET) as in the initial assessment. All data was anonymised.

3.2.5 Analysis

Data was assessed for normality using Shapiro-Wilk tests. Descriptive statistics were used to report excursion of the median nerve at each scanning location. Comparisons of nerve excursion at both scanning locations between those with and without CR were determined using Mann-Whitney U tests. Differences between baseline (T0) and the three month follow-up (T1) were calculated using Wilcoxon Matched-Pairs test. Data is presented as medians and interquartile ranges (IQRs).

Spearman's rho was used to calculate the correlation between the degree of contralateral cervical movement with the excursions of the median nerve in both groups, with values of 0.00-0.29 representing "very weak"; 0.30-0.49 "weak"; 0.50-0.69 "moderate"; 0.70-0.89 "strong" and 0.90-1.0 "very strong" correlation.

Spearman's rho was also used to assess the correlation between signs and symptoms (outcome of physical tests, NDI, NPRS and the GPE) with the differences in median nerve excursion at the three month follow-up only for those with CR. Individual improvement in nerve excursion was considered to be > 0.2mm.

As an indicator of intertester reliability, a total of three randomly selected ultrasound sequences were also assessed by a second investigator (AD), and intraclass correlation (ICC 2,1) estimates, standard error of measurement (SEM), smallest detectable change (SDC) and the 95% confident intervals between raters were determined. All analyses were performed using SPSS 24 (IBM, Chicago, IL)

3.3 RESULTS

The interrater agreement in pilot testing for the assessment of median nerve excursion from the ultrasound videos was excellent (ICC 2,1 = 0.981; 95%CI 0.946-0.994), with a SEM of 0.137 mm and a SDC of 0.38mm.

Twenty consecutive eligible patients were invited and all agreed to participate. Participant characteristics are summarised in Table 3.1

Table 3.1 Participant characteristics

	Patients	**Controls**
N	20	20
Male gender N, (%)	10, (50%)	10, (50%)
Female gender N, (%)	10, (50%)	10, (50%)
Mean age, years (SD)	46.4 (10.3)	46.4 (10.3)
Right side dominant N (%)	18 (90%)	18 (90%)

3.3.1 Baseline measurements (T0)

In 55% of patients, radicular symptoms were reported on the left side and in 75% of the patients, pain was reported over the peri-scapular region. All patients reported pain in their both the neck, shoulder and arm. The average level of pain (NPRS) at the area of most pain was 7.7/10 (SD 1.3). The mean score on the NDI was 31/100 (SD12.3; range 10-56) and PSFS 7.9/10 (SD 0.4). Cutaneous sensitivity was diminished in 59% of patients at baseline, muscle-tendon reflex was reduced in 60% of patients and there was evidence of muscle weakness in 85% of patients (Table 3.2). Magnetic resonance imaging confirmed a relevant C5, C6 or C7 nerve root encroached in all patients. One patient dropped out of the study following the first assessment due to medical care for unrelated co-morbidities.

Table 3.2 Patient signs and symptoms recorded at baseline (T0) and at three month follow-up (T1)

Mean duration in weeks (range)	20.7 (3-104)		
Left side radicular symptoms N, (%)	11 (55%)		
Area of most pain, n (%) Periscapular Upper arm Neck	 15 (75%) 4 (20%) 1 (5%)		
	T0 (n=20)	**T1 (n=19)**	***p*-value**
Mean NPRS most painful area, 0-10 (SD; range)	7.7 (1.3; 3-9)	2.6 (2.1; 0-8)	$p < 0.001$
Mean NDI score, 0-100 (SD; range)	31 (12.3; 10-56)	12 (9.3; 1-26)	$p < 0.001$
Mean PSFS score, 0-10 (SD; range)	7.9 (0.4; 6.7-8.3)	2.1 (2.3; 0-7.7)	$p < 0.001$
Paresthesia present in: n (%)	20 (100%)	9 (47,7%)	$p < 0.001$
Sensibility diminished No loss C6 dermatome C7 dermatome C8 dermatome	 10 (50%) 7 (35%) 2 (10%) 1 (5%)	 18 (94.7%) 1 (5.3%) 0 (0%) 0 (0%)	Overall $p < 0.01$
Muscle reflex • No loss • C5 – biceps • C6 – brachioradialis • C7 – triceps	 • 8 (40%) • 3 (15%) • 3 (15%) • 6 (30%)	 • 17 (89.5%) • 1 (5.3%) • 1 (5.3%) • 0 (0%)	Overall $p < 0.001$
Muscle weakness • No loss • C5 – biceps • C6 – wrist extensors • C7 – triceps	 • 3 (15%) • 1 (5%) • 11 (55%) • 5 (25%)	 • 13 (68.4%) • 0 (0%) • 5 (26.3%) • 1 (5.3%)	Overall $p < 0.001$
Positive provocative tests • Spurling's test, n (%) • Arm squeeze, n (%) • Davidson, n (%) • Traction-distraction, n (%) • Combined ULNTs	 • 19 (95%) • 14 (70%) • 10 (50%) • 9 (45%) • 20 (100%)	 • 9 (47.4%) • 2 (10.5%) • 1 (5.3%) • 1 (5.3%) • 7 (36.8%)	 $p < 0.01$ $p < 0.001$ $p < 0.001$ $p < 0.01$ $p < 0.001$

NPRS = numerical pain rating scale; NDI = Neck Disability Index; PSFS = Patient Specific Functional Scale; ULNT = Upper Limb Neural Test

3.3.2 Nerve excursion at baseline (T0)

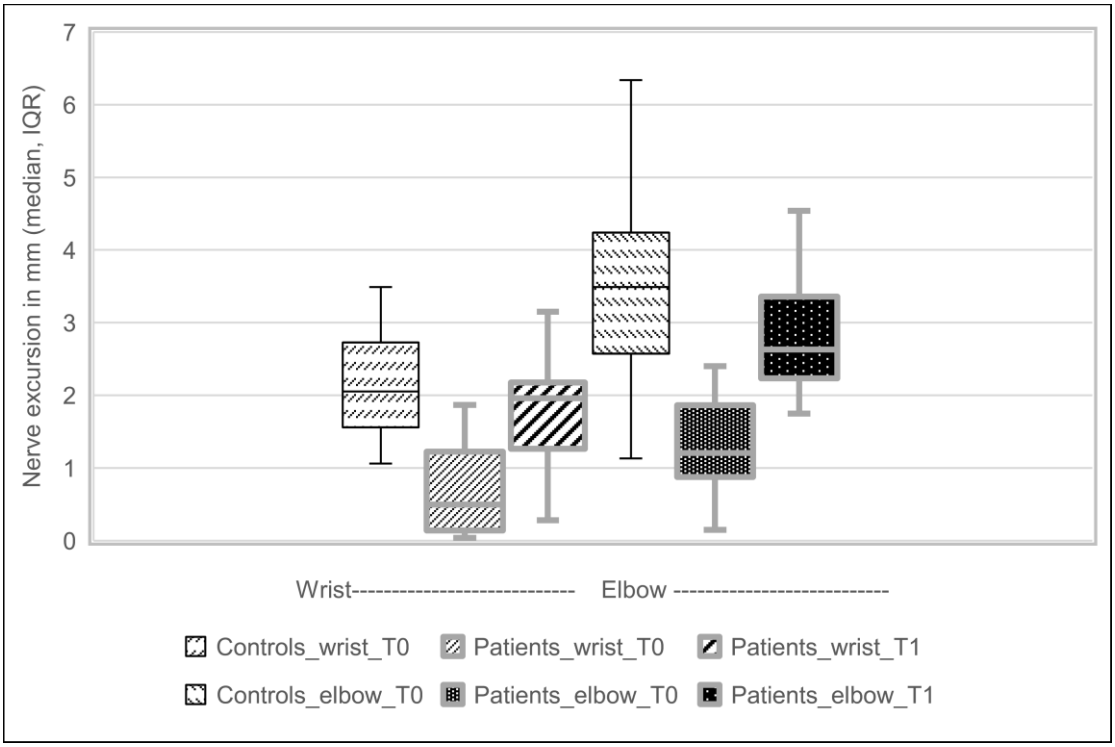
The degrees of pain and resistance free CCLG movement in the Occiflex™ ranged from 2-6° (Patients median (*Mdn)* =3°; IQR = 2° - 4°, Controls (*Mdn* =3.23°; IQR = 2.59° – 4.00°) and did not differ significantly between groups (*p*

= 0.304). One degree of CCLG movement approximately equalled one centimetre of transverse displacement. In all participants, the median nerve moved in a proximal direction during the CCLG. In the asymptomatic participants, the *Mdn* excursion was 2.10 mm (IQR = 1.42 - 2.80) and 3.49 mm (IQR = 2.45 – 4.24) at the wrist and elbow respectively ($p < 0.05$). In those with CR, the median nerve movement was significantly reduced at both the wrist (*Mdn* = 0.50 mm; IQR = 0.13 – 1.30, $p < 0.05$) and the elbow (*Mdn* = 1.21 mm (IQR = 0.85 – 1.94), $p < 0.05$) compared to the control group (Figure 3.3).

3.3.3 Follow-up measurements (T1)

At the three month follow-up (T1), there was a significant reduction of pain intensity (NPRS), disability (NDI) and functional limitations (PSFS) ($p < 0.05$; Table 3.3). Additionally, there was a significant increase in median nerve excursion compared to T0, at both the wrist and elbow ($p < 0.05$; Figure 3.3). Wilcoxon Signed-Ranks Test indicated that the median post-test ranks for the wrist and elbow (*Mdn* = 1.96mm, 2.63mm respectively) were significantly higher than the median pre-test ranks (*Mdn* = 0.5mm, 1.21mm; Z =- 3.82, $p < 0.01$; Z = -3.78, $p < 0.01$ respectively). There was no significant difference in median nerve excursion at the wrist and the elbow between patients at T1 and asymptomatic participants (T0; $p > 0.05$) (Figure 3.3).

Figure 3.3 Excursions of the median nerve at the wrist and elbow in Patients and Controls at T0 and Patients at T1 in mm (median, IQR).



3.3.4 Correlations

For both groups, there was a weak but not statistically significant correlation between the degrees of CCLG movement and the extent of excursion of the median nerve measured at the elbow at T0 (patients: $r = 0.3$, $p = 0.183$ and controls: $r = 0.4$, $p = 0.086$ respectively). In contrast, there was no correlation between the degrees of CCLG movement and the extent of excursion of the median nerve measured at the wrist in patients ($r = 0.0$, $p = 0.963$) and only a weak correlation for the controls ($r = 0.3$, $p = 0.138$).

For the patient group at the three month follow-up (T1), the correlations between the degrees of CCLG movement and the extent of excursion of the median nerve measured at the wrist and elbow were weak and not statistically significant ($r = 0.3$, $p = 0.229$ and $r = 0.3$, $p = 0.146$ respectively).

There was a strong statistically significant correlation between the increase in median nerve excursion at the elbow and scores on the GPE ('completely recovered' or 'significantly improved'; r = 0.8, $p < 0.001$) and also between the reduction of scores on the NPRS ($r = 0.7$, $p < 0.001$) and PSFS ($r = 0.6$, $p < 0.01$) (Table 3.3). And although no causality can be inferred, patients who did not show an improvement in nerve excursion at the elbow at T1 (n = 2), were also non-responders to the conservative management at three months and both went on to have either surgery or (nerve root sleeve) injections.

Table 3.3 Correlation between change in nerve excursion in the patient group (T1-T0) measured at the wrist and elbow and GPE score, decrease in NPRS and PSFS and CCLG movement

Correlation	**Difference in median nerve excursion (T1-T0; mm) at the wrist**			**Difference in median nerve excursion (T1-T0; mm) at the elbow**		
GPE	$r = 0.3$ ($p = 0.255$)			$r = 0.8$ ($p < 0.001$)		
Decrease in NPRS	$r = 0.2$ ($p = 0.345$)			$r = 0.7$ ($p < 0.001$)		
Decrease in PSFS	$r = 0.4$ ($p = 0.106$)			$r = 0.6$ ($p < 0.01$)		
CCLG movement	Controls T0	Patients T0	Patients T1	Controls T0	Patients T0	Patients T1
	$r = 0.3$ ($p = 0.138$)	$r = 0.0$ ($p = 0.963$)	$r = 0.3$ ($p = 0.229$)	$r = 0.4$ ($p = 0.086$)	$r = 0.3$ ($p = 0.183$)	$r = 0.3$ ($p = 0.146$)

GPE = Global Perceived Effect; NPRS = Numerical Pain Rating Score; PSFS = patient Specific Functional Scale; CCLG = Contra-lateral Cervical Lateral Glide

3.4 DISCUSSION

This is the first study to demonstrate a difference in longitudinal median nerve excursion at the wrist and elbow during a mechanically induced CCLG movement between patients with CR with radicular pain and healthy controls. It is also the first to demonstrate an increase in median nerve excursion back to normal range in patients with CR following 3 months of personalised

physiotherapy management. The significant correlation between change in median nerve excursion at the elbow following treatment and changes in pain intensity (NPRS), disability (PSFS) and GPE-score suggests a potential role for nerve sliding in pain management in patients with CR.

The level of median nerve excursion in the healthy control groups was comparable to previous reports [163, 177, 182]. The increase in nerve excursion at the elbow compared to wrist (i.e. at a more proximal location) is consistent with straightening, and possibly stretching, of the nerve trunk during the CCLG. As the nerve bed length is increased, the nerve straightens proximally, at which point, movement is transferred distally along the length of the nerve. Once the neural slack has been taken up, by positioning the arm in 45° of abduction (similar to how participants in this study were positioned), there should be an optimal amount of sliding transferred along the neural track [182, 183]. In patients, longitudinal nerve sliding has been considered to reduce intraneural oedema [82, 85, 87, 184].

A reduction in median nerve sliding has been reported in clinical populations such as carpal tunnel syndrome [166, 185-187], non-specific arm pain [188, 189], whiplash associated disorders [188]. Reduction of sciatic nerve displacement [190] as well as reduction of conus medullaris excursion [191] has been reported in patients with spinally referred leg pain. The current study has confirmed a similar finding in patients with CR with radicular pain.

Diminished median nerve excursion in patients with CR might be due to either oedema and swelling of the nerve root within the interforaminal space and/or extraneural fibrosis, which may in turn have caused a localised restriction. All participants with CR had evidence of nerve root compression on MRI. This

swelling is generally not restricted to the nerve root alone but may involve the entire nerve bed [192-194], which is consistent with the spread of nerve inflammation distal from the site of injury [195]. Animal experiments have demonstrated that local nerve inflammation results in the development of mechanical sensitivity of otherwise intact axons [196-198]. Minimal elongation (< 3%) can trigger ectopic impulse generation in an inflamed nerve [198]. As such, limb movements in patients with CR may lead to the development of painful symptoms.

3.4.1 Clinical Considerations

In this study, we deliberately chose a neurodynamic mobilisation technique (the CCLG) which we expected would improve nerve excursion, since this technique has been shown to be effective in reducing symptoms in patients with nerve-related neck and arm pain [79, 82] It is of interest to note that nerve excursion remained relatively unchanged in those that were not responding to the intervention. Additionally, many of these patients went on to have either surgery or (nerve root sleeve) injections.

Many controversies exist regarding the timing of surgical intervention for CR [12, 199]. Nowadays, the timing of an elective surgical intervention is often based on the preference of the individual neurologist and neurosurgeon [199]. A survey of Dutch neurosurgeons reported that a minimum duration of 8 to 12 weeks of radicular arm pain was considered the optimal timing to perform surgery by the majority of the neurosurgeons [200]. As this study showed a strong correlation between the increase in median nerve excursion at the elbow and patient reported outcomes on the GPE, NPRS and PSFS,

assessment of longitudinal median nerve excursions could assist clinical decision making with regards to either continuing or suspending conservative management.

It is also relevant to note that there was no significant correlation between the extent of the CCLG and extent of the excursion of the median nerve, which may be explained by the large between-subject variation found in this study and others [166]. It also suggests that taking the CCLG movement to the individual patient's end of range has a sufficient enough effect on median nerve excursions, irrespective of the absolute range of motion. This is in line with research on the sciatic nerve which also reported a large between-subject variation in nerve excursion during a modified straight leg raise [201].

Another interesting finding was the discrepancy in outcome regarding disability between the NDI and the PSFS, compared to the health transition as assessed with the GPE. The NDI has long been advocated as a premier patient reported outcome measure (PROM) to establish the level of perceived disability in patients with neck pain [202]. Recently however, it has been questioned whether in clinical research the NDI should be the instrument of choice for use as a primary outcome measure [203]. As patients with CR generally suffer more from arm and periscapular pain than neck pain [1, 204, 205], the NDI might not be the most suitable PROM for patients with CR [203, 206]. Of relevance, there was no correlation between increase in median nerve excursion and improvement in perceived disability (NDI) as opposed to the strong statistically significant correlation with scores on the NPRS, PSFS and GPE .

3.4.2 Implications for future research

The conservative management that was provided included neurodynamic mobilisation, especially in the early stages of management. Given the multi-modal nature of the intervention program, it is not possible to attribute changes in median nerve excursion or clinical status to this particular component of the conservative management program. Furthermore, since there was no comparison group, technically improvements in median nerve excursion and clinical status cannot necessarily be attributed to the intervention program. However, the current observation of increased nerve excursion following the multi-modal intervention does provide the incentive to examine the influence of neurodynamic mobilisation on nerve excursion in a future RCT. Additionally, there is a need for fundamental research into the proposed mechanisms and theories associated with neurodynamic movements as an intervention to understand why improved nerve excursion is associated with improved clinical outcome. Recent animal research into the influence of the immune system on (neuropathic) pain indicates that active exercise has the ability to modulate the immune system, promoting an anti-inflammatory phenotype of macrophages in uninjured muscle, and an increase in anti-inflammatory cytokines which in turn can promote healing and analgesia [207]. Inhibition of neuropathic pain by exercise in rats was accompanied by decreases in interleukin (IL)-1β, IL-6, and tumour necrosis factor (TNF)-α levels and downregulated expression of their receptors [207-209]. It would be of interest to see if, as a result of intraneural fluid dispersion during passive neurodynamic mobilisation techniques, relying on the thixotrophic properties of nerve movement against its mechanical interface,

similar decreases in IL and TNF levels can be observed. Additionally, research is needed to establish the optimal dosage of neurodynamic mobilisation in patients with CR and other musculoskeletal disorders. Finally, future research should examine the potential of the PSFS as a clinically more useful outcome measure compared to the NDI (currently the most often used for assessing the level of disability in patients with neck) and/or other PROMs especially designed for patients with CR.

3.4.3 Methodological considerations

One of the strengths of this study was the highly reproducible and constant CCLG executed by the Occiflex™, which allowed us to capture high quality ultrasound videos of median nerve excursion. We also included matched controls for all cases and had only one patient lost to follow-up.

It was challenging to maintain the transducer head not only perpendicular, but also parallel to the three dimensional plane of excursion of the nerve. It was also challenging to keep the transducer completely immobile on the exact same anatomical position on the skin during scanning and even though the pixel tracking software adjusts for this, it still may have influenced the measurements and as such it influences the intra-rater reliability. However, the interrater agreement in pilot testing for the assessment of median nerve excursion from the ultrasound videos was excellent.

3.5 CONCLUSION

Longitudinal median nerve excursion differs significantly between patients with CR and asymptomatic volunteers at baseline but this difference is no

longer present after 3 months of conservative physiotherapy management. Monitoring of the improvement in median nerve movement, using ultrasound imaging, has the potential to assist clinical decision making with regards to either continuing or suspending conservative management. There is strong statistically significant correlation between improvement in nerve excursion and scores on the NPRS, PSFS and GPE. Whether neurodynamic mobilisations are an effective treatment modality in patients with a CR is still relatively unknown and thus this was examined in the following Chapter via a systematic review of the literature.

CHAPTER 4
EFFECTIVENESS OF NEURODYNAMIC MOBILISATION FOR PATIENTS WITH CERVICAL RADICULOPATHY: A SYSTEMATIC REVIEW

4.1 INTRODUCTION

In the previous chapter, we showed a strong and statistically significant correlation between improvement in neurodynamic mobility of the median nerve during a CCLG movement and improvement in health transition (scores on the NPRS, PSFS and GPE). Neurodynamic mobilisation is a conservative treatment modality often used in patients with nerve related arm pain [79, 210, 211].

Conservative management of patients with CR is a first treatment option, because the risk–benefit ratio for surgery is less favourable [52, 53, 57, 58, 60]. Nearly 30% of patients having had surgery for their CR, return for adjacent level surgery within one year [53].

Several different conservative interventions have been proposed for the management of CR based on evidence from systematic reviews [57, 58, 60] and international practice guidelines [61-63]. This includes cervical axial traction, a collar, spinal manipulative therapy, neurodynamic mobilisations and a range of general and focused exercises.

Neurodynamic mobilisation involves either specific active or passive movements of the limbs and/or the spine that aim to mobilise the nervous system itself or facilitate movement between neural structures and surrounding tissues [212]. Biomechanically, neurodynamic mobilisations may be divided into ‘tensioners’, where movements of two or more joints longitudinally load the neural tissue in opposite directions (e.g., cervical contralateral side flexion and elbow extension), or ‘sliders’, where loading

created by movement of one joint is counterbalanced by movement of other joints (e.g., cervical contralateral side flexion and elbow flexion). In vivo studies in humans have shown that ‘tensioners’ cause greater strain of the nerve and lower longitudinal excursion, whereas ‘sliders’ cause lower strain and greater longitudinal excursion [213-215].

Animal studies have shown that neurodynamic mobilisations induce modulation of nerve mechanosensitive ion channel expression [216], lower concentrations of proinflammatory cytokines (TNF-α and IL-1β) at the nerve branches and trunk [217], and normalise necrosis growth factor production at the dorsal root ganglion [218], resulting in a reduction in hyperalgesia and allodynia. Although extrapolation of results from animal studies to humans is significantly limited due to several factors (e.g., different species, lack of clinical translation, methodology and inconsistency), it is nevertheless less worthwhile to consider that these physiological and clinical results could potentially be occurring in humans too [219]. However, the clinical effectiveness of neurodynamic mobilisations in patients with nerve-related cervicobrachial pain is still unclear.

The case control study presented in **CHAPTER 2,** compared the longitudinal excursions of the median nerve in patients with CR and healthy controls during a specific neurodynamic mobilisation technique (the contra-lateral cervical lateral glide (CCLG) or “Elvey-glide”) [160]. That study reported a significant difference in longitudinal nerve excursions during a CCLG before the start of a conservative management programme which also included neurodynamic mobilisations as a treatment technique. But this difference nearly completely disappeared after 3 months of conservative management,

suggesting that neurodynamic mobilisations are an effective treatment modality for patients with CR [160].

A recent systematic review examined the effectiveness of neurodynamic mobilisations on patients with a range neuromusculoskeletal conditions [82]. They reported that using cervical lateral glide techniques for people with nerve-related arm pain had a positive effect on pain, with a clinically meaningful effect size [82]. However, nerve-related arm pain in this review included both patients with radicular pain as patients with somatic referred pain. The aim of this study is to systematically assess the current literature on the effectiveness of neurodynamic mobilisations on pain, disability and physical function for patients with CR only.

4.2 METHODS

4.2.1 Protocol and Registration

This systematic review was registered in the PROSPERO database (CRD42023493747) in December 2023 and written in compliance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 guidelines [129].

4.2.2 Inclusion criteria

As endorsed by the Cochrane Collaboration, the PICO framework as a commonly used tool for quantitative systematic reviews to identify different components of clinical evidence for a systematic review was followed, focusing on the Population, Intervention, Comparison and Outcomes [220]. The PICO framework is designed to reduce the time and retrieve related

documents, thus ensuring a bias-free quality systematic review, while also helping to determine the transparency of evidence synthesis results and findings [220].

Published RCTs on adult patients (age ≥ 18 years), with a clinical diagnosis of CR treated with neurodynamic mobilisations were included. Studies had to use neurodynamic mobilisations as an intervention for CR. The technique could be provided once or multiple times during a single session or over multiple sessions. Co-interventions could also be included within the treatment session if these were also included in the comparison group. This allows for differences in treatment effect to be attributed to the addition of neurodynamic mobilisations in the experimental group.

Comparisons which were evaluated should consist of: (a) placebo, waiting list control or no treatment or (b) other type(s) of conservative (i.e., non-surgical) treatment.

Following guidelines as advised by the Cochrane Back Review Group in establishing the primary outcomes, studies were included that used at least one of the outcome measures that are considered to be the most important, namely: pain intensity (e.g. NPRS or Visual Analogue Scala (VAS)), GPE (e.g. proportion of patients recovered), subjective improvement of symptoms), disability (e.g. NDI), Northwick Park Neck Questionnaire (NPQ), return to work (e.g. days off work) or quality of life (e.g. EQ-5D).

Outcomes of physical examinations (e.g., range of motion (ROM), spinal flexibility, muscle strength, ULNT), and psycho-social outcomes (e.g., anxiety, depression, pain behaviour) were considered as secondary outcomes. Other

outcomes such as drug consumption or adverse side effects were also considered as secondary outcomes.

Studies treating patients in both primary and secondary care settings were included if they included ≥ 30 patients (15 in each study arm, to adjust for too much downgrading the quality of evidence due to imprecision [221]) and for which full texts were available in English, Dutch, or German were included.

4.2.3 Exclusion criteria

Abstracts for which full reports were not available or studies without the outcome of interest were excluded.

4.2.4 Search strategy

A research librarian together with one review author (ET) performed the electronic searches. The databases Medline (via OVID), Embase (via Embase.com), PEDro and CINAHL were searched with relevant search terms from inception to September 1st, 2023. Both MeSH (Medline), Thesaurus (EMBASE) and free text words were used depending on the search engine of the electronic library. Combinations were made based on a) localisation of pain (e.g., cervical or neck); b) disorder (e.g., cervical radiculopathy, nerve related arm pain, cervico-brachialgia); c) intervention (e.g., neurodynamic mobilisation) and d) design: (randomised clinical trial or randomised controlled trial). Manual searches of published review bibliographies and reference lists of primary studies were undertaken to search for possible studies not captured by the electronic searches (see **APPENDIX 5**).

The search results were uploaded and managed using EndNote v20 software (Clarivate Analytics, London UK). Two review authors (ET, BV) independently screened and selected potentially eligible studies. Firstly, the title and abstract were screened for eligibility. Secondly, the full text papers were assessed to ascertain whether the study met the inclusion criteria regarding design, participants, and interventions. Disagreements on inclusion were resolved by discussion or through arbitration by a third review author (DF).

4.2.5 Data extraction

Using a standardized data extraction form, two review authors (ET, BV) independently extracted the data from each included study needed to compare and analyse the included RCTs (including sample size, participant characteristics, eligibility criteria, types of interventions and comparators, outcome measures, follow up times and results).

4.2.6 Risk of bias assessment

Two review authors (ET, BV) independently assessed the risk of bias (RoB) using the Cochrane Back Review Group's recommended ROB2 tool [222]. This tool is structured into five different domains of bias (arising from the randomisation process, due to deviations from intended interventions, due to missing outcome data, in measurement of the outcome and in selection of the reported result). Within each domain, the assessment comprises: a series of signalling questions, a judgment about risk of bias for the domain, free text boxes to justify responses to the signalling questions and risk-of-bias judgments and optional free text boxes to predict (and explain) the likely

direction of bias. When disagreement persisted, a third review author (DF) was consulted. A low risk of bias was defined as being judged to be at low risk of bias for all domains for the result [223]. The inter-observer reliability of the risk of bias assessments was calculated in SPSS 29 (IBM SPSS Statistics for Windows, Version 29.0. Armonk, NY: IBM Corp) using Kappa values and categorised agreement as “poor” (0.0), “slight” (0.0-0.2), “fair” (0.21-0.4), “moderate” (0.41-0.6), “substantial” (0.61-0.8), or “almost perfect” (0.81-1.0) [224].

4.2.7 Data analysis

For continuous data, standardized mean differences (SMD) with 95% confidence intervals (95%CI) were calculated. SMD was used because different measures are frequently used to address the same clinical outcome. Where applicable, the weighted mean difference (WMD) was calculated. All data from Visual Analogue Scales (VAS) or Numerical Rating Scales (NRS) were converted to scales ranging from 0-10, where necessary. If the published article did not provide enough data, the original authors were contacted in an effort to retrieve additional necessary data, with a reminder being sent after two weeks.

Where possible, a subgroup analysis is presented by comparator intervention. Prior to pooling, clinical heterogeneity sources such as differences in participant characteristics (e.g., age, baseline disease severity, ethnicity, comorbidities), types or timing of outcome measurements and intervention characteristics (e.g., dose, frequency of dose, training of interventionists) were

assessed [225]. If the research author decided pooling was appropriate, sub-grouping and meta-analysis was considered. Since each study we included provided information about a different effect size and we wanted to be sure that all these effect sizes were represented in the summary estimate, for pooling a random-effects model was used and mean differences and 95%CIs were presented [226]. The operating premise of the random effects model is that whenever τ^2 (an estimate of the variance of the underlying distribution of true effect sizes) is nonzero, the relative weights assigned under a random effects model will be more balanced than those assigned under a fixed effects model. Therefore extreme studies will lose influence if they are large, and will gain influence if they are small. RevMan Analyses (RevMan 5.3) was used to analyse the data.

4.2.8 Strength of the evidence

The overall quality of the evidence evaluated was graded using the GRADE method [227]. The quality of the evidence is based upon five principal factors: (1) limitations in study design (downgraded when >25% of the participants are from studies with a high risk of bias), (2) inconsistency of results (downgraded when there is statistical heterogeneity (I2 >50%) or inconsistent findings (defined as ≤75% of the participants reporting findings in the same direction), (3) indirectness (e.g. generalizability of the findings), (4) imprecision (downgraded when the total number of participants across studies is <300 for each outcome) and (5) other considerations, such as reporting bias. The quality of the evidence was downgraded by one level when one of the factors described above was met [223, 228]. Single studies were considered as

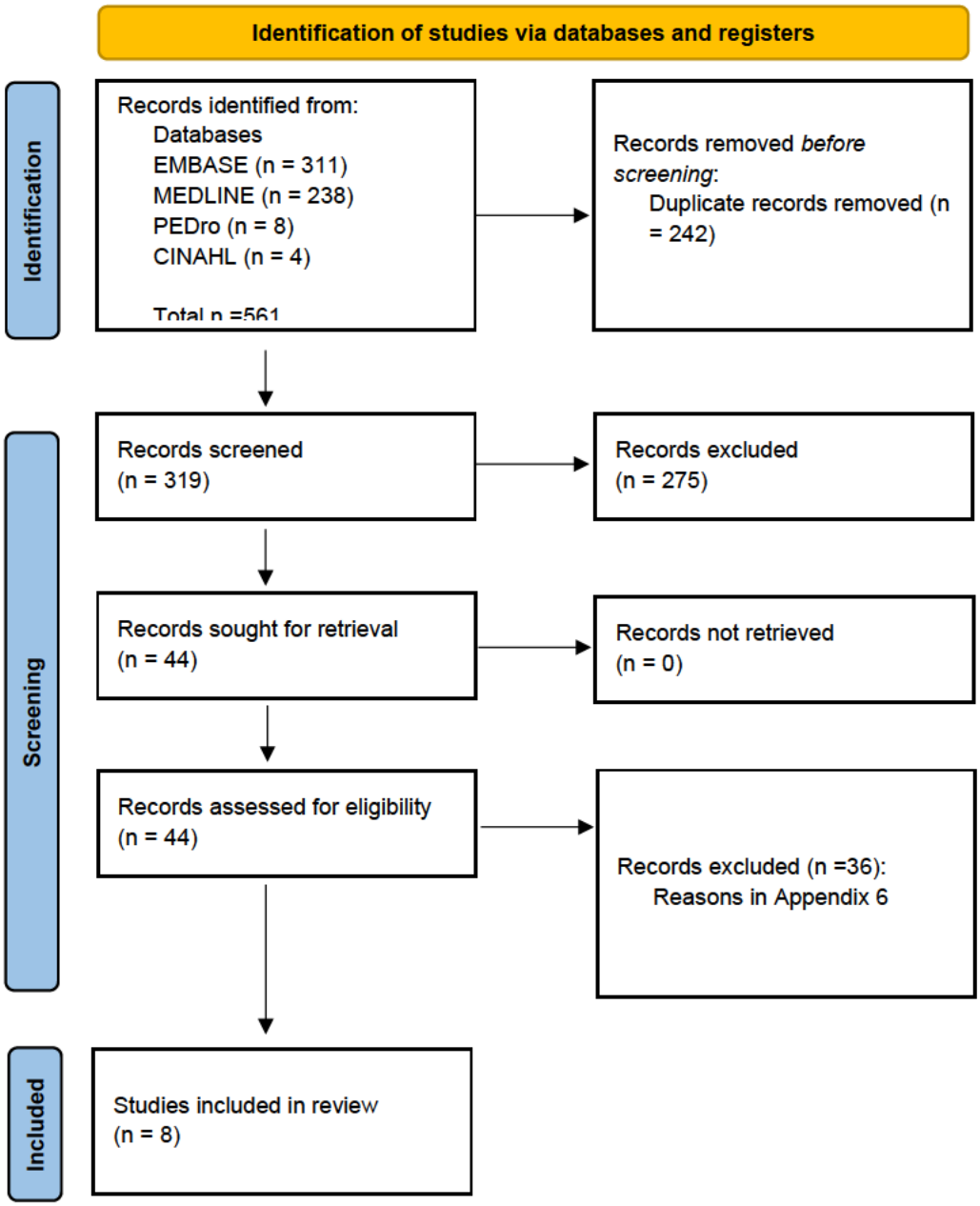
inconsistent and imprecise (i.e., sparse data) and providing ‘‘low quality evidence’’, which can be further downgraded to ‘‘very low quality evidence’’ if there are also limitations in design or indirectness. The following grading of quality of the evidence was applied [227]:

- High quality evidence: further research is very unlikely to change confidence in estimate of effect.
- Moderate quality evidence: further research is likely to have an important impact on confidence in estimate of effect and may change the estimate.
- Low quality evidence: further research is very likely to have an important impact on confidence in estimate of effect and is likely to change the estimate.
- Very low quality evidence: very little confidence in the effect estimate.
- No evidence: no RCTs were identified that addressed this outcome

4.3 RESULTS

The study selection process is presented in Figure 4.1. The systematic literature search resulted in 347 hits. A total of 44 studies were initially selected based on title and abstract screening. After reading the full text, 36 studies were excluded for a variety of reasons (see **APPENDIX 6**) and 8 studies were included [210, 229-235].

Figure 4.1. Prisma flowchart of included studies



4.3.1 Study characteristics

Eight studies reported on the effectiveness of neurodynamic mobilisations for patients with CR [210, 229-235]; three studies compared the effectiveness of neurodynamic mobilisations to a passive comparator (e.g. waiting list or sham intervention) [233-235] and five studies to an active comparator (e.g. additional interventions or usual care) [210, 229-232] (see Table 4.1). All studies reported on pain and six on disability for which five used the NDI [229, 231, 232, 234, 235], three the PSFS also [210, 234, 235] and one the Quick Disabilities of the Arm Shoulder and Hand (quickDASH) [233]. Cervical ROM was assessed in six studies [229, 231-235] and one study reported the quality of life using the EQ-5D questionnaire [210].

All studies had an intermediate follow-up time of between 3 and 6 weeks and two an additional follow-up time of 8 weeks [232] and 12 months [210]. A complete overview of study characteristics and outcomes is presented in Table 4.2.

Table 4.1 Comparator interventions to neurodynamic mobilisations

Passive comparison:	**Active comparison:**
• Neural mobilisation to waiting list [233] • Neural mobilisation plus cervical traction to waiting list [234, 235] • Neural mobilisation to control (sham), as add-on to cervical traction [235]	• Neural mobilisation as add-on to cervical traction (cervical traction vs cervical traction + neurodynamic mobilisation) [230, 232] • Neural mobilisation as add-on to exercise [231] • Neural mobilisation as add-on to manual therapy (and exercises) [210] • Active neural mobilisation to passive neural mobilisation [229]

Table 4.2. Study Characteristics

Study reference	**Study characteristics**	**Patient characteristics**	**Intervention (I)**	**Comparison / control (C)**	**Follow-up**	**Outcome measures and effect size**	**Comments**
Ayub, 2019	Type of study: RCT Setting and country: Single centre, Pakistan Funding and conflicts of interest: No conflict of interest, information on funding not disclosed.	Inclusion criteria: Female patients aged 30-50 years with chronic CR and neck pain for ≥6 months, and positive provocation tests. Exclusion criteria: (1) Recent neck trauma, (2) positive vertebrobasilar insufficiency signs, (3) receiving any form of physiotherapy or medical treatment for the last 6 weeks N total at baseline: 44 Intervention: 22 Control: 22 Important prognostic factors:	Intervention treatment: Moist heat packs for 10 minutes followed by mechanical traction of the cervical spine for 15 minutes. Also 3 sets of slow gentle segmental mobilisation (unilateral posterior anterior glide) with at least 15 to 20 repetitions on the first session, thereafter modified based	Control treatment: Moist heat packs for 10 minutes followed by mechanical traction of the cervical spine for 15 minutes. Also 3 sets of slow gentle segmental mobilisation (unilateral posterior anterior glide) with at least 15 to 20 repetitions on the first session, thereafter modified based	Length of follow-up: 4 weeks Loss-to-follow-up: Intervention: 0 Control: 0 Incomplete outcome data: 0	Outcome measures and effect size (95%CI): Pain on NRS (mean difference, 95%CI) 0.0 [-1.86to 1.86] NDI (mean difference, 95%CI) *No reporting of scale used* Cervical ROM (mean difference, 95%CI) *Reported in medians*	Selection bias (convenience sampling)

		Age (median ± IQ): I: 41 ± 12 C: 40 ± 11 *Sex:* not reported *Neck pain (median ± IQ):* I: 6 ± 2 C: 6 ± 2 *NDI (median ± IQ):* I: 10 ± 5 C: 10 ± 10 <u>Groups comparable at baseline?</u> Yes	on patient response. Then **active** upper extremity neurodynamic mobilisation, for 6 to 8 repetitions. 3 sessions per week, for 4 weeks.	on patient response. Then **passive** upper extremity neurodynamic mobilisation. 3 sessions per week, for 4 weeks.			
Basson, 2020	<u>Type of study:</u> RCT <u>Setting and country:</u> Multicentre, South-Africa <u>Funding and conflicts of interest:</u> Funding received by orthopaedic research investment fund of South African society of physiotherapy and the	<u>Inclusion criteria</u>: (1) Aged > 18 years, (2) nerve related neck and arm pain by physical examination, (3) recent onset of pain (≤12 weeks), and (4) positive upper limb neurodynamic test <u>Exclusion criteria</u>: (1) Surgery or recent fractures of the cervical	<u>Intervention treatment:</u> neurodynamic mobilisation along the tract of the nerve, directly and indirectly, concentrating on areas where the nerve is mechano-sensitive to	<u>Control treatment:</u> Usual care with (unilateral) posterior-anterior mobilisation of the cervical and thoracic spine, exercises, and advice to stay active.	<u>Length of follow-up</u>: 6 weeks, 6 months, 12 months <u>Loss-to-follow-up</u>: Intervention: 7 (11.7%) *Reasons:* could not be reached (of	Outcome measures and effect size (95%CI): <u>Pain on NRS (mean difference, 95%CI)</u> -0.60 [-1.77 to -0.51]	

	faculty research committee of the University of Witwatersrand	spine, (2) serious neurological signs, (3) RA, neurological disease, stroke, cerebral palsy, carcinoma, or any other red flags <u>N total at baseline</u>: 86 Intervention: 60 Control: 26 <u>Important prognostic factors</u>: *Age (mean ± SD):* I: 46.5 ± 14.1 C: 48.6 ± 13.6 *Sex:* not reported *Duration of pain (mean days* ± SD*):* I: 30.2 ± 27.4 C: 23.5 ± 22.9 <u>Groups comparable at baseline?</u> Yes	palpation. From hand or elbow up along the arm, first rib, scalene and into the neck, first in a non-tensioned position, progressing into a more tensioned position as pain and irritability improved. In addition, patient received usual care similar to patients in the usual care group. The number of treatments was determined by the treating physiotherapist	The number of treatments was determined by the treating physiotherapist.	whom 2 had relocated) Control: 1 (3.8%) *Reasons*: could not be reached <u>Incomplete outcome data</u>: 0 Multiple imputation applied.	<u>Function on PSFS (mean difference, 95%CI) (scale 0 to 30, high score is better)</u> 0.05 [0-0.41 to 0.51] <u>Quality of Life (EQ-5D) (mean difference, 95%CI)</u> 1.1 [4.3 to 6.3]	

			with a mean of 4.				
Ibrahim, 2021	Type of study: RCT Setting and country: Single centre, Egypt Funding and conflicts of interest: No conflicts of interest, funding information not explicitly reported.	Inclusion criteria: Patients (1) 20-40 years of age, (2) history of pain >3 months, (3) radiating pain in one upper limb, (4) met at least 3 of Wainner criteria Exclusion criteria: (1) history of high level spinal cord injury, (2) malignancy, (3) any medical red flag (tumour, fracture, RA, osteoporosis, prolonged steroid use), (4) circulatory disturbances of upper extremity, (5) traumatic injuries of upper limb and cervical spine, (6) dizziness N total at baseline: 40 Intervention: 20 Control: 20	Intervention treatment: Tensioning neurodynamic mobilisation of brachial plexus, with the arm in neurodynamic testing position, 10 cycles of elbow extension and flexion (each 3 seconds) were administered Plus tradition physiotherapy (consisting of infrared radiation and manual traction), for 3 sessions per week, over a total course of 3 weeks.	Control treatment: Traditional physiotherapy: - Infrared radiation 50/60 Hz for 20 minutes - Manual traction 15 seconds pull with 30 seconds rest, for 3 sets of 10 repetitions, with 60 seconds rest between sets. For 3 sessions per week, over a total course of 3 weeks.	Length of follow-up: 3 weeks Loss-to-follow-up: Intervention: 0 Control: 0 Incomplete outcome data: 0	Outcome measures and effect size (95%CI): Pain on VAS (mean difference, 95%CI) 0.0 [-1.17 to 1.17]	Selection bias

		Important prognostic factors: *Pain (median ± range):* I: 3.75 ± 7 C: 3.75 ± 7 *Further no baseline characteristics reported* Groups comparable at baseline? No information					
Kayiran, 2021	Type of study: RCT Setting and country: Single centre, Turkey Funding and conflicts of interest: None	Inclusion criteria: Patients for whom surgery was not recommended by the neurosurgeon, with (1) cervical disc herniation at C5/C6/C7/C8 confirmed by MRI, (2) aged 20-50 years, (3) cervicobrachial radicular pain for ≥6 weeks (4) pain severity ≥5 on VAS, (5) sensitivity and numbness in radial, median and/or ulnar nerve dynamic tests, (6) not receiving any	Intervention treatment: neurodynamic mobilisation on radial, median and ulnar nerves, 10 times 10 seconds for each nerve. For 10 sessions over 3 weeks. Plus conservative physiotherapy (hotpacks,	Control treatment: Conservative physiotherapy: - Hotpack for 20 minutes - Transcutaneous electric nerve stimulation (TENS) for 20 minutes at 100Hz - Continuous mode ultrasound for deep	Length of follow-up: 3 weeks Loss-to-follow-up: Intervention: 6 (16.7%) *Reasons:* no belief in treatment (n = 3), no adaptation to treatment time (n = 2), relocation (n = 1)	Outcome measures and effect size (95%CI): Pain on VAS (mean difference, 95%CI) -1.04 [-1.57 to -0.51] NDI (mean difference, 95%CI) *No reporting of scale used*	

		other treatment or pharmacological agents. <u>Exclusion criteria</u>: (1) Spinal stenosis, (2) RA, (3) previous c-spine surgery, (4) severe neurological loss, (5) upper extremity vascular problems, (6) severe osteoporosis, (7) diabetes mellitus, (8) pregnant women. <u>N total at baseline</u>: 71 Intervention: 36 Control: 35 <u>Important prognostic factors</u>: *Age (mean ± SD):* I: 47.2 ± 12.5 C: 43.3 ± 12.0 *Sex:* not reported *Neck pain (mean ± SD):*	TENS, ultrasound and exercises) for 3 weeks, 5 sessions per week.	heating for 5 minutes at 1 MHz - Exercises for stretching and strengthening for 5 seconds with 10 repetitions For 3 weeks, 5 sessions per week	Control: 5 (14.3%) *Reasons:* no belief in treatment (n = 2), no adaptation to treatment time (n = 2), quit treatment because of poor health (n = 1) <u>Incomplete outcome data</u>: Intervention: 11 (15.5%) *Reasons:* as mentioned above.	<u>Cervical ROM (mean difference, 95%CI)</u> Flexion: 3.9 [1.1 to 6.7] Extension: 6.2 [3.0 to 9.5] Side bending right: 4.4 [1.5 to 7.3] Side bending left: 5.6 [2.6 to 8.6] Rotation right: -0.7 [-5.3 to 3.8] Rotation left: -0.3 [-5.4 to 4.8]	

		I: 4.83 ± 1.12 C: 4.83 ± 1.23 NDI (mean ± SD) I: 18.93 ± 6.43 C: 18.93 ± 5.10 <u>Groups comparable at baseline?</u> Yes					
Kim, 2017	<u>Type of study:</u> RCT <u>Setting and country:</u> Single centre, Korea <u>Funding and conflicts of interest:</u> No conflict of interest. Funding information not disclosed.	<u>Inclusion criteria</u>: Patients with (1) a diagnosis of CR ≥3 months, (2) aged 26 to 60 years, (3) unilateral pain, (4) ≥3 out of 4 positive provocation tests <u>Exclusion criteria</u>: *None reported* <u>N total at baseline</u>: 30 Intervention: 15 Control: 15 <u>Important prognostic factors</u>: *Age (mean ± SD):* I: 29.3 ± 3.3 C: 29.3 ± 3.1	<u>Intervention treatment:</u> Similar treatment as control treatment group, yet during the manual cervical traction, another physiotherapist applied neurodynamic mobilisation using a slider technique for the median nerve in a smooth and rhythmic	<u>Control treatment:</u> Conservative physiotherapy (total 35 minutes): - Hot pack for 20 minutes - TENS at 60Hz for 15 minutes Plus manual cervical traction for 6 repetitions of 1 minute pull with 30 seconds rest (total 10 minutes)	<u>Length of follow-up</u>: 4 and 8 weeks <u>Loss-to-follow-up</u>: Intervention: 0 Control: 0 <u>Incomplete outcome data</u>: 0	Outcome measures and effect size (95%CI): <u>Pain on NRS (mean difference, 95%CI)</u> -1.0 [-1.69 to -0.31] <u>NDI (mean difference, 95%CI)</u> -6.92 [-11.41 to -2.43] <u>Cervical ROM (mean</u>	

		Sex: I: 40% M C: 33% M *NRS (mean ± SD):* I: 7.0 ± 0.85 C: 7.1 ± 0.80 *NDI (mean ± SD):* I: 21.7 ± 4.1 C: 22.1 ± 3.0 <u>Groups comparable at baseline?</u> Yes	manner (with elbow extension/flexion and wrist flexion/extension), for 6 times 1 minute with 30 seconds rest in between. For 8 weeks, 3 times per week.	For 8 weeks, 3 times per week.		<u>difference, 95%CI)</u> Flexion: 3.3 [0.3 to 6.4] Extension: 5.1 [2.2 to 8.0] Side bending right: 2.6 [0.7 to 4.5] Side bending left: 2.4 [0.9 to 3.9] Rotation right: 2.4 [0.3 to 4.5] Rotation left: 3.6 [1.8 to 5.4]	
Rodriguez-sans, 2017	<u>Type of study:</u> RCT <u>Setting and country:</u> Single centre, Venezuela <u>Funding and conflicts of interest:</u> none	<u>Inclusion criteria</u>: Consecutive patients seeking treatment for cervicobrachial pain, who (1) had clinical signs of cervicobrachial pain (arm pain, paraesthesia, numbness in upper limb), confirmed through MRI, (2) aged	<u>Intervention treatment:</u> Cervical lateral glide (CLG) neural mobilisation administered by a physiotherapist, to the contralateral	<u>Control treatment:</u> Waiting list for 6 weeks (did not receive an type of pain-modulating treatment)	<u>Length of follow-up</u>: 6 weeks (30 treatment days) <u>Loss-to-follow-up</u>: Intervention: 4 (13.8%)	Outcome measures and effect size (95%CI): <u>Pain on NRS (mean difference, 95%CI)</u> -2.96 [-3.54 to -2.38]	

		18 to 45, (3) unilateral symptoms for at least 3 months, (4) 3 positive provocation tests Exclusion criteria: (1) Use of any type of treatment to relieve pain (therapy, procedures or drugs), (2) using anticonvulsant, antidepressant, or psychotropic medication, (3) vertebral instability, osteoporosis or spine infection, (4) neurologic diseases, (5) cervical stenosis myelopathy, (6) kinesiophobia, (7) pregnancy, (8) endocrine disorders and menopause, (9) history of spine surgery, (10) severe mental illness, (11) intoxication, (12) intellectual disability, (13) severe sleep	side of pain in a slow oscillating manner. CLG was applied continuously for two minutes in 5 consecutive applications, with one minute rest in between. For 5 days per week, for 6 weeks.		*Reasons:* did not complete treatment as allocated Control: 2 (6.9%) *Reasons*: did not complete treatment as allocated Incomplete outcome data: 6 (10.3%) *Reasons:* see above	Function (Quick DASH) -21.5 [-27.4 to -15.73] Function (ipsilateral cervical rotation) (mean difference, 95%CI) 8.0 [4.9 to 11.1]	

		deprivation, (14) Alzheimer's disease N total at baseline: 58 Intervention: 29 Control: 29 Important prognostic factors: *Age(mean ± SD):* I: 33.3 ± 5.0 C: 32.5 ± 4.6 *Sex:* I: 56% M C: 44% M *NRS (mean ± SD):* I: 6.08 ± 0.99 C:6.44 ± 0.93 Groups comparable at baseline? As far as information is provided, yes					
Savva, 2016	Type of study: RCT Setting and country: Single centre, Cyprus	Inclusion criteria: Consecutive patients with unilateral CR diagnosed by MRI or CT referred to the	Intervention treatment: Intermittent (pain-free) cervical traction	Control treatment: Did not receive any type of treatment, with	Length of follow-up: 4 weeks	Outcome measures and effect size (95%CI):	

	Funding and conflicts of interest: None.	physiotherapy department, with (1) unilateral sharp pain, muscle weakness and numbness in upper arm, (2) ≥3 out of 4 positive provocation tests. Exclusion criteria: (1) current cervical myelopathy or signs of upper motor neuron disease, (2) bilateral complaints, (3) other musculoskeletal conditions in the affected limb, (4) use of analgesia or anti-inflammatory medication in the prior 2 weeks. N total at baseline: 42 Intervention: 21 Control: 21 Important prognostic factors: *Age (mean ± SD):*	with 1 minute pull and 1 minute rest for 6 sets. During the cervical traction, slider neurodynamic mobilisation using a median nerve bias were performed in slow and oscillatory fashion, with the patients' elbow, wrist and finger repositioning. 3 treatment sessions per week, for 4 weeks. In addition, patients received advice to avoid prescription or over-the-	advice to avoid prescription or over-the-counter analgesia or anti-inflammatory medication, for the duration of 4 weeks.	Loss-to-follow-up: Intervention: 0 Control: 0 Incomplete outcome data: 0	Pain on NRS (mean difference, 95%CI) -3.36 [-4.56 to -1.96] NDI (mean difference, 95%CI) -15.33 [-23.26 to -7.40] Function on PSFS (mean difference, 95%CI) (scale 0 to 10) 1.62 [0.91 to 2.32] Cervical ROM (mean difference, 95%CI) Flexion: 5.7 [0.5 to 11.0]	

		I: 45.2 ± 13.5 C: 49.2 ± 8.5 *Sex:* I: 38% M C: 62% M *NRS (mean* ± SD): I: 5.62 ± 2.52 C: 5.19 ± 2.11 NDI (mean ± SD): I:33.3 ± 17.6 C: 30.2 ± 16.4 <u>Groups comparable at baseline?</u> Yes	counter analgesia or anti-inflammatory medication.			Extension: 8.8[-0.5 to 18.1] Side bending ipsilateral: 6.4 [1.6 to 11.1] Side bending contralateral: 6.0 [1.5 to10.4] Rotation ipsilateral: 7.9 [1.5 to 14.3] Rotation contralateral: 10.6 [3.6 to 17.6]	
Savva, 2021	<u>Type of study:</u> RCT <u>Setting and country:</u> Single centre, Cyprus <u>Funding and conflicts of interest:</u> None.	<u>Inclusion criteria</u>: Consecutive patients with unilateral CR referred to the physiotherapy department, (1) aged 20 to 75 years, with (2) unilateral upper limb pain, sensory and/or motor symptoms, (3)	<u>Intervention treatment:</u> *Group 1 (G1): Cervical traction with neurodynamic mobilisation* Intermittent (pain-free) cervical traction with 1 minute	<u>Control treatment:</u> Waiting list without any type of treatment for 4 weeks.	<u>Length of follow-up</u>: 4 weeks <u>Loss-to-follow-up</u>: Intervention: 0 Control: 0	Outcome measures and effect size (95%CI): <u>Pain on NRS (mean difference, 95%CI)</u>	

		≥3 out of 4 positive provocation tests. Exclusion criteria: (1) bilateral complaints, (2) other musculoskeletal conditions in the affected limb, (3) evidence of central nervous system involvement, (4) history of medical red flags (tumour, metabolic disease, RA, osteoporosis), (5) use of analgesia or anti-inflammatory medication in the prior 2 weeks. N total at baseline: 66 Intervention: 22 (G1), 22 (G2) Control: 22 Important prognostic factors: *Age (mean ± SD):*	pull and 30 seconds rest for 10 sets. During the cervical traction, slider neurodynamic mobilisation of the median nerve was performed in slow and oscillatory fashion, with repeated passive flexion and extension of the patients' elbow, wrist and fingers. 3 treatment sessions per week, for 4 weeks. *Group 2 (G2): cervical traction with sham neurodynamic mobilisation*		Incomplete outcome data: 0	NM + cervical traction to waiting list -3.30 [-4.51 to -2.09] NM as add on to cervical traction to sham NM -2.4 [-3.75 to -1.05] NDI (mean difference, 95%CI) -32.60 [-47.56 to -17.64] Function on PSFS (mean difference, 95%) 1.39 [0.72 to 2.05] Cervical ROM Flexion: 5.9 [0.8 to 11.0]	

		I: 47.7 ± 10.8 (G1), 48.1 ± 11.9 (G2) C: 48.5 ± 12.3 *Sex:* I: 50% M (G1), 59% M (G2) C: 36% M *Duration of symptoms >3 months:* I: 54% (G1), 41% (G2) C: 55% *NRS (mean ± SD):* I: 6.1 ± 2.2 (G1), 6.1 ± 2.6 (G2) C: 5.4 ± 1.8 *NDI (mean ± SD):* I: 33.3 ± 17.6 (G1), 34.5 ± 14.2 (G2) C: 29.0 ± 15.9 <u>Groups comparable at baseline?</u> Gender seems to differ slightly at baseline between intervention and control groups.	Intermittent (pain-free) cervical traction with 1 minute pull and 30 seconds rest for 10 sets. During the cervical traction, sham neurodynamic mobilisation with sustained position of elbow and wrist, and repeated passive flexion and extension of the patients' fingers within the ROM. 3 treatment sessions per week, for 4 weeks.			Extension: 5.8[-3.1 to 14.7] Side bending ipsilateral: 6.2 [1.4 to 11.1] Side bending contralateral: 6.3 [2.2 to10.4] Rotation ipsilateral: 8.7 [1.7 to 15.7] Rotation contralateral: 13.5 [6.7 to 20.3]	

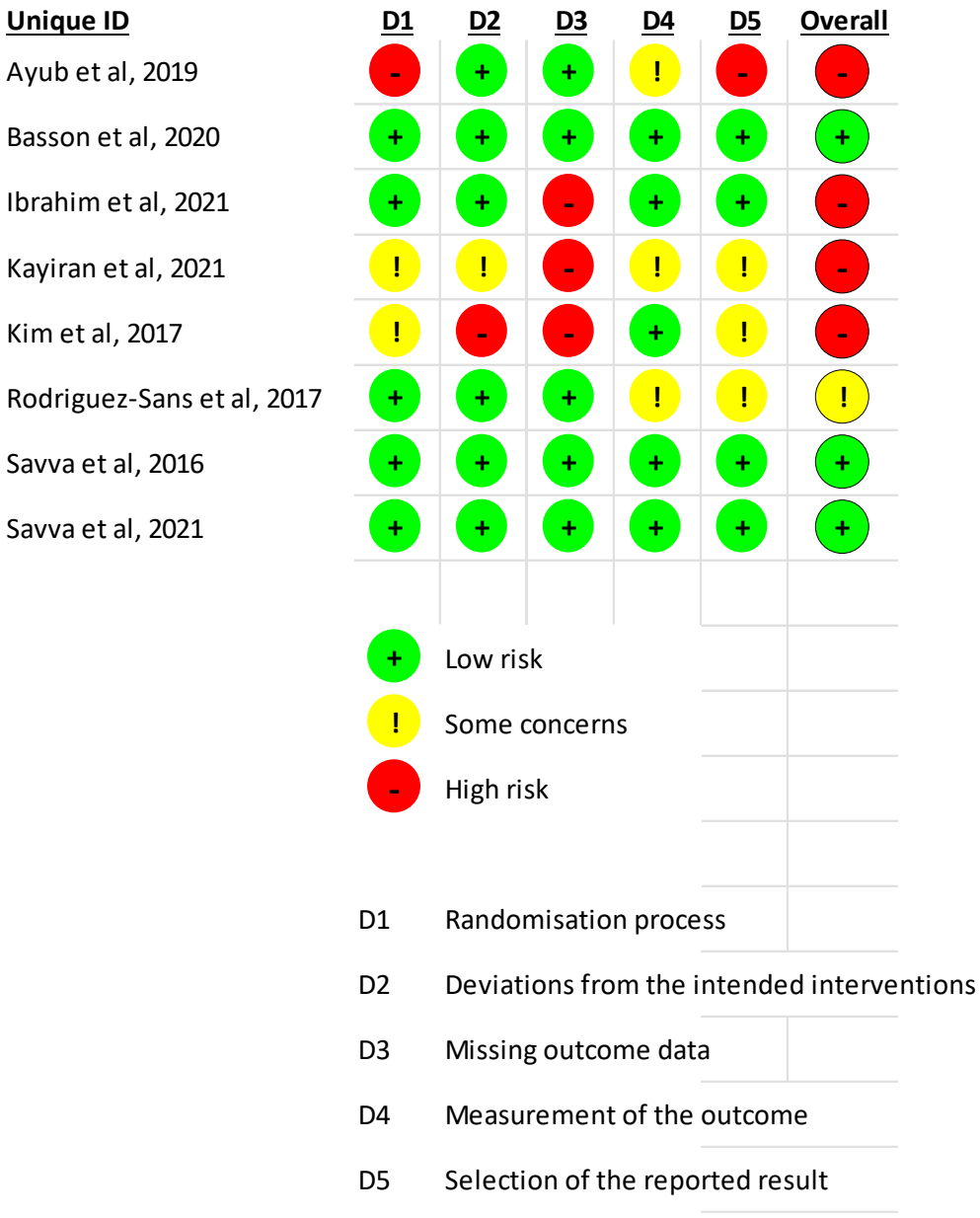
Abbreviations (alphabetical): CI: confidence interval, CNS: central nervous system, c-spine: cervical spine, CT: computed tomography, EQ-5D: EuroQol-5D questionnaire, FABQ: Fear-avoidance beliefs questionnaire, GP: general practitioner, CR: cervical radiculopathy, MCS: Mental Component Score, MRC scale: Medical Research Council scale for measurement of muscle power, MRI: magnetic resonance imaging, NDI: neck disability index, NM: neurodynamic mobilisations, NRS: Numeric Rating Scale, NSAID: non-steroid anti-inflammatory drugs, PCS: Physical Component Score, PSFS: Patient-Specific Functional Scale, RA: rheumatoid arthritis, RCT: randomised controlled trial, ROM: range of motion, SF-36: Short Form 36, t-spine: thoracic spine, VAS: visual analogue scale

4.3.2 Risk of Bias assessment

The overall agreement between review authors on the RoB assessment was “almost perfect” ($k = 0.92$, $p < 0.01$), and therefore consultation of the third review author was not needed. Two studies had “some concerns” [231, 232] and one study had a “high risk” [229] with regard to the randomisation process. One study [231] had “some concerns” and one study [232] had a “high risk” with regard to deviation from intended interventions. Three studies had a “high risk” with regard to missing data [230-232]. Three studies had a “some concerns” with regard to measurement of the outcome [229, 231, 233]. Three studies [231-233] had “some concerns” and one study [229] had a “high risk” with regard to the selection of the reported results.

Overall, three studies had a low RoB [210, 234, 235], one study had “some concerns” [233] and four studies had a high RoB [229-232] (see Table 4.3).

Table 4.3. Risk of Bias assessment.

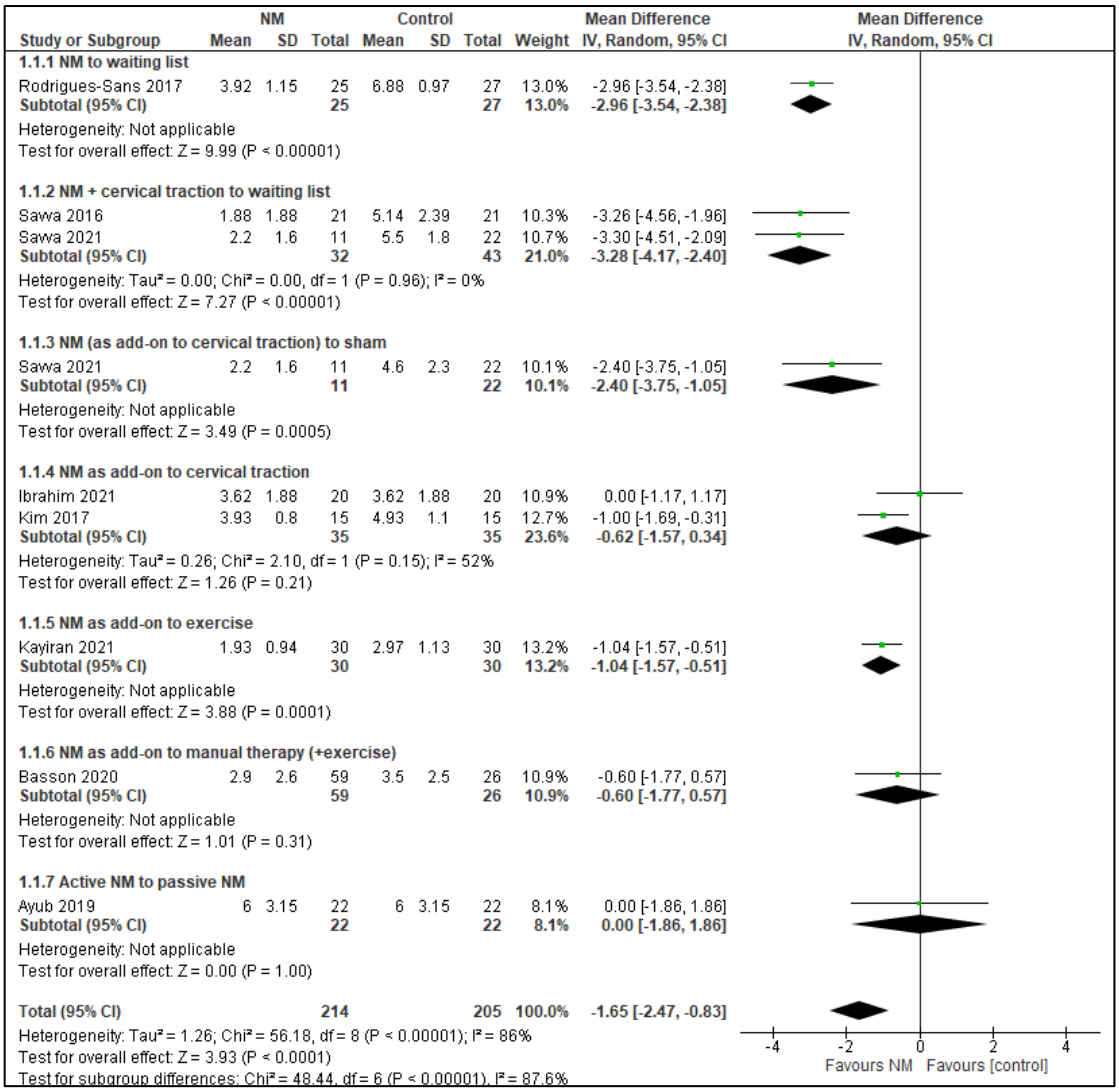


4.3.3 Outcomes

Pain intensity

All studies reported on pain outcomes using either the NRS or VAS and this was assessed either after 3 weeks [230, 231], 4 weeks [229, 232, 234, 235], or after 6 weeks [210, 233]. All scores on VAS were converted to values on a 0 to 10 scale, to enable comparison between studies. The results of the study of Ayub et al [229] are reported in median with interquartile range, and Ibrahim et al [230] reported median and range, for which the mean and SD were recalculated [140, 236-238]. The different comparisons from the studies are shown in Figure 4.2. For those arms used more than once for comparison [235], the population is divided by the number of comparisons in which it was used.

Figure 4.2 Studies comparing neurodynamic mobilisation to control treatment or sham (i.e., passive comparator) or to other forms of treatment (i.e., active comparator), for the outcome pain intensity



NM: neurodynamic mobilisation, SD: standardised difference, CI: confidence interval

The use of a passive control (Figure 4.2) resulted in a mean difference of -2.98 (95%CI: -3.44 to -2.52). This difference is statistically significant and clinically relevant [169]. The use of an active comparator (Figure 4.2) resulted in a mean difference -0.88 (95%CI: -1.25 to -0.5). This difference is statistically significant, but not clinically relevant as the minimal clinical important difference (MCID) of the NPRS in patients with CR is reported to be 2.2 [169].

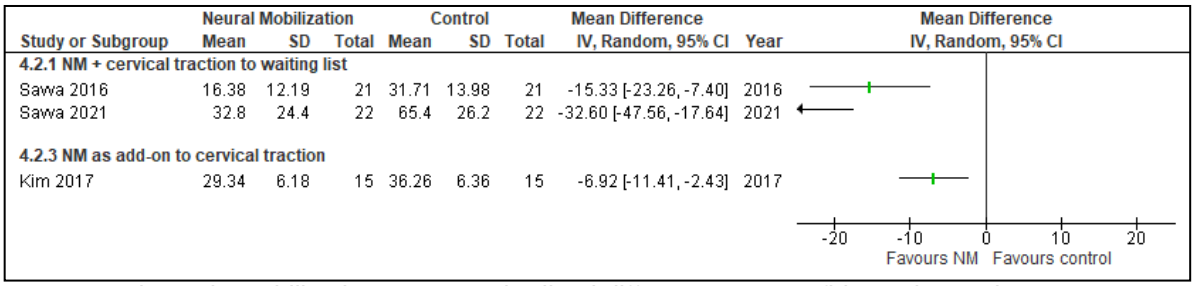
The overall comparison resulted in a difference of -1.65 (95%CI: -2.74 to, -0.83). This difference is statistically significant, but not clinically relevant.

Disability

Five studies reported disability results using the NDI, yet two studies did not define which NDI scale (50 or 100 maximum score) was used and are therefore excluded from this analysis [229, 231]. The other three studies reported on a scale from 0 to 50 [232, 235] or from 0 to 100 [234]; the former two were converted to a 0 to 100 scale. All scores were measured after 4 weeks and are presented in Figure 4.3.

The studies comparing neurodynamic mobilisation to a passive comparator (waiting list, Figure 4.3; 4.2.1) [234, 235]) resulted in a mean difference of -22.75 (95%CI -39.5 to -6.0); both were statistically significant and clinically relevant, as the MCID of the NDI in patients with CR is reported to be 8.5 [169].

Figure 4.3. Studies comparing neurodynamic mobilisation to control treatment or to other forms of treatment, for the outcome disability.



NM: neurodynamic mobilisation, SD: standardised difference, CI: confidence interval

Physical Function

Cervical Range of Motion (ROM)

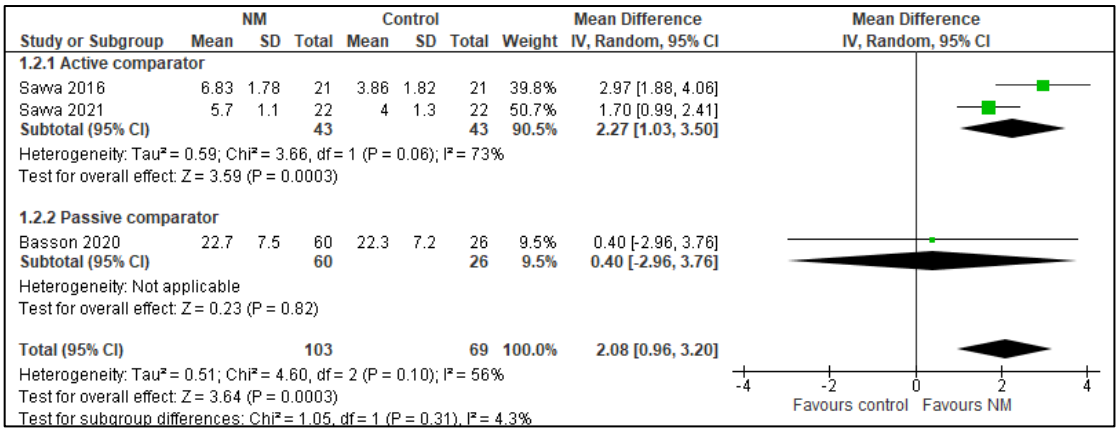
Six studies reported changes in cervical ROM (measured with a goniometer) [229, 231-235]. The study of Ayub et al [229] reported medians with interquartile range and were recalculated for calculating the pooled values. The ROM values are presented in Table 4.4.

All authors comparing neurodynamic mobilisation to an active comparator [229, 231, 232], showed increasing values of cervical ROM for both the intervention and control group, whereas in studies comparing neurodynamic mobilisation with passive treatment (e.g., waiting list) [233-235], patients in the control group appeared to have less cervical ROM at the follow-up.

Patient-specific Functional Scale (PSFS)

Three studies reported functional outcomes on the PSFS, either on a scale from 0 to 10 [234, 235], or on a scale from 0 to 30 [210], with higher scores representing higher function. A standardized mean difference was 2.08 (95%CI 0.96 to 3.20) and is reported in Figure 4.4. This difference is statistically significant, but not clinically relevant as the MCID of the PSFS in patients with CR is reported to be 2.2 [169].

Figure 4.4. Studies comparing neurodynamic mobilisation to control treatment (passive comparator) or to other forms of treatment (active comparator), for the outcome function on the PSFS.



NM: neurodynamic mobilisation, SD: standardised difference, CI: confidence interval

Quick Disability of Arm, Shoulder and Hand (QuickDASH)

One study reported on function and symptoms of the upper limb via the QuickDASH [233]. After 6 weeks of treatment, the score in the waiting list control group barely decreased (change from 58.7 ± 9.5 to 58.6 ± 9.4), whereas a >30% decrease was observed for those allocated to the cervical lateral glide intervention (change from 56.6 ± 8.9 to 37.1 ± 11.4). This resulted in a statically significant and clinically relevant mean difference of -21.5 (95%CI -27.4 to -15.73) as the MCID of the QuickDASH is reported to be 15.9 for patients with upper-limb musculoskeletal disorders [239].

Quality of Life

One study measured quality of life through the EQ-5D after 6 weeks of treatment [210]. Perceived quality of life increased similarly in the usual care and neurodynamic mobilisation group, from 72.4 ± 15.8 to 83.0 ± 11.8 and from 72.4 ± 19.6 to 84.1 ± 11.1, respectively. This resulted in a non-significant mean difference of 1.1 (95%CI -4.3 to 6.3) in favour of the neurodynamic

mobilisation group. After 12 months, this difference increased slightly, yet remained non-significant.

The outcomes of return to work, drug consumption, psychosocial outcomes, and adverse effects were not reported in the studies.

Table 4.4. Studies comparing neural mobilisation to control treatment or sham (i.e., passive comparator) or to other forms of treatment (i.e., active comparator), for the outcome of cervical range of motion (ROM) measured in degrees.

Study	**Comparison**	**ROM mean difference [95%CI]**					
				Side bending		**Rotation**	
		Flexion	**Extension**	**Ipsilateral (or right*)**	**Contralateral (or left*)**	**Ipsilateral (or right*)**	**Contralateral (or left*)**
Passive comparator							
Rodriguez-sans et al, 2017	neurodynamic mobilisation to waiting list	N.R.	N.R.	N.R.	N.R.	8.0 [4.9 to 11.1]	N.R.
Savva et al, 2016	neurodynamic mobilisation plus cervical traction to waiting list	5.7 [0.5 to 11.0]	8.8 [-0.5 to 18.1]	6.4 [1.6 to 11.1]	6.0 [1.5 to10.4]	7.9 [1.5 to 14.3]	10.6 [3.6 to 17.6]
Savva et al, 2021		5.9 [0.8 to 11.0]	5.8 [-3.1 to 14.7]	6.2 [1.4 to 11.1]	6.3 [2.2 to 10.4]	8.7 [1.7 to 15.7]	13.5 [6.7 to 20.3]
Pooled result		***5.8 [2.2 to 9.5]***	***7.2 [0.8 to 13.6]***	***6.3 [2.9 to 9.7]***	***6.2 [3.2 to 9.2]***	***8.1 [5.5 to 10.7]***	***12.1 [7.2 to 17.0]***
Active comparator							
Kayiran et al, 2021	neurodynamic mobilisation as add-on to exercise	3.9 [1.1 to 6.7]	6.2 [3.0 to 9.5]	4.4 [1.5 to 7.3]*	5.6 [2.6 to 8.6]*	-0.7 [-5.3 to 3.8]*	-0.3 [-5.4 to 4.8]*
Kim et al, 2017	neurodynamic mobilisation as add-on to cervical traction	3.3 [0.3 to 6.4]	5.1 [2.2 to 8.0]	2.6 [0.7 to 4.5]*	2.4 [0.9 to 3.9]*	2.4 [0.3 to 4.5]*	3.6 [1.8 to 5.4]*
Ayub et al, 2019	Active neurodynamic mobilisation to passive neurodynamic mobilisation	0.0 [-0.8 to 0.8]	0.0 [-10.2 to 10.2]	0.0 [-4.7 to 4.7]*	0.0 [-4.9 to 4.9]*	0.0 [-3.2 to 3.2]*	-0.0 [-0.6 to 0.6]*
Pooled result		***3.6 [1.6 to 5.7]***	***5.6 [3.4 to 7.8]***	***3.2 [1.6 to 4.7]***	***3.0 [1.7 to 4.3]***	***1.5 [-1.3 to 4.3]***	***2.4 [-1.1 to 5.9]***

N.R.: not reported
** right or left instead of ipsilateral or contralateral.*

4.3.4 Level of evidence of the literature

Pain intensity

The level of evidence for pain intensity was downgraded by 3 levels to *"very low"* because of possible selection bias and selective or biased outcome reporting in some studies (-1, risk of bias); heterogeneity in methodology and results (-1, inconsistency); and intervals of estimates crossing the border of clinical relevance and clinical difference (-1, imprecision).

Disability

The level of evidence for disability was downgraded by 3 levels to *"very low"* because of possible selective outcome reporting (-1, risk of bias); and a low number of included studies and patients (-2, imprecision).

Function

The level of evidence for function was downgraded by 3 levels to *"very low"* because of possible selection bias and selective or biased outcome reporting in some studies (-1, risk of bias); methodological heterogeneity (-1, inconsistency); and the intervals of pooled estimates crossing the border of clinical relevance (-1, imprecision).

Quality of life

The level of evidence for quality of life was downgraded by 3 levels to *"very low"* because of an early stop in recruitment of patients (-1, risk of bias); and the inclusion of a single study with a low number of included patients (-2, imprecision).

4.3.5 Conclusions on the level of evidence

Pain intensity

There is very low-level evidence of effectiveness of neurodynamic mobilisation on pain intensity in patients with CR [210, 229-235]. A stronger positive effect of neurodynamic mobilisation on pain is found when compared to passive comparators, and a neutral effect on pain intensity was found when compared to active comparators. The evidence is very uncertain whether active neurodynamic mobilisation is preferential over passive neural mobilisation.

Disability

There is very low-level evidence of effectiveness of effect of neurodynamic mobilisation on disability in patients with CR [232, 234, 235]. A stronger positive effect of neurodynamic mobilisation on disability is found when compared to passive interventions, than when compared to active interventions.

Function

There is very low-level evidence of effectiveness of neurodynamic mobilisation on range of motion and the Patient Specific Functional Scale in patients with CR [210, 229, 231-235]. A stronger positive effect of neurodynamic mobilisation on disability is found when compared to passive comparator, than when compared to active comparators.

There is very low-level evidence of a larger positive effect found of neurodynamic mobilisation on the Quick Disability of Arm, Shoulder and Hand outcome measure, compared to waiting-list controls, in patients with CR [233].

Quality of life

There is very low-level evidence of effectiveness of effectiveness of neurodynamic mobilisation as add-on to manual therapy and exercise on quality of life, in patients with CR [210].

4.4 DISCUSSION

This systematic review assessed the effectiveness of neurodynamic mobilisation in patients with CR and showed that neurodynamic mobilisation is potentially effective for pain, disability, function, cervical ROM and quality of life when compared to either a passive comparator or as an add-on to an active comparator. All studies assessed a series of neurodynamic mobilisation treatments with a follow-up of between 3 and 6 weeks which is comparable to usual clinical care in patients with CR [240]. The comparators used differed widely across study settings from either waiting list or manual traction and exercises to moist heat packs and infrared radiation. Whether some of these were meant to resemble local usual care or an inactive or sham comparator is unknown.

The type of neurodynamic mobilisation differed from either active and/or passive slider or tensioner techniques using the upper extremity, to using the cervical spine in a contralateral cervical lateral glide technique. This makes comparisons of type and dosage very difficult, given the low number of studies.

The level of evidence for all outcome measures was very low, meaning that new studies could lead to new insights. The very low-level of evidence was mainly due to the fact that the majority of studies had either a high [229-232] or an unclear [233] overall RoB. Most studies [229, 230, 232-235] included between 15 and 29 patients in each study arm leading to imprecise results. For pilot studies, a minimum of 60

patients in each study arm has been suggested to guard against the lack of precision by using inflated estimates [241]. In RCTs, as soon as a between-groups variable or an interaction is involved, numbers of 100, 200, and even more participants are needed to guard against underpowered studies with unclear results [242].

The outcomes of the current review are comparable to a recent systematic review which concluded that a multimodal strategy incorporating neurodynamic mobilisations appeared to be the most successful short-term management strategy on Health-Related Quality of Life and the endurance capacity of the cervical deep flexor muscles in patients with a CR [243]. In addition, one other very recent systematic review assessing the effectiveness of neurodynamic mobilisations in a broader group of patients labelled as having “nerve related cervicobrachial pain”, also concluded that neurodynamic mobilisations are likely to result in a moderate reduction in disability when compared with non-specific active range of motion and isometric exercises of the neck and shoulder [244].

It is relevant to note that we found no difference in the effectiveness between active and passive neurodynamic mobilisations. This could implicate that neurodynamic mobilisation exercises performed at home are equally effective which increases self-empowerment of patients. Combined with emerging reports of the validity of clinical assessment via telerehabilitation of patients with low back pain [245, 246] and other musculoskeletal disorders [247], this could facilitate using telerehabilitation more often in patients with CR.

The largest difference between comparators was between a waiting list and a sham treatment as ineffective comparators, but also compared to cervical traction. This increases the level of evidence of ineffectiveness of cervical traction, as has been reported in recent systematic reviews [57, 248].

In patients with a lumbar radiculopathy, evidence on the effectiveness of neurodynamic mobilisations are also slowly emerging. One recent study reported that the addition of neurodynamic mobilisation to a motor control exercise program led to a reduction in neuropathic symptoms and mechanical sensitivity (straight leg raise). However, it did not result in greater changes of pain, related disability, or pressure pain thresholds over a motor control exercise program alone [249]. One other recent study reported that both slider and tensioner neural mobilisation exercises demonstrated improvements in pain and ROM in patients with low back-related leg pain with peripheral nerve sensitization compared to those in the control group [250]. Considering the effectiveness from the viewpoint of the MCIDs of the various outcome measures, it would appear that neurodynamic mobilisations are significantly more effective when compared to an inactive control. When used as an add-on to an already proven effective comparator, it is clinically much more difficult to cross the MCID using an intervention. Nevertheless, neurodynamic mobilisations did show an additional effect when used in combination with exercises or spinal manipulation, further strengthening the evidence of using multimodal conservative management strategies for patients with CR.

4.4.1 Strengths and limitations

One of the strengths of this study is its adherence to guidelines to ensure methodological rigor such as the guidelines for search strategies and assessing ROB from the Cochrane Back Review Group and grading the level of the evidence using the GRADE tools.

As a limitation, the heterogeneity of study populations and comparator interventions made it difficult to compare studies and outcomes, precluding firm conclusions from

being made. Another limitation is the uncertainty if in fact patients with a CR were included in some of the studies. The study of Ayub et al [229] included a convenience sample of female patients aged 30–50 years with chronic CR according to a positive compression, distraction, Spurling and ULNTs, but no other diagnostic criteria. Given the fact that the majority of patients with a CR are predominantly male in the 5th and 6th decade of life, perhaps these were not all “true” CR patients. The study by Kayiran et al [231] included patients “for whom surgery was not recommended by the neurosurgeon”, questioning if these patients had an objectifiable operable patho-anatomical construct i.e. a relevant compressed nerve root.

In this first systematic review on the effectiveness of NM for patients with a CR, we decided to also include studies with a high or questionable RoB to show the width of results being presented. If we had only included studies of low RoB we could only have included three studies [210, 234, 235].

4.4.2 Implications for clinical practice

Conservative management of patients with CR is recommended to be multimodal [57, 61-63, 240]. Even though the level of evidence on the effectiveness of neurodynamic mobilisations on pain, disability, function and quality of life is very low and it is therefore uncertain if neurodynamic mobilisations have a positive effect in patients with CR, a stronger effect is found when neurodynamic mobilisation is compared to a “passive” control. Combined with the results of a recent Delphi study [240] proposing that neurodynamic mobilisations are effective in the sub-acute and chronic stages through the evolution of the disorder, we suggest that neurodynamic mobilisations are a treatment intervention to be considered in patients with CR. As we found no difference in the effectiveness between active and passive

neurodynamic mobilisations, we would recommended using both in management programs. The passive neurodynamic mobilisations using both the upper extremity and the cervical spine during treatment sessions could be used to tailor and direct the active neurodynamic mobilisations in exercises patients will be instructed to perform at home in between treatment sessions.

4.4.3 Future research

This systematic review revealed that there is a lack of high quality RCTs evaluating the effectiveness of neurodynamic mobilisations for patients with CR. Studies with larger sample sizes and longer follow-up periods are required to present more high-quality scientific data. Future research should focus on the difference between active and passive neurodynamic mobilisations, the difference in effect between “slider” and “tensioner” techniques and also focus on the dosage of neurodynamic mobilisations. Future research should also assess factors influencing the outcome of management plans in an effort to investigate the potential of creating prediction rules. Assessing a large variety of baseline patient characteristics in all domains of the International Classification of Functioning, Disability and Health might provide an insight into which factors contribute to effective management strategies.

4.5 CONCLUSION

This review provided very low-level evidence of potential effectiveness of neurodynamic mobilisations on pain, disability and function in patients with a CR, especially when compared to an inactive control. Results need to be treated with caution given the low methodological quality of most of the included studies. There is no evidence however if neurodynamic mobilisations are effective in every stage

during a conservative management plan: i.e. the acute, sub-acute and/or chronic stage, and therefore this was examined in the following Chapter via a Delphi study.

CHAPTER 5
TIMING OF EVIDENCE BASED NON-SURGICAL INTERVENTIONS AS PART OF MULTI-MODAL TREATMENT GUIDELINES FOR THE MANAGEMENT OF CERVICAL RADICULOPATHY.

This chapter reports in full a manuscript which has been published previously (Thoomes et al., 2022) [240]. Changes have been made in the text of this chapter for the purposes of a thesis, specifically;
- The abstract as published has been removed from the text in the thesis.
- The introduction has been edited to reflect the content of previous chapters in this thesis and avoid repetition.
- The discussion and conclusion have been edited to increase cohesion between linked studies in later chapters.

However, the majority of the text in this chapter reflects the published manuscript verbatim and has been reprinted with permission from Physical Therapy.

5.1 INTRODUCTION

In the previous chapter we showed that neurodynamic mobilisation is an effective treatment modality for pain, disability, function, cervical ROM and quality of life for patients with a CR.

Several systematic reviews [57, 58, 60] and contemporary (inter)national clinical practice guidelines [61-65] suggest that effective non-surgical management strategies for patients with CR could include: information and patient education, advice to stay physically active, manual therapy alone or in combination with different types of supervised exercise, traction, neurodynamic mobilisation and the use of a cervical collar. Systematic reviews traditionally include outcomes from RCTs and sometimes controlled clinical trial (CCTs). RCTs have a limitation in that the management strategies are often not tailored to the individual [66, 67]; RCTs usually report central tendencies of a cohort, which is not representative of individual patients [251]. The limited external validity is partly related to the inclusion of patients and practitioners in RCTs which are different from those in routine practice. Additionally, RCTs often do not consider the different stages of the condition studied. Rather, all

participants are managed identically, regardless of whether the condition is acute, sub-acute or chronic [68]. Rehabilitation programs, however, are based on the logical assumption that some treatment modalities might potentially be better suited in the early acute stage of the disorder, while others might be better for management during the subacute or chronic phases [69, 70]. Current evidence on the effectiveness of non-surgical management of patients with CR reports a lack of consensus on the optimal timing and dosage of treatment modalities [56-58].

A Delphi technique is an approach which could be used to determine expert opinion on the most suitable timing of different interventions for the conservative management of CR. The Delphi technique is described as “a method used to obtain a consensus of opinion of a group of experts by a series of questionnaires interspersed with controlled feedback” [71, 72]. Delphi studies are often used to combine clinical expertise and achieve consensus on what preferred management options should or could be included in the management of patients, in this case with CR, at varying stages [72, 73].

The aim of this study was to establish consensus on effective non-surgical treatment modalities for patients in different stages (i.e. acute, sub-acute and chronic) of CR, using the Delphi method approach.

5.2 METHODS AND ANALYSIS

5.2.1 Ethical considerations

Ethical approval was granted from the University of Birmingham ethics committee (ERN_20-1121) (**APPENDIX 7**). Formal consent and declaration of conflict of interests was required from all panel members prior to participation. Quasi-anonymity was guaranteed which referred to blinding of participation between panel members but

not to the researchers. All participants were assigned a unique identification code to aid the feedback process and to protect confidentiality of responses. No conflicts of interest were reported between the steering committee and this project.

5.2.2 Design

An electronic version of the Delphi method was used, modified for the purpose of this study [72, 73, 252, 253] and in line with recent studies [254-257]. The e-Delphi technique involved the iterative process of administering rounds of surveys to an international expert panel, using an electronic platform to construct and distribute three rounds of surveys to panellists [252, 258]. This design allowed the recruitment of a homogenous group of international experts (participants) and also allowed participation without geographical constraints, avoided dominance of opinion from minority members, and offered anonymity therefore encouraging freedom of expression and removing peer or authoritative pressure [73]. The study was reported in line with the Conducting and Reporting Delphi Studies (CREDES) recommendations to ensure rigour [72]. To increase methodological rigour, the study protocol was published in an open access peer-reviewed journal [259].

5.2.3 Definition of stages of CR

The different clinical stages of CR were aligned with established pain terminology e.g.: ‘acute’, ‘sub-acute’ and ‘chronic’ as proposed by the International Association for the Study of Pain (IASP) [260, 261]. ‘Acute’ pain is pain that has been present for up to 6 weeks [261]. ‘Subacute’ pain is a subset of acute pain; it is defined as pain that has been present for at least 6 weeks but less than 3 months

[262]. ‘Chronic’ pain is defined as pain that persists or recurs for more than 3 months [260, 261].

5.2.4 Participants

In line with the CREDES recommendations, experts were sought globally from a variety of different professional backgrounds (physiotherapy, medicine, allied health care, academia) [72]. Experts were defined and agreed upon by the steering committee according to pre-defined eligibility criteria as described in the published study protocol [259] and informed by previous similar studies [254, 256, 257, 259]. Past work suggested that 20-30 panellists are appropriate in a Delphi study to enable consensus. [73, 263, 264]. An upper limit for panellist numbers was not defined.

5.2.5 Recruitment

Electronic libraries (PubMed, Embase, CINAHL, Google Scholar) were searched for individuals meeting the eligibility criteria. Potential panellists were then contacted via e-mail informing them that they had been identified by the steering committee as an expert within the field, together with a provision of the study objective and an outline of the Delphi procedure. The recruitment period duration was set at 6 weeks. A snowballing strategy was adopted by the recruiting author (ET), requesting contacted panellists to recommend peers who satisfy the eligibility criteria. Additionally, members of the steering committee were also eligible to recommend potential panellists from their professional network and posted invitations on social media.

5.2.6 Steering Committee

The steering committee consisted of the 5 authors of this study: the lead investigator (ET) and four senior academics (MTdG, JC, AG and DF), all with experience in the Delphi technique, qualitative and quantitative research methods and more than 10 years of clinical experience within musculoskeletal medicine. The responsibility of the committee was to recruit experts and to design, circulate and analyse the questionnaires. The steering committee made collective decisions regarding methodology, data analysis and quality assurance.

5.2.7 Delphi procedure

A pilot was conducted with eight students at the University of Birmingham with musculoskeletal expertise (PhD/MRes/MSc) who were invited to complete the round 1 survey over a 1-week period and asked to feedback any points to help improve the usability of the survey.

Once the survey was finalised, panellists received an email containing a link to the platform hosted on LimeSurvey® (www.limesurvey.com). Participant information including age, country of origin, country of current habitation/ work, highest qualification, current occupation, professional background and duration working with patients with CR or nerve related arm pain were collected.

The steering committee composed a list of proposed treatment modalities collated from systematic reviews and (inter)national guidelines [56, 57, 61-63, 265]. For Round 1, these were then classified in different intervention group categories: ‘counselling, advice and behavioural therapy’, ‘physical therapy’, ‘spinal manipulative therapy’, ‘traction’, ‘miscellaneous’, ‘medication’ and a final group labelled as ‘additional interventions suggested by panellists’.

Panellists were invited to provide their level of agreement for each proposed treatment modality for each stage of CR. Additionally, an open question was provided in each section in order to explore any missing treatment modalities which may have been overlooked. All additional treatment modalities, which were suggested by at least one panellist, were added into round 2. In round 2, items that had reached pre-determined criteria (see data analysis and criteria) were retained and returned to the panellists, including a summary of comments from round 1. A third repeat round of this process was carried out to reach consensus [266]. The treatment modalities generated following round 3 were collated to create the final list of treatment modalities for each stage of CR. Figure 5.1 details the procedure and timeline for the study. Round 1 of the questionnaire (**APPENDIX 8**) was sent out in December 2020. Questions were sent to the panellists en bloc and comments were returned in a non-blinded fashion to the lead investigator (ET), who incorporated the comments. A five-point Likert scale (1 = strongly disagree, 2 = disagree, 3 = do not agree or disagree, 4 = agree, 5 = strongly agree) was used to evaluate the level of agreement throughout [140, 267, 268]. Consensus was assessed through analysing descriptive statistics against pre-defined criteria for consensus.

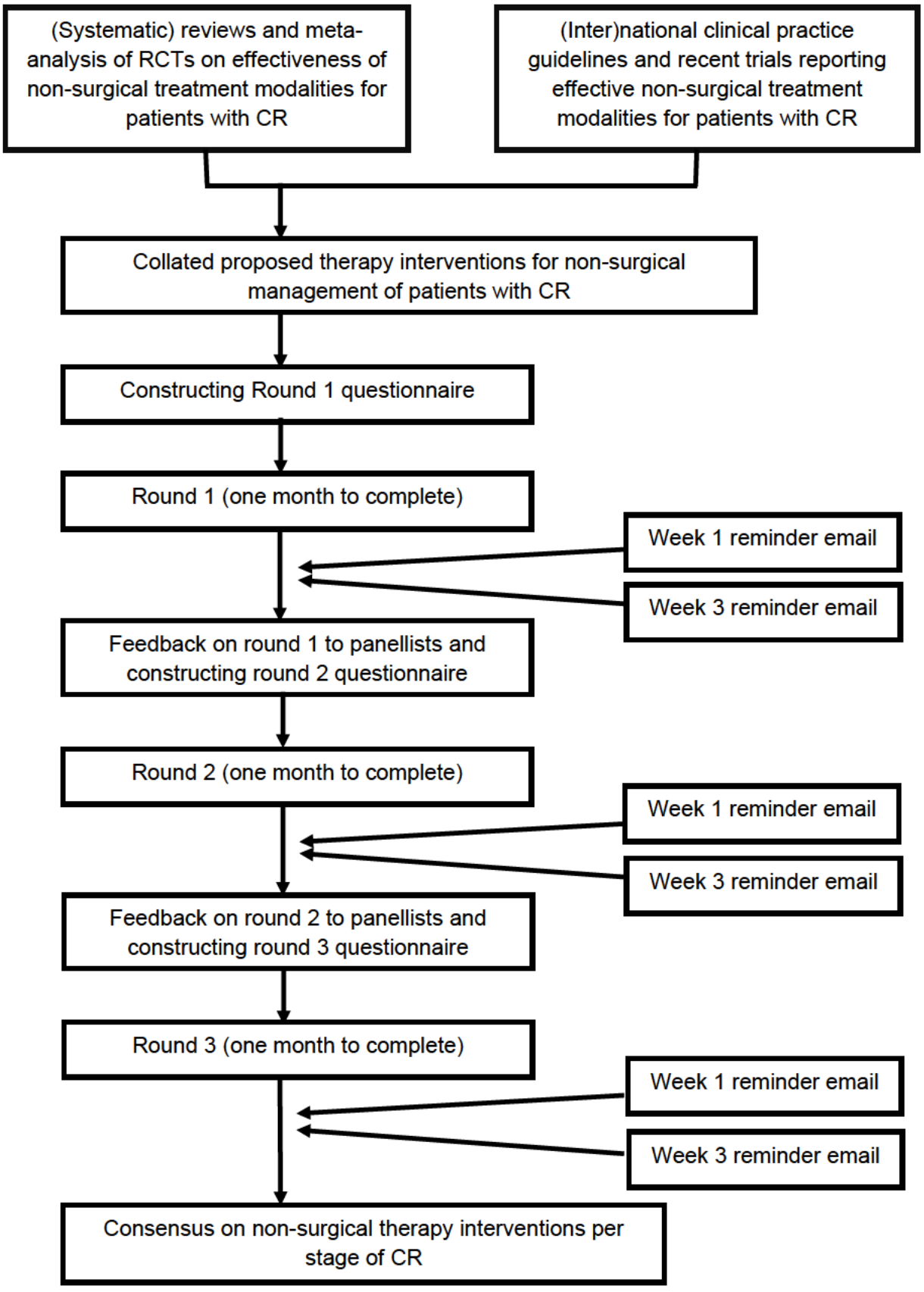


Figure 5.1 Procedure and timelines for participants in Delphi study

5.2.8 Data collection and analysis

All data was stored offline on a password encrypted computer in a locked office with access only available to the researchers. Content analysis was used to analyse data from the free text boxes; treatment modalities were identified by two authors (ET, MTdG) which helped to inform the construction of round 2 and 3 of the survey. Results of the descriptive statistics and content analysis were fed back to the steering committee and discussed before constructing the round 2 and 3 survey. Qualitative data were extracted deductively (to identify treatment modalities) and inductively (to identify additional treatment modalities). Descriptive statistics including (where applicable) means or median, interquartile range (IQR), and percentage of agreement [140] were used to assess consensus in each round according to the following criteria [254, 255, 269]:

Round 1: criteria of consensus

- Mean value of participants' Likert scale data ≥3
- Percentage of agreement ≥50%

Round 2: criteria of consensus

- Mean value of participants' Likert scale data ≥3.5
- IQR value of participants' Likert scale data ≤2
- Percentage of agreement ≥60%

Round 3: criteria of consensus

- Mean value of participants' Likert scale data ≥4
- IQR value of participants' Likert scale data ≤1
- Percentage of agreement ≥70%

Two or more criteria needed to be met for consensus. Descriptive statistics and quantitative data were analysed using IBM SPSS V.26.

5.3 RESULTS

A total of 78 potential experts were identified and contacted, of which 7 responded with a reason to decline and 44 did not respond to repeated individualised emails, which left a total of 27 panellists meeting the inclusion criteria and agreeing to participate (Table 5.1). There were no differences in panellist characteristics between the experts who participated and those that declined or did not respond to the invitation. All panellists completed all three survey rounds and none needed additional time to complete a round. The deletion, addition and modification of treatments based on previous rounds is listed in Table 5.2.

In Round 1, consistent feedback was that patient specific response to interventions needed to be monitored with regards to effectiveness. In the intervention category ‘Counselling, Advice and Behavioural Therapy’, there was an 88-100% agreement on the items ‘counselling’ and ‘advice’. The use of ‘(cognitive) behavioural therapy’ in the acute (67% agreement) and sub-acute stage (74% agreement) was under debate by a number of panellists, as it was pointed out that “no evidence of effectiveness of behavioural therapy” was found in systematic reviews and also in the outcomes in an upcoming trial (the PACeR trial [270]). This high level of consensus led to the creation of a statement for this intervention category in Round 2, rather than continue to rate the individual treatment items. In the intervention category ‘Physical Therapy’, there was feedback from 12 of the 27 panellists proposing to delete “chiropractic” and to add the intervention category.

Table 5.1 Panellist Characteristics

N =	27
Average age (range):	50.5 (27-72) years
Continent:	- North Americas (USA & Canada): 7 - Europe: 8 - Australasia:7 - Africa: 5
Occupation: (multiple answers possible)	- Academia: 20 - Medicine: 2 - Physiotherapy: 27 - Chiropractic: 2
Highest academic qualification	- BSc: 1 - MSc: 4 - DC: 1 - MD: 1 - PhD / DSc: 20
Years of experience with CR (median, range)	- 15**,** 6 – 27 years

BSc: Bachelor of Science; MSc: Master of Science; DC: Doctor of Chiropractic; MD: Medical Doctor; PhD: Doctor of Philosophy; DSc: Doctor of Science

‘Spinal Manipulative Therapy’ and ‘Traction’ to the Physical Therapy section. A need to better define ‘Spinal Manipulative Therapy’ was also suggested, which resulted in quoting and referencing the International Federation of Orthopaedic Manipulative Physical Therapists’ (IFOMPT) “Glossary of Terms” [271]. Feedback from additional comments of the ‘Medication’ category showed that many panellists did not have the ability to prescribe or suggest prescription of medication, which led to a rewording these questions and their answers slightly to reflect what panellists saw or perceived to be effective in their clinical practice. In the section ‘additional interventions suggested by panellists’, 12 interventions were suggested and were included in the respective stages in the round 2 questionnaire (see Table 5.2).

In Round 2, an additional comment on the consensus in the intervention category ‘Counselling, Advice and Behavioural Therapy’ was that ‘Behavioural Therapy’ was deemed not useful in the acute stage, useful only in specific situations in the sub-acute stage, but useful in the chronic stage depending on the cognitive/affective profile of the individual patient. In the re-arranged ‘Physical Therapy’ intervention category, most treatments were retained as consensus was reached. For the acute stage ‘general aerobic exercise’, ‘focused strength training’, ‘thoracic manipulation’ and ‘intermittent mechanical traction’ were removed, whereas for the sub-acute stage ‘general strength training’, ‘cervical manipulation’, and both ‘manual’ and ’intermittent mechanical’ traction were removed. For the chronic stage, ‘directional preference exercise’, ‘cervical manipulation’, thoracic manipulation’ and ‘manual traction’ were removed.

An agreement of ≥ 60% was not reached for any of the interventions in the ‘Miscellaneous’ intervention group (‘hard collar’, ‘soft collar’, ‘massage’,

‘acupuncture’, ‘dry needling’, ‘KinesioTape™/ medical taping’, ‘transcutaneous electrical nerve stimulation’) resulting in them being deleted from Round 3. For 6 of the 12 ‘additional interventions suggested by panellists’ an agreement of ≥ 60% was reached for some of the stages (‘specific soft tissue mobilization combined with neural mobilization’, ‘Mulligan’s “mobilisation with movement”, ‘foraminal opening exercise’, ‘sustained pain relieving positions’, ‘postural education’, ‘work place / vocational / ergonomic assessment’, ‘top down treatment interventions’ (e.g. mental imagery, graded motor imagery, mirror therapy etc.)) In the ‘Medication’ group no agreement was reached in the chronic stage and for only two in the acute / sub-acute stage an agreement of ≥ 60% was reached (see Table 5.2).

In Round 3 (Table 5.3), the consensus in the intervention category ‘Counselling, Advice and Behavioural Therapy’ remained unchanged from Round 2 with high percentages of agreement for the acute, sub-acute and chronic stages (89.7%; 89.7% and 93.1% respectively). The number of treatments in the intervention category ‘Physical Therapy’ were diminished substantially. This was mainly due to the strict agreement criteria set a priori. In the acute stage, only ‘cervical mobilisation’ and ‘spinal manipulative therapy combined with (specific) exercise’ reached consensus. In the sub-acute stage, ‘individualized physical activity’, ‘supervised exercise’, ‘motor control exercise’, ‘directional preference exercises’, ‘neurodynamic mobilisation’, ‘cervical mobilisation’ and ‘spinal manipulative therapy combined with (specific) exercise and neurodynamic mobilisation’ reached consensus. In the chronic stage, ‘general aerobic exercise’, ‘general strength training’, ‘focussed / targeted strength training’, ‘individualized physical activity’, ‘motor control exercise’ and ‘neurodynamic mobilisation’ were considered to be effective treatment

interventions. From the remaining ‘Additional interventions suggested by panellists’ from Round 2, in the acute stage only ‘foraminal opening" exercises’ and ‘sustained pain-relieving positions’ reached consensus. In the subacute stage, only for ‘specific soft tissue mobilisation combined with neural mobilisation’ and ‘work place / vocational / ergonomic assessment’ was consensus reached and in the chronic stage, only ‘postural education’ and ‘work place / vocational / ergonomic assessment’ reached consensus. In the ‘Medication” category, agreement could only be reached on the use of NSAIDs in the acute stage and a general wariness to the use of opioids and anti-epileptic drugs with a tendency to only consider them in the presence of neuropathic pain components. As only 2 participants were able to prescribe medication, we decided to not include these results in the final recommendations.

Table 5.2. Deletion, addition and modification of treatments based on previous rounds

	ROUND 1		ROUND 2			ROUND 3		
Intervention group	**Likert Scale (median)**	**Agreement (%)**	**Likert Scale (median)**	**IQR (median)**	**Agreement (%)**	**Likert scale (median)**	**IQR (median)**	**Agreement (%)**
ACUTE STAGE								
Counselling, Advice and Behavioural Therapy								
Providing Information								
Pain Education								
Behavioural Therapy								
Physical Therapy								
General Aerobic Exercise								
General Strength Training								
Focused /Targeted Strength Training								
Individualized Physical Activity								
Supervised Exercise								
Motor Control Exercise								
Directional Preference (MDT) Exercise								
Neurodynamic Mobilisation								
SMT as a stand-alone treatment								
Cervical manipulation								
Cervical mobilisation								
Thoracic manipulation								
Thoracic mobilisation								
Chiropractic treatment (in Round 2 under SMT)								
SMT combined with specific exercise								
SMT combined with neurodynamic mobilisation								
SMT combined with neurodynamic mobilisation & specific exercise								
Mechanical “over the door” traction								
Continuous mechanical traction								
Intermittent mechanical traction								
Manual traction								
Hard collar								
Soft collar								
Massage								
Acupuncture								

Dry Needling								
Medical Tape / Kinesiotape								
TENS								
Medication								
NSAIDs								
Opioids								
Combination of NSAIDs and Opioids								
Anti-epileptic drugs								
Combination of NSAIDs and Anti-epileptic drugs								
Combination of Opioids and Anti-epileptic drugs								
Combination of NSAIDs and Opioids and Anti-epileptic drugs								
Additional Interventions Suggested by Panellists in Round 1								
Tricyclic medication								
Specific Soft tissue mobilisation combined with neural mobilisation								
Mulligan's "Mobilisation with Movement"								
"Foraminal opening" exercise								
Sustained pain relieving positions								
Heat								
Cryotherapy								
Interferential therapy								
Postural education								
Work place / Vocational / ergonomic assessment								
SUBACUTE STAGE								
Counselling, Advice and Behavioural Therapy								
Providing information								
Pain Education								
Behavioural therapy								
Physical Therapy								
General Aerobic Exercise								
General Strength Training								
Focused /Targeted Strength Training								
Individualized Physical Activity								
Supervised Exercise								
Motor Control Exercise								

Directional Preference (MDT) Exercise								
Neurodynamic Mobilisation								
SMT as a stand-alone treatment								
Cervical manipulation								
Cervical mobilisation								
Thoracic manipulation								
Thoracic mobilisation								
Chiropractic treatment (in Round 2 under SMT)								
SMT combined with specific exercise								
SMT combined with neurodynamic mobilisation								
SMT combined with neurodynamic mobilisation and specific exercise								
Mechanical "over the door" traction								
Continuous mechanical traction								
Intermittent mechanical traction								
Manual traction								
Hard collar								
Soft collar								
Massage								
Acupuncture								
Dry Needling								
Medical Tape / Kinesiotape								
TENS								
Medication								
NSAIDs								
Opioids								
Combination of NSAIDs and Opioids								
Anti-epileptic drugs								
Combination of NSAIDs and Anti-epileptic drugs								
Combination of Opioids and Anti-epileptic drugs								
Combination of NSAIDs and Opioids and Anti-epileptic drug								
Additional Interventions Suggested by Panellists in Round 1								
Tricyclic medication								
Specific Soft tissue mobilisation combined with neural mobilisation								

Mulligan mobilisation with movement								
"Foraminal opening" exercise								
Sustained pain relieving positions								
Heat								
Cryotherapy								
Mesotherapy								
Interferential therapy								
Postural education								
Work place / Vocational / ergonomic assessment								
Top down treatment interventions e.g. meditation, mental imagery, graded motor imagery, mirror therapy								
CHRONIC STAGE								
Counselling, Advice and Behavioural Therapy								
Providing Information								
Pain Education								
Behavioural therapy								
Physical Therapy								
General Aerobic Exercise								
General Strength Training								
Focused /Targeted Strength Training								
Individualized Physical Activity								
Supervised Exercise								
Motor Control Exercise								
Directional Preference (MDT) Exercise								
Neurodynamic Mobilisation								
SMT as a stand-alone treatment								
Cervical manipulation								
Cervical mobilisation								
Thoracic manipulation								
Thoracic mobilisation								
Chiropractic treatment (in Round 2 under SMT)								
SMT combined with specific exercise								
SMT combined with neurodynamic mobilisation								
SMT combined with neurodynamic mobilisation and specific exercise								
Mechanical “over the door” traction								

Continuous mechanical traction								
Intermittent mechanical traction								
Manual traction								
Hard collar								
Soft collar								
Massage								
Acupuncture								
Dry Needling								
Medical Tape / Kinesiotape								
TENS								
Medication								
NSAIDs								
Opioids								
Combination of NSAIDs and Opioids								
Anti-epileptic drugs								
Combination of NSAIDs and Anti-epileptic drugs								
Combination of Opioids and Anti-epileptic drugs								
Combination of NSAIDs and Opioids and Anti-epileptic drugs								
Additional Interventions Suggested by Panellists in Round 1								
Tricyclic medication								
Specific Soft tissue mobilisation combined with neural mobilisation								
Mulligan mobilisation with movement								
"Foraminal opening" exercise								
Heat								
Postural education								
Work place / Vocational / ergonomic assessment								
Top down treatment interventions e.g. mediation, mental imagery, graded motor imagery, mirror therapy etc.								

*: value ≥ consensus criterium for that Round; MDT: Mechanical Diagnosis and Treatment; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs e.g.: Ibuprofen, Diclofenac, Meloxicam, Naproxen, Celecoxib, Indomethacin, etc.; Opioids e.g.: Codeine, Hydrocodone, Vicodin, Morphine, Oxycodone, Percocet, Fentanyl, etc.; Anti-epileptic drugs e.g.: Pregabalin, Gabapentin, Lyrica, etc.; Tricyclic medication (amitriptyline/nortriptyline); SMT: Spinal Manipulative Therapy; TENS: Transcutaneous Electrical Nerve Stimulation.

Table 5.3. Proposed effective interventions per stage.

Intervention group	Likert Scale (mean)	Agreement (%)
ACUTE STAGE (≤ 6 weeks)		
Counselling , Advice and Behavioural Therapy		
"Providing Information" ,"Pain Education": useful. "Cognitive Behavioural Therapy": rarely useful.	4.2*	89.7*
Physical Therapy		
Cervical mobilisation	3.9	75.9*
Spinal Manipulative Therapy combined with (specific) exercise	4.1*	79.3*
Panellist Added Interventions		
"Foraminal opening" exercise	3.9	75.9*
Sustained pain-relieving positions	3.9	75.9*
SUB-ACUTE STAGE (6 – 12 weeks)		
Counselling , Advice and Behavioural Therapy		
"Providing Information" , "Pain Education": useful. "Cognitive Behavioural Therapy": worth considering	4.2*	89.7*
Physical Therapy		
Individualized physical activity	4.1*	82.8*
Supervised exercise	4.0*	75.9*
Motor control exercise	4.0*	79.3*
Directional preference exercise	3.7	72.4*
Neurodynamic mobilisation	4.1*	86.2*
Cervical mobilisation	4.0*	86.2*
Spinal Manipulative Therapy combined with (specific) exercise and/or neurodynamic mobilisation	4.3*	86.2*
Panellist Added Interventions		
Specific Soft tissue mobilisation combined with neural mobilisation	3.9	72.4*
Workplace / Vocational / ergonomic assessment	4.0*	79.3*
CHRONIC STAGE (≥ 12 weeks)		
Counselling , Advice and Behavioural Therapy		
"Providing Information", "Pain Education" and "Cognitive Behavioural Therapy": useful	4.3*	93.1*
Physical Therapy		
General aerobic exercise	4.3*	86.2*
General strength training	4.2*	82.8*
Focussed / targeted strength training	4.1*	72.4*
Individualized physical activity	4.1*	69.0
Motor control exercise	4.0*	72.4*
Neurodynamic mobilisation	4.0*	72.4*
Panellist Added Interventions		
Postural education	3.8	72.4*
Workplace / Vocational / ergonomic assessment	4.1*	89.7*

*: value ≥ consensus criterium for that Round;

5.4 DISCUSSION

This is the first study establishing consensus from international experts on effective non-surgical treatment modalities for patients in different stages (i.e. acute, sub-acute and chronic) of CR.

This study's consensus is that in the acute stage, the focus of management should lie in patient education with positive reinforcing and non-nocebo content, together with Spinal Manipulative Therapy combined with specific (foraminal opening) exercise and advice on sustaining pain-relieving positions. In the sub-acute stage, management should consist of continued positive patient education, but Cognitive Behavioural Therapy is worth considering depending on the cognitive/affective profile of the individual patient, e.g., when fear avoidance appears to become relevant in specific individual situations. The main component of management should consist of Spinal Manipulative Therapy but combined with increasing active individualized physical activity including supervised motor control and other specific exercises and/or neurodynamic mobilisation. Additionally, a workplace and vocational or ergonomic assessment should be considered. While some Spinal Manipulative Therapy and neurodynamic mobilisation might still be useful in the chronic stage, the focus should shift to a more active approach including both general aerobic exercise as well as focussed strength training of both local as well a global musculature. Postural education and workplace and vocational / ergonomic assessment should also be considered.

The results from this study could help to facilitate the formulation of an individualised management plan for patients with CR depending on the state of their condition. By grouping separate effective treatment modalities based on expert opinion with

respect to the stage of recovery, clinicians could potentially be better able to tailor management plans to the individual patient through their course of recovery, instead of using a standardized “one size fits all” approach. The results from this study may also serve a need both clinically and within the contemporary literature to inform further research projects.

The results of this study are comparable with a recent Danish clinical guideline for non-surgical treatment of patients with CR [63]. Even though they found a lack of evidence for the efficacy of many of the interventions for CR, they recommended several similar treatments such as patient education, individualised exercises including motor control and directional preference exercises and spinal manipulative therapy [63]. In 2017, The Orthopaedic Section of the American Physical Therapy Association published a revision of clinical practice guidelines also relating to patients with radiating arm pain [62]. For patients with acute radiating neck pain, they recommended mobilising and stabilising exercises, laser, and short-term use of a cervical collar. For patients with chronic radiating neck pain, they recommended mechanical intermittent cervical traction, combined with other interventions such as stretching and strengthening exercise plus cervical and thoracic mobilisation/ manipulation. They also recommended education and counselling to encourage participation in occupational and exercise activities [62]. In the Delphi study in this thesis (**CHAPTER 5**), laser was not mentioned or proposed as an effective intervention, while cervical traction was considered but did not achieve the consensus criteria in Round 3. In 2010, North American Spine Society released an evidence-based clinical guideline for the diagnosis and treatment of CR from degenerative disorders [60]. They reported to have found insufficient evidence to

adequately address the role of any form of physical therapy or exercise in the management of CR from degenerative disorders [60]. The Ontario Protocol for Traffic Injury Management (OPTIMa) Collaboration also published an evidence-based guideline in 2016 for the management of neck pain and associated disorders including CR [265]. For patients with recent onset CR, clinicians were recommended to consider structured patient education in addition to supervised strengthening exercises, cervical collar, low-level laser therapy, or traction. In the Delphi study in the thesis (**CHAPTER 5**), a cervical collar was mentioned but did not achieve consensus criteria in Round 2.

In the current study, some of the proposed interventions for which there is evidence of effectiveness did not reach the required level of consensus to be included in the panel's final recommendations. The use of a soft collar in the first three weeks was reported to be effective in one study [54], but this intervention did not reach consensus in Round 2 of the current Delphi. Thoracic manipulation was reported to be effective in another study with a heterogeneous population of acute, sub-acute and chronic patients [272], but the panel of experts in the current study deemed it only useful in the sub-acute stage. The panel also judged neurodynamic mobilisations not to be useful in the acute stage, even though there is evidence to suggest it is useful at this stage. [56, 79, 82, 215]

5.4.1 Implications for clinical practice

The results from this study are meant to be used as a framework from which an individualised management plan can be designed. It is not meant to be prescriptive or to exclude specific treatments on an individual basis, and patient's response to

treatment should be monitored to avoid aggravation, especially in the acute and sub-acute stages.

5.4.2 Implications for future research

Current clinical practice is driven by evidence gathered from RCTs and meta-analyses. A “classic” RCT usually compares one effective treatment to another effective treatment and assesses which is the more effective one. One of the recognised flaws in RCTs is that the randomisation process requires clinical equipoise: one cannot ethically randomise patients unless both treatments have equal support in the clinical community [273] . In light of this, it becomes difficult to achieve enough difference between interventions studied, to achieve a level of improvement that is clinically meaningful. In an effort to overcome this, a recent study randomised 2 groups into one receiving standard care and one receiving individualized interventions [274]. Still, some elements of the individualised treatment program will most likely be art of the generic treatment program in the other arm of the study, in order gain ethical approval.

Single case intervention designs (SCIDs) are a class of interrupted time-series designs and are characterized by the inclusion of only a few participants or other entities (“cases”), two or more “phases” (e.g., baseline and intervention phases), and multiple outcome observations per case [275-277]. They should not be confused with traditional “clinical case reports” or “case studies” based on a specific individual’s ongoing records and protocols. Single case research can be done when a limited number of patients are available, and per definition also in just one patient. The method can be used both as a formal research tool and as clinical audit tool. In both

cases single case methods provide continual feedback on the progress of treatment and results are available in real time [276, 277]. Future research should incorporate SCIDs alongside the use of well-designed RCTs as a means to implement the result of this study and gather more evidence on timing and dosage of specific multi-modal interventions throughout the course of the disorder.

5.4.3 Strengths and limitations of this study

One of the strengths of this study was the spread of panellists across continents and different professions, from both a medical / neurosurgical as well as a physiotherapy and chiropractic background. Also, all panellists completed all three rounds of the Delphi survey.

This study was reported in line with CREDES recommendations and utilised both qualitative and quantitative data. However, the views of the Delphi panellist may differ from those experts that declined to participate and so may not fully represent an opinion of all experts in the field. The evidence-based opinion of the panellists was based on a mixture of clinical experience, patient's perspectives and scientific evidence [278-280]. With respect to the latter, this panel, repeatedly mentioned the lack of evidence from high quality RCTs, which was also mentioned in previously published guidelines and systematic reviews [56, 57, 61-63, 265].

Only two panellists had the direct ability to prescribe medication and only a few more were able to confer with prescribing colleagues. This resulted in many panellists not feeling competent to form an opinion on the preferred prescription of the different types of medication. Therefore, these results were not included in the final recommendations.

5.5 CONCLUSION

Current literature provides clinicians with a list of potentially effective individual treatment modalities derived from RCTs and CCTs. It does not allow for individualised management plans tailored to the patient's stage of recovery. This Delphi study proposes a consensus derived set of treatment modalities considered to be most effective during certain stages of recovery. The findings of this study could facilitate the decision-making process of clinicians in formulating individualised management plans through the course of recovery for patients with CR. Additional evidence from high quality clinical trials with staged personalised non-surgical management programs is needed. It was the consensus of this expert panel that neurodynamic mobilisations, the major focus of the research presented in this thesis, appear to be an treatment modality to be considered using in the sub-acute as well as in the chronic stage.

CHAPTER 6
GENERAL DISCUSSION

6.1 SUMMARY OF THESIS FINDINGS

This thesis aimed to increase the generally acknowledged lack of evidence [21, 63, 135] with respect to the clinical reasoning journey for clinicians from diagnosing to successfully conservatively managing patients with a CR, with a focus on what role altered neurodynamics play in patients with a CR.

Building on from studies I published prior to the start of this thesis [10, 38] and incorporating results from other previously published studies [1, 19, 60, 126], this thesis first updated information gathered from the systematic review published in 2018 [38]. In this update, the validity of neurodynamic and other provocation tests used for CR was assessed. The most recent study published from this thesis concluded that, when consistent with the patient history and other clinical signs, clinicians may use a combination of Spurling's test and a combination of four ULNTs (with at least one positive test), to increase the likelihood of the presence of CR [38]. This outcome implies there is a difference in neurodynamics between patients with CR and healthy controls. In order to investigate this hypothesis, another study was conducted, which found that there was a significant difference between patients and controls in the excursion of the median nerve at both the wrist and elbow at baseline (T0) during a mechanically induced contralateral cervical lateral glide (CCLG) neurodynamic mobilisation technique. There was also a significant increase in median nerve excursion at both sites between T0 and at three month follow up (T1) in those with CR. Patients received individualised conservative physiotherapy management which included neurodynamic mobilisations during these 3 months. There was a strong correlation between improvement in median nerve excursion at

the elbow at T1 and improvement in pain intensity and functional limitations. We concluded that longitudinal median nerve excursion differs significantly between patients with CR and asymptomatic volunteers at baseline, but this difference is no longer present after 3 months of conservative management which included neurodynamic mobilisations. Improvement in nerve excursion strongly correlates with improvement in clinical signs and symptoms, suggesting that it has the potential to assist clinical decision making with regards to either continuing or suspending conservative management.

For patients with CR, conservative management is a preferred first treatment option over surgery, since the risk-benefit ratio for surgery is less favourable [52, 53]. In two other studies I published prior to this thesis which assessed the effectiveness of conservative management, it was proposed that conservative management should consist of a multimodal intervention with neurodynamic intent, and that the use of a collar can be advised in early onset CR. Additionally, evidence from previously published studies show there is low-level evidence that traction is no more effective than placebo traction [56, 57].

Next, this thesis assessed the current evidence on the effectiveness of neurodynamic mobilisations for patients with CR in a systematic review. This study concluded there was low-level evidence of effectiveness of neurodynamic mobilisations on pain, disability and function in patients with a CR, especially when compared to an inactive control.

Continuing on from the evidence mentioned above, a Delphi study was performed. In this study, a consensus of clinical experts further defined the content and timing of a conservative management programme during the course of the condition. These

experts concluded that multi-modal physiotherapy management should consist of positive reinforcing patient education and Spinal Manipulative Therapy, combined with slowly increasing physical activity including both general aerobic exercise as well as focussed strength training of both local and global musculature and should also include neurodynamic mobilisation. Additionally work place ergonomic assessment should be considered [240].

6.2 OVERALL STRENGTHS AND LIMITATIONS

The information is this thesis is underpinned by information generated by two systematic reviews, a Delphi study and a case control clinical trial. To ensure methodological rigour, the reviews all followed recommendations by the Cochrane Handbook for Systematic Review of Interventions [281] and guidelines set by the Cochrane Diagnostic Test Accuracy group. The search strategy was designed in close collaboration with a research librarian and followed the PICO tool. Assessment of methodological quality of the included studied was done using the Cochrane Risk of Bias tool [282], and the QUADAS-2 tool [136]. The level of evidence was graded using the GRADE system [283]. Likewise, for study design and reporting, the Delphi study adhered to the CREDES guidelines [72] while the clinical trial conformed to the STROBE statement [164].

Nevertheless, no matter how rigorous the methodology, systematic reviews only provide a level of evidence no better than the number and quality of the included studies. And for all review study aims, there was a recognised paucity of evidence with respect to the clinical diagnosis, effectiveness of conservative management and assessment of patients with CR. All reviews presented in this thesis were influenced

by the variable methodological level of the included studies and the heterogeneity and low number of patients included in the relatively few studies. The individual conclusions of the studies included in the reviews also reflected that, and cautioned against over-interpreting outcomes.

While updating the previously published review for the purpose of this thesis, I chose to continue on from the data from that review in **CHAPTER 2**. As a consequence, I did not reassess the methodological quality of all included studies with the QUADAS-2 tool, but only of the newly included studies. In doing so I had to use a different appropriate statistical technique from the one used in the original published review. In the original review there were multiple raters assessing the initial agreement on the QUADAS-2, which meant the ICC was the correct statistical analysis. For the newly included studies in the update there were only two raters, meaning that now Cohen's kappa *k* was the correct statistic to use [140]. And while both analyses showed a high level of agreement, if I was to pursue publication in a relevant peer-reviewed journal, it would be better to use either two raters (or multiple raters) consistently for all included studies. I also pooled data for the Shoulder abduction test, the ULNT1 alone and combined ULNTs with one positive test, and presented sensitivity, specificity, PPV, NPV and an accuracy percentage. PPV and NPV however, are very dependent on the prevalence of the studied condition and in the review these differed across the studies, leading to a lesser degree of accuracy of the pooled results. However, the width of the 95%CIs reported do reflect the lesser degree of accuracy.

The ultrasound scanning of the longitudinal excursion of the median nerve during a contra-lateral cervical lateral glide movement in people with and without CR (**CHAPTER 3**) presented some methodological and technical difficulties. Originally,

the median nerve was scanned distally at the wrist and elbow and also at the upper arm underneath the medial head of the biceps muscle. While it was relatively easy to scan the median nerve there in situ, it proved difficult to track the median nerve while the Occiflex™ produced the CCLG movement. In analysing the data, there was a discrepancy between the longitudinal movement at the elbow and the wrist, compared to the upper arm, both at T0 as well as at T1. This is most likely due to the fact that at that site, the median nerve does not lie completely perpendicular to the skin surface in a proportion of patients. After originating from the brachial plexus in the axilla, the median nerve descends down the arm, initially lateral to the brachial artery. Halfway down the arm, the nerve crosses over the brachial artery, and becomes situated medially. The exact site at which the median crossed differs between individuals [284].

The interrater agreement for assessment of median nerve excursion form the ultrasound videos was pilot tested with three randomly selected ultrasound sequences. The results of the study could have been more robust if all videos had been assessed by two authors. However, this proved not to be executable due to time constraints of the second author. Nevertheless, the ICC from the pilot data was excellent (ICC 2,1 = 0.981; 95%CI 0.946-0.994), with a SEM of 0.137 mm and a SDC of 0.38 mm. The results of studying a difference in longitudinal median nerve excursion between patients with CR and healthy matched controls for the first time, necessitates a need for this to be replicated in larger cohorts and different accessible scanning sites in the arm, before more firm conclusions can be drawn. For now this prospective cohort study provides only level II evidence with regard to this [285]. In

section 6.5, I will discuss options on how future research could be performed to provide higher level of evidence.

In the systematic review of the effectiveness of neurodynamic mobilisations in patients with CR (**CHAPTER 4**) the strength of the evidence (using the GRADE method) was assessed by the lead review author only. The evidence could have been more robust if this had also been done by two review authors, blinded to each other's original assessment.

The type, chosen treatment technique and manner of execution of neurodynamic mobilisation differed greatly between the eight included studies. Soft tissue mobilisation, tensioner and slider techniques in differently positioned upper limbs of either the cervical spine and/or the upper limb were described. Naturally this has implications for the generalisability of the results. Additionally, the overall RoB assessment showed only three of the eight included studies to be of high methodological quality [210, 234, 235], two of which assessing the same technique by the same authors [234, 235].

For the purpose of the Delphi study in establishing consensus on the timing of evidence-based nonsurgical interventions as part of multimodal treatment guidelines for the management of CR (**CHAPTER 5**), the different stages of CR were aligned with established pain terminology e.g.: 'acute', 'sub-acute' and 'chronic' as proposed by the IASP [261, 286]. In clinical practice however, this might not always be the most opportune classification. The 'acute' or early onset stage of CR in which patients experience higher levels of both radicular and/or neuropathic pain often lasts for more than six weeks. This means that choosing effective treatment modalities in this stage is not always determined by time alone but much more by the clinical

presentation. Currently, there is hardly any evidence with regards to this. From an evidence based perspective, clinical expertise of the individual health care provider combined with the individual patient's perspective are the pillars of management plans [287].

With respect to the composition of the panellists, it proved difficult to trace exactly how much recent clinical experience the individual experts had. It therefore was not always clear if their opinion on the level of effectiveness of the individual treatment modalities was based on evidence presented in systematic reviews and RCTs or on their personal expert opinion. In hindsight, specific questions could have been added to the Round 1 questionnaire to establish the amount of recent clinical contact with patients with CR. It could also have been useful to add questions assessing on which evidence the answers were based; clinical and/or published research.

Even though there is a logical flow within the studies in this thesis, a more condensed time frame could have provided the opportunity to actually progress from one study to the next. The COVID-19 pandemic, which started early 2020, necessitated national lockdowns of society lasting well into 2022. Apart from the disruption of usual medical care through overflowing hospital's Intensive Care Units and departments, it also caused a standstill in the potential to include patients into research. This warranted opening up a different strategy and line of research such as electronic surveys and Delphi procedures.

6.3 CLINICAL IMPLICATIONS

Patients visiting a clinician with radiating arm pain due to CR can be differentiated from patients with somatic referred arm pain by including positive results of a

combination of Spurling's, and four ULNT tests into a patient profile with a consistent history and other clinical signs. Once CR is diagnosed, a conservative multi-modal physiotherapy management should be a first treatment option for most patients with a CR. This should consist of positively reinforcing patient education and Spinal Manipulative Therapy, combined with slowly increasing physical activity including both general aerobic exercise as well as focussed strength training of both local as well a global musculature and neurodynamic mobilisation. Additionally, work place ergonomic assessment should be considered [240]. Even though cervical axial traction has traditionally been advocated as an effective therapy for CR, evidence from this thesis [56, 57, 240] as well as a more recent systematic review [248] does not support this.

The effect of neurodynamic mobilisation could be monitored using ultrasound imaging of the longitudinal excursions of the median nerve at the elbow as it has the potential to assist clinical decision making with regards to either continuing or suspending conservative management. Integrating this into clinical practice requires not only access to ultrasound imaging equipment, which is increasingly more popular in physiotherapy and GP clinics, but also access to frame-by-frame cross correlation algorithm software which is not (yet) readily commercially available.

6.4 RECENT DEVELOPMENTS

6.4.1 Diagnostic process

Recent developments with respect to the diagnostic process of differentiating patients with CR from those with non-specific neck pain has aided to underpin results

discussed in this thesis. The updated systematic review on the diagnostic accuracy of physical test was able to incorporate three additional studies.

In a retrospective study, Park et al., (2017) introduced the Neck Torsion test (NTT) as an alternative to Spurling's test [142]. The NTT, like the recently introduced "Arm Squeeze Test' [35] we included in a previously published systematic review [38], has not yet been assessed in other studies. To date, Spurling's test remains the only provocative test studied in more than one study [37, 144, 146].

Sleijser-Koehorst et al., (2020) studied the diagnostic accuracy of both patient interview items as well as clinical tests for CR [135]. They included patients based on a medical specialist's diagnosis of CR based on the patient's clinical presentation and corresponding Magnetic Resonance Imaging findings. They concluded that history items 'arm pain worse than neck pain', 'provocation of symptoms when ironing', 'reduction of symptoms by walking with your hand in your pocket', together with a Spurling test and the presence of reduced reflexes showed high specificity and are therefore useful to increase the probability of CR when positive. The presence of 'paraesthesia and/or numbness' showed high sensitivity, indicating that the absence of these patient interview items decreases the probability of CR [135].

Another recent study aimed to assess the agreement between the clinical neurological assessment and an MRI to identify the level of a radiculopathy-affected cervical nerve root. They reported that out of a total of 83 patients, there was full agreement regarding root level and side according to clinical evaluation and MRI, in 26 cases, compared to those with the adjacent level agreement (n = 23) and those with no agreement (n = 34) [288]. Unfortunately their clinical evaluation did not include physical provocation tests such as the Spurling's test or ULNTs, nor did they

aim to assess diagnostic accuracy of the clinical examination of sensory and reflex testing [288].

A recent E-Delphi study aimed to establish a set of uniform classification criteria (CC) for CR, in an effort to facilitate future recruitment of homogenous populations to clinical trials [289]. The Delphi panel concluded that a cluster criterion consisting of 1) radicular pain with arm pain worse than neck pain; 2) paraesthesia or numbness and/or weakness and/or altered reflex and 3) MRI confirmed nerve root compression compatible with clinical findings, was most likely to classify patients correctly [289]. Recently Kapitza et al., (2020) published a study protocol aiming to investigate the application of a previously proposed clinical framework [290] adapted from one in patients with radiating leg pain [291] in patients with neck-arm pain [292]. This framework classifies patients with neck-arm pain into (1) somatic pain, (2) neural mechanosensitivity, (3) radicular pain, (4) radiculopathy and mixed pain presentations [290]. The study also aims to determine their somatosensory, clinical and psychosocial profile and observe their clinical course over time. They aim to show that comprehensive sensory and clinical profiling can assist in the characterisation of each subgroup and the possible predictive role of measured parameters for pain and disability persistency over 12 months [292]. Results have not yet been published but this clinical reasoning approach of comprehensive sensory and clinical profiling might assist clinicians in the characterisation of each subgroup and the possible predictive role of measured parameters for pain and disability persistency.

In conclusion, new evidence supports the conclusions on the validity of physical tests for CR in a previously published SR [38] as well as in the SR presented within this thesis.

6.4.2 Conservative management

Recent developments with respect to the conservative management of patients with CR support the potential effectiveness of some treatment techniques. Below, I will discuss those studied in this thesis:

Exercise therapy

Multifidus wasting (identified using MRI) has been shown to occur in patients with CR [293, 294]. A recent study measured the cross sectional area (CSA) of multifidus and reported significantly smaller multifidus muscles in the affected side and cervical level corresponding with the afflicted nerve root [294]. One other study reported denervation oedema of the multifidus muscles correlating with clinical/electrophysiological tests and weakness severity [293]. Another study used ultrasound imaging, a much less expensive and more easily available technique, to assess the CSA of multifidus and longus colli muscle dimensions and reported similar results [295]. These results support the clinical notion of including (focused) exercises in a multimodal treatment plan, in line with the recommendations from the Delphi study presented in this thesis [240]. The effectiveness of having exercise as part of a multimodal management strategy in managing has been further supported by a recent review [296]. This study reported that exercise alone or exercise plus other treatment interventions may be helpful to patients with CR but that exercise

options should be carefully considered for each patient with CR in accordance with their different situations and individual relevant dysfunctions [296]. One other study compared stabilisation exercises to a general home-exercise program in patients with CR and found no clinical difference [297]. Identically, Dedering et al., (2018) reported that a 12-week neck-specific training (NST) program did not significantly improve outcomes of pain, disability and psychological outcomes in conservatively managed individuals with CR, compared to a prescribed physical activity (PPA) in patients with CR [298]. They concluded that participants improved regardless of the intervention received and suggested that CR has a natural favorable long-term outcome when patients are prescribed neck-specific training and exercise in combination with a behavioral approach [298]. But this conflicting information might well be caused by the necessary treatment protocols used in RCTs; they do not assess the individual patient's dysfunction. Instead, they provide the same standardised treatment to all, regardless of the individual's need for specific interventions or lack of it.

Counselling, pain education and behavioural approaches

The consensus from the Delphi study presented in this thesis (**CHAPTER 5)** on the timing of treatment interventions was that counselling, pain education and behavioural approaches were an important part of multi-modal management across the evolution of CR. In order to study the effect of psychological factors on the difference in outcome, Liew et al, (2021) [299] continued on the work by Dedering et al., (2018) [298]. In the study by Dedering et al., (2018), patients received either a Neck Specific Training (NST) programme with a cognitive behavioural approach delivered continuously throughout the program or a Prescribed Physical Activity

(PPA) programme with a cognitive behavioural approach delivered only at the first session [298]. Liew et al., (2021) built a Bayesian Network model, including: treatment group (NST vs. PPA), age, sex, self-efficacy, catastrophizing, kinesiophobia, anxiety, neck-arm pain intensity, headache pain intensity and disability [299]. The model was used to quantify the contribution of different mediating pathways on the outcome of disability at 12 months. They concluded that while the specific characteristics investigated in their study did not explain the differences in mechanisms of effect between NST and PPA, this could well be due to the fact there was too little contrast between the NST and PPA interventions in their study [299].
A recent systematic review which aimed to summarise the diagnostic and therapeutic recommendations from (inter)national guidelines for management of patients with lumbosacral radicular pain (LRP) concluded that a consistent recommendation for 'should do' was: educational care [300]. This is consistent with the recommendation from the Delphi study presented in this thesis (**CHAPTER 5**) [259]

Spinal manipulative therapy

My previously published narrative review from 2016 concluded that there was low to very low evidence for the effectiveness of some forms of spinal manipulative therapy in patients with CR [56]. Young et al. (2019) reported that a single session of thoracic manipulation resulted in improvements in pain, disability, cervical ROM, and deep neck flexor endurance in patients with CR. Patients treated with manipulation were more likely to report at least moderate change in their neck and upper extremity symptoms up to 48 to 72 hours following treatment [272]. An earlier study by Waqas et al. (2016) corroborated this effect [301].

With respect to tailoring specific treatment techniques to a specific condition, a recent study assessed the effects of oscillatory mobilisation as compared to sustained stretch mobilisation in the management of CR [302]. They specifically wanted to determine the effects of Maitland's oscillatory mobilisation as compared to Kaltenborn's sustained stretch mobilisation in the management of patients with CR [302]. The study reported both techniques to be effective in the management of patients with CR in terms of pain, range and disability, but found Maitland's oscillatory mobilisation to be superior in terms of functional ability and range of motion [302]. Perhaps the oscillatory mobilisation was less likely to induce an inflammatory response of the nerve root and supported restoring homeostasis of the nerve root in the area of the neuroforamen [302]. One other study reported that adding a specific manual therapy technique (mobilisation with movement or “Mulligan’s” mobilisation) on a treatment regime of neurodynamic mobilisation (NM) and manual traction was more effective [303].

Spinal manipulative therapy might by some be construed as merely a passive treatment modality. And contemporary physiotherapy focuses on providing patients with active treatment programs and many guidelines advocate these should be the primary focus, with passive interventions as an adjunct. Nevertheless, there is a place for passive treatment modalities too. Costello et al., (2016) compared a single session of therapeutic ultrasound (as a “sham” treatment) to soft tissue mobilisation (STM) on Global Rating of Change (GROC), ROM during the ULNT, and pain rating during the ULNT [304]. STM was defined as a manual pressure being applied to the soft tissues of the upper quadrant in a deep, stroking manner with the intention to improve the mobility of the soft tissues surrounding the pathway of the neural

structures of the upper limb as well as any tender or tight tissues, whilst the arm was in positioned in abduction and external rotation to preload the neural structures of the upper limb in a manner similar to that used by Coppieters et al., (2003) [305]. Secondary measures included the NDI, PSFS, NPRS, and active range of shoulder abduction motion combined with the wrist neutral or wrist extension [304]. They reported that a greater proportion of patients in the STM group reported a significant improvement on the GROC immediately after treatment (p=0.003, STM=75%, US=9%), and at 2-4 day follow-up (p=0.027, STM=58%, US=9%). Patients who received STM demonstrated greater improvements in ROM during ULNT (p=0.026), PSFS (p=0.007), and shoulder active ROM combined with wrist extension (p=0.028). Improvements in NPRS and pain during the ULNT were observed only in the STM group. However, there was no difference between groups for the NDI or shoulder abduction ROM with wrist neutral [304].

In conclusion, there continues to be evidence of effectiveness of spinal manipulative therapy as we have reported in this thesis [56, 160].

Results from an RCT that started including patients in 2014, (the CASINO trial) aiming to evaluate the (cost-) effectiveness of surgery versus prolonged conservative care during one year of follow-up, and to evaluate the timing of surgery are pending still [199]. Results from another RCT of multimodal physiotherapy (consisting of manual therapy, exercise and neural unloading tape), compared to weekly phone advice and versus advice alone for recent onset, painful CR (the PACeR trial protocol that started including patients in 2019) are also still pending [270]. In a personal e-mail communication however, the author mentioned having found that the probability of meaningful improvement was 70% with treatment versus 30% with advice.

Attending a short course of physiotherapy increased probability of improvement at 4 weeks.

Traction

Cervical axial traction has historically been a proposed as an effective treatment modality. The previously published review on the effectiveness of conservative management included an assessment of cervical traction and found no evidence of effectiveness over sham traction [57]. A recent review, solely assessing cervical traction in patients with CR, also concluded that traction therapy for cervical radicular syndrome was statistically significant but not clinically relevant for pain relief [248]. One other study compared 3 weeks of supine axial traction to traction in sitting and reported a significant difference in NDI score at the end of treatment in favour of the supine traction (19.45±7.12 vs. 11.05±4.40; $p<0.0001$) [306]. However, there was no control group, so the influence of the natural course of recovery could not be established.

In contrast, a review in 2015 with the aim to establish a new Chinese clinical consensus of the treatment for CR using the Delphi method concluded a set of passive modalities to be effective [307]. They found neck immobilisation to be effective and suggested that for mild symptoms or standing activities, routinely wearing a cervical collar for 1–3 weeks was effective. This is in line with the conclusion of the previously published review [57]. For severe symptoms or lying in bed, use of a low and hard pillow and a hard bed for resting (as much as possible) for 1–3 weeks was recommended. Physiotherapy could consist of cervical traction, infrared spectrum irradiation, and acupuncture therapy to relieve symptoms [307]. It

would appear that in China, physiotherapy treatment modalities might differ from that of what is common practice in the West.

Neurodynamic mobilisations

With respect to potential mechanisms behind the effectiveness of neurodynamic mobilisations, a recent study aimed to evaluate the potential peripheral and central adaptations that may result in individuals with carpal tunnel syndrome (CTS) who had completed a neurodynamic mobilisation program [308]. They quantified the biological integrity and mechanical properties of the median nerve using musculoskeletal ultrasound imaging and the corticospinal excitability using transcranial magnetic stimulation. Upon completion of the program, participants reported both large and moderate improvements in pain ($p \leq 0.03$) and upper limb functional abilities ($p = 0.02$), respectively. The biological integrity and mechanical properties of the median nerve remained unchanged ($p \geq 0.22$), whereas a small significant increase in corticospinal excitability ($p = 0.04$) was observed, suggesting that improvements might be preferentially mediated via central, rather than peripheral, adaptations [308].

A recent systematic review assessed the effectiveness of slider and tensioner NM techniques in the management of upper quadrant pain and concluded that most of the studies they included, combined NM with other techniques in the intervention group (e.g. stabilisation and mobility exercises, cervical mobilisation, or advice to participants) [309]. As a result, the authors concluded it was not yet clear if improvement in pain was due to the NM effects or the combination

with other interventional techniques. However, they did suggest that NM in combination with cervical traction can improve a patent's symptoms compared to no treatment [309].

6.4.3 Ultrasound evaluation

Ultrasound evaluation of nerve excursions and nerve health are also evolving. A study by Ökmen et al., (2018) investigated the effects of CR on the cross-sectional area (CSA) values of the cervical nerve roots (CNRs) as well as the CSA of the median, ulnar, and radial nerves with high-resolution ultrasonography [310]. They hypothesized that symptomatic nerve roots have a larger CSA than asymptomatic nerve roots due to the presence of oedema. Peripheral nerves have also been shown to develop oedema, fibrosis, and changes distal to the affected nerve as a result of mechanical compression. In addition, according to the "double-crush syndrome" hypothesis, the peripheral nerves are more sensitive to pressure, and a proximal nerve lesion makes the distal segment of the nerve more susceptible to anatomic deterioration by causing interruption in the axoplasmic conduction due to compression [310]. The study by Ökmen et al., (2018) assessed forty patients with chronic CR. Both affected CNRs and the contralateral nerve roots (as a control group) were evaluated with high-resolution ultrasonography. Ulnar and median nerve CSA measurements were performed at four measurement points and radial nerve measurements at a single measurement point. They reported that CSA measurements were statistically significantly higher at the CNR of the affected side compared to the unaffected side, but there was no statistically significant difference between affected and unaffected sides of the peripheral nerves at all measurement

points [310]. Their findings are in contrast to two animal studies reporting that nerve root swelling is generally not restricted to the nerve root alone but may involve the entire nerve bed [192-194]. It is evident that more research on this is warranted.

A relatively new development in ultrasonography is shear wave elastography (SWE). SWE is an operator-independent, developing form of ultrasound examination and measures tissue elasticity by tracking shear wave velocity. In tissues with greater stiffness, shear waves travel faster [311]. SWE imaging can provide measures of tissue stiffness that can act as a surrogate measure of nerve and muscle health. Photoacoustic imaging may overcome neuromuscular ultrasound's current lack of contrast agents to detect inflammation and other functional changes within nerve and muscle [312]. Studies have shown that the median nerve is entrapped in CTS, influencing its elasticity [313]. Therefore, SWE can become an accessible screening test in CTS diagnosis and perhaps also in CR. However, there is discussion with respect to the heterogeneity of normative values [314, 315] as well as the influence of limb positioning with regards to nerve tension [316, 317]. More research in this area is needed and ongoing [318-320].

6.5 FUTURE RESEARCH

One important aspect for future research with respect to CR is to address the lack of epidemiological data. Therefore, a repeat of a large population-based epidemiological study, similar to Radhakrishnan et al., in 1994 [6], is needed. This study should incorporate current knowledge and evidence on CR and compare prevalence, incidence and the natural course of patients with CR in a slightly different but still comparable cohort that Radhakrishnan et al., used in 1994, e.g. in Europe. A

recent systematic review of the epidemiology of CR reported a variable incidence rate and prevalence of CR among specific populations; however, this was based on nine studies only and relied heavily on the Radhakrishnan study [6] from 1994 and the authors suggested a priority to investigate CR epidemiology across other populations globally and standardising CR diagnostic criteria [21]. A large population-based epidemiological study focussing on upper quadrant musculoskeletal disorders could provide better information on incidence, prevalence, course and prognosis of CR.

More studies on neurodynamic mobilisation are also warranted. Currently, neurodynamic mobilisation is thought to improve neural vascularity, nerve movement and restoration of optimal intraneural homeostasis by reducing intraneural oedema [85-87]. But there is a need for more fundamental research to gain a better understanding of the mechanisms involved in order to understand why improved nerve excursion is associated with improved clinical outcomes. Recent animal research into the influence of the immune system on (neuropathic) pain indicates that active exercise has the ability to modulate the immune system, promoting an anti-inflammatory phenotype of macrophages in uninjured muscle, and an increase in anti-inflammatory cytokines which in turn can promote healing and analgesia [207]. Inhibition of neuropathic pain by exercise in rats was accompanied by decreases in interleukin (IL)-1β, IL-6, and tumour necrosis factor (TNF)-α levels and downregulated expression of their receptors [207-209]. It would be of interest to see if, as a result of intraneural fluid dispersion during passive neurodynamic mobilisation techniques and relying on the thixotropic properties of nerve movement against its mechanical interface, similar decreases in IL and TNF levels can be observed.

From a diagnostics point of view, future studies should also assess the optimal manner of executing Spurling's test as a provocative test, as it has only been assessed in five studies, each performing a slightly different variation [37, 135, 142, 144, 146]. Especially the variant of combined cervical ipsilateral side flexion, rotation and extension has a large potential of a false positive outcome, provoking somatic referred pain through excessive compressive forces loading the uncovertebral joints as reported in the study by Shah et al., (2004) [146].

Once an optimal manner has been established, future research with regards to the accuracy of diagnosing a CR should focus on a prospective diagnostic test study, similar to a previous study by Wainner et al., in 2003 [126], but in a cohort of patients diagnosed with a combination of history taking, clinical tests and diagnostic imaging. History taking should then also include items identified in a recent study [135] and physical examination should include provocative tests identified in the previously published review [38] and its update presented in this thesis. Statistical analysis however, should be wary of potential incorporation bias.

Furthermore, future research is needed on generally accepted and often used neurological examination such as muscle strength, reflex and testing, as they have yet to be studied prospectively. The only studies to partially do so have been by Wainner et al., (2003) [126] and Sleijser-Koehorst et al., (2020) [135]. The former however, used an combination of history taking and EMG as a comparator [126]; the latter is the first to use a combination of patient interview items, clinical signs and symptoms and an MRI as a comparator [135]. Ideally this study should include patients seeing a first-contact health care practitioner, ensuring that information from

patient interview combined with clinical tests is used in the clinical reasoning process of hypothesising a CR could well be the cause of the patient's problem.

Future research on effective conservative management should focus on finding optimal timing and dosage of different interventions and treatment techniques, taking information from this thesis's Delphi study into consideration. Additionally, longitudinal excursions of the median nerve at the elbow during neurodynamic mobilisation techniques such as the CCLG should be studied in a larger cohort of conservatively managed patients and compared through the natural course of the condition and perhaps also compared to a cohort of patients with early surgical management.

6.6 CONCLUSION

Differentiating patients with CR from patients with (somatic) referred pain is necessary, as it has implications on the course, management and prognosis of patients. This thesis proposes that, when consistent with the patient history, clinicians may use a combination of Spurling's test and four ULNT tests to increase the likelihood of CR. However, differentiating a patient with CR from patients with neck pain and somatic referred pain still relies on a bronze standard of history taking, clinical tests and diagnostic imaging.

Once diagnosed, there is some evidence on the course and prognosis of CR. Evidence on the conservative management of CR from systematically reviewing the literature concluded that due to the low to very low-levels of evidence, no single intervention can be recommended as the optimal treatment of CR. Low-level evidence suggests that neurodynamic mobilisations are an effective treatment

component of a multimodal management program. This management program should also consider cervico-thoracic mobilisation, specific exercises and sometimes the use of a collar at short term follow up, as this seems promising compared to a wait and see policy.

Although there is still a lack of evidence on optimal timing and dosage, consensus statements suggest a gradual increase in loading the neuromuscular system in patients with CR, but monitoring any increase in the individual patient's specific symptoms closely. Additionally, monitoring an increase in the longitudinal excursion of the median nerve at the elbow, using ultrasound, has the potential to assist clinical decision making with regards to either continuing or suspending conservative management. Overall, this thesis supports using neurodynamic testing and mobilisation as an important aspect in diagnosing and managing patients with CR.

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APPENDIX 1: Embase and Medline search strategies for Diagnostic Review in Chapter 2

Embase

No.	Query	Results
#11	#4 AND (#7 OR #8) NOT (#9 OR #10) = observational	145
#10	#4 AND #6 NOT #9 = RCT	72
#9	#4 AND #5 = SR	46
#8	'case control study'/de OR 'comparative study'/exp OR 'control group'/de OR 'controlled study'/de OR 'controlled clinical trial'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'pretest posttest design'/de OR 'pretest posttest control group design'/de OR 'quasi experimental study'/de OR 'single blind procedure'/de OR 'triple blind procedure'/de OR (((control OR controlled) NEAR/6 trial):ti,ab,kw) OR (((control OR controlled) NEAR/6 (study OR studies)):ti,ab,kw) OR (((control OR controlled) NEAR/1 active):ti,ab,kw) OR 'open label*':ti,ab,kw OR (((double OR two OR three OR multi OR trial) NEAR/1 (arm OR arms)):ti,ab,kw) OR ((allocat* NEAR/10 (arm OR arms)):ti,ab,kw) OR placebo*:ti,ab,kw OR 'sham-control*':ti,ab,kw OR (((single OR double OR triple OR assessor) NEAR/1 (blind* OR masked)):ti,ab,kw) OR nonrandom*:ti,ab,kw OR 'non-random*':ti,ab,kw OR 'quasi-experiment*':ti,ab,kw OR crossover:ti,ab,kw OR 'cross over':ti,ab,kw OR 'parallel group*':ti,ab,kw OR 'factorial trial':ti,ab,kw OR ((phase NEAR/5 (study OR trial)):ti,ab,kw) OR ((case* NEAR/6 (matched OR control*)):ti,ab,kw) OR ((match* NEAR/6 (pair OR pairs OR cohort* OR control* OR group* OR healthy OR age OR sex OR gender OR patient* OR subject* OR participant*)):ti,ab,kw) OR ((propensity NEAR/6 (scor* OR match*)):ti,ab,kw) OR versus:ti OR vs:ti OR compar*:ti OR ((compar* NEAR/1 study):ti,ab,kw) OR (('major clinical study'/de OR 'clinical study'/de OR 'cohort analysis'/de OR 'observational study'/de OR 'cross-sectional study'/de OR 'multicenter study'/de OR 'correlational study'/de OR 'follow up'/de OR cohort*:ti,ab,kw OR 'follow up':ti,ab,kw OR followup:ti,ab,kw OR longitudinal*:ti,ab,kw OR prospective*:ti,ab,kw OR retrospective*:ti,ab,kw OR observational*:ti,ab,kw OR 'cross sectional*':ti,ab,kw OR cross?ectional*:ti,ab,kw OR multicent*:ti,ab,kw OR 'multi-cent*':ti,ab,kw OR consecutive*:ti,ab,kw) AND (group:ti,ab,kw OR groups:ti,ab,kw OR subgroup*:ti,ab,kw OR versus:ti,ab,kw OR vs:ti,ab,kw OR compar*:ti,ab,kw OR 'odds ratio*':ab OR 'relative odds':ab OR 'risk ratio*':ab OR 'relative risk*':ab OR 'rate ratio':ab OR aor:ab OR arr:ab OR rrr:ab OR ((('or' OR 'rr') NEAR/6 ci):ab)))	13928703
#7	'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'comparative study'/de OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	6767914
#6	'clinical trial'/exp OR 'randomisation'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomised controlled trial'/exp OR placebo*:ab,ti	3302394
#5	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*)	733409

	NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	
#4	#1 AND #2 AND #3 AND [01-03-2016]/sd NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	449
#3	'sensitivity and specificity'/de OR sensitivity:ab,ti OR sensitive:ab,ti OR specificity:ab,ti OR 'roc curve':ab,ti OR 'receiver operator':ab,ti OR 'receiver operators':ab,ti OR likelihood:ab,ti OR 'diagnostic error'/exp OR 'diagnostic accuracy'/exp OR 'diagnostic test accuracy study'/exp OR 'inter observer':ab,ti OR 'intra observer':ab,ti OR interobserver:ab,ti OR intraobserver:ab,ti OR validity:ab,ti OR kappa:ab,ti OR reliability:ab,ti OR reproducibility:ab,ti OR ((test NEAR/2 're-test'):ab,ti) OR ((test NEAR/2 'retest'):ab,ti) OR 'reproducibility'/exp OR accuracy:ab,ti OR 'differential diagnosis'/exp OR 'validation study'/de OR 'measurement precision'/exp OR 'diagnostic value'/exp OR 'reliability'/exp OR 'predictive value'/exp OR ppv:ti,ab,kw OR npv:ti,ab,kw OR (((false OR true) NEAR/3 (negative OR positive)):ti,ab)	4684170
#2	'physical examination'/de OR 'physical medicine'/de OR 'physiotherapy'/de OR 'physiotherapist'/de OR 'neurodynamic test'/exp OR 'medical examination'/exp OR 'movement (physiology)'/exp OR physiotherap*:ti,ab,kw OR ((medical* NEAR/3 examin*):ti,ab,kw) OR provocat*:ti,ab,kw OR movement*:ti,ab,kw OR abduction*:ti,ab,kw OR spurling*:ti,ab,kw OR 'arm squeeze test*':ti,ab,kw OR wainner:ti,ab,kw OR (test NEAR/3 cluster):ti,ab,kw OR 'neck tornado test*':ti,ab,kw OR ((tendon* NEAR/3 reflex*):ti,ab,kw) OR manipulat*:ti,ab,kw OR (((manual OR physical* OR neurodynamic OR 'neuro dynamic' OR neurolog*) NEAR/3 (measur* OR assess* OR rating* OR test* OR exam*)):ti,ab,kw) OR (((sensor* OR sensat*) NEAR/3 (impair* OR dysfunction* OR abnormal*)):ti,ab,kw) OR 'valsalva* maneuv*':ti,ab,kw OR (((elvey OR davidson* OR distraction* OR relief* OR tension OR motor OR 'upper limb' OR 'brachial plexus') NEAR/3 test*):ti,ab,kw) OR ultt*:ti,ab,kw OR ('shoulder abduction' NEAR/3 (sign OR test*)):ti,ab,kw	1930391
#1	'cervicobrachial neuralgia'/exp OR 'brachial plexus neuropathy'/de OR 'myeloradiculopathy'/de OR 'cervical spondylosis'/de OR 'cervical myelopathy'/exp OR cervicobrachial*:ti,ab,kw OR 'cervico brachial*':ti,ab,kw OR 'cervical brachial*':ti,ab,kw OR (((cervic* OR brachial*) NEAR/3 (neuralg* OR compress* OR radiculop* OR avulsion* OR radiculitis* OR radiculitides* OR syndrome* OR myelopath* OR spondylos* OR osteophytos* OR stenosis* OR degenerat* OR neuritis*)):ti,ab,kw) OR ((radiculalgia:ti,ab,kw OR radiculitis:ti,ab,kw OR radiculitides:ti,ab,kw OR radiculopath*:ti,ab,kw OR polyradiculopath*:ti,ab,kw OR neuralgia:ti,ab,kw OR 'herniated disc*':ti,ab,kw OR hernia:ti,ab,kw OR ((radicular NEAR/3 (pain* OR neuralgia* OR symptom* OR syndrom*)):ti,ab,kw) OR (('nerve root' NEAR/3 (pain* OR inflammation* OR disorder* OR compression* OR avulsion* OR impingement)):ti,ab,kw)) AND ('cervical spine'/exp OR 'neck'/exp OR cervical:ti,ab,kw OR cervico*:ti,ab,kw OR neck:ti,ab,kw)) OR (('radicular pain'/exp/mj OR 'radiculopathy'/exp/mj) AND ('cervical spine'/exp OR 'neck'/exp OR cervical:ti,ab,kw OR cervico*:ti,ab,kw OR neck:ti,ab,kw)) OR (('spinal cord compression'/de OR 'intervertebral disk hernia'/de OR 'intervertebral disk degeneration'/de OR 'stenosis'/de OR 'vertebral canal stenosis'/de OR 'spondylosis'/de OR 'radiculopathy'/de OR 'nerve root compression'/de) AND ('neck'/exp OR 'neck pain'/exp OR 'neck injury'/de OR 'cervical spine'/exp OR 'cervical plexus'/de OR 'cervical spine injury'/de OR 'cervical spinal cord'/exp OR 'cervical spinal cord injury'/exp OR 'cervical vertebral canal'/de))	41947

Ovid/Medline

#	Searches	Results
11	(4 and (7 or 8)) not (9 or 10) = observational	108
10	(4 and 6) not 9 = RCT	41
9	4 and 5 = SR	25
8	Case-control Studies/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or comparative study/ or control groups/ or controlled before-after studies/ or controlled clinical trial/ or double-blind method/ or historically controlled study/ or matched-pair analysis/ or single-blind method/ or (((control or controlled) adj6 (study or studies or trial)) or (compar* adj (study or studies)) or ((control or controlled) adj1 active) or "open label*" or ((double or two or three or multi or trial) adj (arm or arms)) or (allocat* adj10 (arm or arms)) or placebo* or "sham-control*" or ((single or double or triple or assessor) adj1 (blind* or masked)) or nonrandom* or "non-random*" or "quasi-experiment*" or "parallel group*" or "factorial trial" or "pretest posttest" or (phase adj5 (study or trial)) or (case* adj6 (matched or control*)) or (match* adj6 (pair or pairs or cohort* or control* or group* or healthy or age or sex or gender or patient* or subject* or participant*)) or (propensity adj6 (scor* or match*))).ti,ab,kf. or (confounding adj6 adjust*).ti,ab. or (versus or vs or compar*).ti. or ((exp cohort studies/ or epidemiologic studies/ or multicenter study/ or observational study/ or seroepidemiologic studies/ or (cohort* or 'follow up' or followup or longitudinal* or prospective* or retrospective* or observational* or multicent* or 'multi-cent*' or consecutive*).ti,ab,kf.) and ((group or groups or subgroup* or versus or vs or compar*).ti,ab,kf. or ('odds ratio*' or 'relative odds' or 'risk ratio*' or 'relative risk*' or aor or arr or rrr).ab. or (("OR" or "RR") adj6 CI).ab.))	5384889
7	Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or cohort.tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ [Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies]	4395890
6	exp clinical trial/ or randomised controlled trial/ or exp clinical trials as topic/ or randomised controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomised controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.	2568292
5	meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.	656938
4	(1 and 2 and 3 and 20160301:20230322.(dt).) not (comment/ or editorial/ or letter/) not ((exp animals/ or exp models, animal/) not humans/)	278
3	exp "Sensitivity and Specificity"/ or (sensitivity or sensitive or specificity).ti,ab. or (ROC-curve or receiver-operator*).ti,ab. or (likelihood or LR*).ti,ab. or exp Diagnostic Errors/ or (inter-observer or intra-observer or interobserver or intraobserver or validity or kappa or reliability).ti,ab. or reproducibility.ti,ab. or (test adj2 (re-test or retest)).ti,ab. or "Reproducibility of Results"/ or accuracy.ti,ab. or Diagnosis, Differential/ or Validation Studies.pt. or exp "Predictive Value of Tests"/ or ppv.ti,ab,kf. or npv.ti,ab,kf. or ((false or true) adj3 (negative or positive)).ti,ab.	3827816
2	Physical Examination/ OR Physical Therapy Specialty/ OR Physical Therapists/ OR exp Neurologic Examination/ OR physiotherap*.ti,ab,kf. OR (medical* adj3 examin*).ti,ab,kf. OR provocat*.ti,ab,kf. OR movement*.ti,ab,kf. OR abduction*.ti,ab,kf. OR spurling*.ti,ab,kf. OR 'arm squeeze test*'.ti,ab,kf. OR wainner.ti,ab,kf. OR (test adj3 cluster).ti,ab,kf. OR 'neck tornado test*'.ti,ab,kf. OR (tendon* adj3 reflex*).ti,ab,kf. OR manipulat*.ti,ab,kf. OR ((manual OR physical* OR neurodynamic OR 'neuro dynamic' OR neurolog*) adj3 (measur* OR assess* OR rating* OR test* OR exam*)).ti,ab,kf. OR (((sensor* OR sensat*) adj3 (impair* OR dysfunction* OR abnormal*)).ti,ab,kf.) OR valsalva* maneuv*.ti,ab,kf. OR (((elvey OR davidson* OR distraction* OR relief* OR tension OR motor OR	1057190

	'upper limb' OR 'brachial plexus') adj3 test*).ti,ab,kf.) OR ultt*.ti,ab,kf. OR ('shoulder abduction' adj3 (sign OR test*)).ti,ab,kf.	
1	exp Radiculopathy/ or Brachial Plexus Neuropathies/ or Brachial Plexus Neuritis/ or cervicobrachial*.ti,ab,kf. or 'cervico brachial*'.ti,ab,kf. or 'cervical brachial*'.ti,ab,kf. or ((cervic* or brachial*) adj3 (neuralg* or compress* or radiculop* or avulsion* or radiculitis* or radiculitides* or syndrome* or myelopath* or spondylos* or osteophytos* or stenosis* or degenerat* or neuritis*)).ti,ab,kf. or ((radiculalgia or radiculitis or radiculitides or radiculopath* or polyradiculopath* or neuralgia or 'herniated disc*' or hernia or (radicular adj3 (pain* or neuralgia* or symptom* or syndrom*)) or ('nerve root' adj3 (pain* or inflammation* or disorder* or compression* or avulsion* or impingement))).ti,ab,kf. and (exp Cervical Vertebrae/ or exp Neck/ or cervical.ti,ab,kf. or cervico*.ti,ab,kf. or neck.ti,ab,kf.)) or ((Spinal Cord Compression/ or Intervertebral Disc Displacement/ or Spinal Stenosis/ or Intervertebral Disc Degeneration/ or Spondylosis/) and (exp Neck/ or Neck Pain/ or Neck Injuries/ or exp Cervical Vertebrae/ or Cervical Plexus/ or exp Spinal Injuries/ or Cervical Cord/ or exp Spinal Cord Injuries/))	40133

APPENDIX 2: QUADAS-2 signalling questions and guidance for assessors

Phase 1: please state the review question:

Patients (setting, intended use of index test, presentation, prior testing): Patients with radicular arm and neck pain in primary or secondary care
Index test(s): specific tests carried out during the physical examination for the diagnosis of CR: i.e.: Spurling, Valsalva, ULNT, Shoulder abduction relief, traction, reflex, key muscles
Reference standard and target condition: (Physical examination combined with) MRI / CT and or surgery

Phase 2: Draw a flow diagram for the primary study

Phase 3: Risk of bias and applicability judgments

QUADAS-2 is structured so that 4 key domains are each rated in terms of the risk of bias and the concern regarding applicability to the research question (as defined above). Each key domain has a set of signalling questions to help reach the judgments regarding bias and applicability.

DOMAIN 1: PATIENT SELECTION

A. Risk of Bias

Describe methods of patient selection:
Please describe the method as you understand it from the description in the manuscript.

From the answers to the signaling questions below, please derive a final score. The lowest score should determine the final score

- Was a consecutive or random sample of patients enrolled? Yes/No/Unclear
- Was a case-control design avoided? Yes/No/Unclear
- Did the study avoid inappropriate exclusions? Yes/No/Unclear

Could the selection of patients have introduced bias? RISK: LOW / HIGH / UNCLEAR

B. Concerns regarding applicability

Describe included patients (prior testing, presentation, intended use of index test and setting):
Please describe the included patients as you understand them from the description in the manuscript.

Is there concern that the included patients do not match the review question?

Do you feel the included patients might have disorders not related to the review question? Eg. if the objective is to differentiate between NonSpecificArmPain and CR that is okay. But not so if the included patients might have completely unrelated disorders or have a spectrum of the disorder too different from the review question

CONCERN: LOW / HIGH / UNCLEAR

DOMAIN 2: INDEX TEST(S)

If more than one index test was used, please complete for each test

A. Risk of Bias

Describe the index test and how it was conducted and interpreted:
Please describe the index test(s) and the manner of applying them as you understand it from the description in the manuscript

From the answers to the signaling questions below, please derive a final score. The lowest score should determine the final score

- Were the index test results interpreted without knowledge of the results of the reference standard? Yes /No /Unclear
- If a threshold was used, was it pre-specified? Yes /No /Unclear

Could the conduct or interpretation of the index test have introduced bias?

RISK: LOW / HIGH / UNCLEAR

B. Concerns regarding applicability

Is there concern that the index test, its conduct or interpretation differ from the review question?

Do you feel the index test or its manner of applying or interpreting the outcome (pos/ neg scoring) is too different so the review question cannot be answered from the result?

CONCERN: LOW /HIGH/UNCLEAR

DOMAIN 3: REFERENCE STANDARD

A. Risk of Bias

Describe the reference standard and how it was conducted and interpreted:
Please describe the reference standard(s) and the manner of applying and interpreting the outcome (pos/neg) as you understand it from the description in the manuscript.
In the absence of a true gold standard we state that the combination of a neurological examination (consisting of testing of tendon reflexes, manual muscle testing of key muscles for muscle weakness or atrophy and testing for sensory deficits) and results from MRI/ CT imagingand/or the postoperative results is to be seen as correctly classifying the target condition.
A sole assessment of an MRI / CT (eg. by a radiologist) potentially has too many false positives and is therefore usually to be scored as "Unclear"

From the answers to the signaling questions below, please derive a final score. The lowest score should determine the final score

- Is the reference standard likely to correctly classify the target condition?
  Yes /No /Unclear
- Where the reference standard results interpreted without knowledge of the results of the index test?
  Yes /No /Unclear

Could the reference standard, its conduct, or its interpretation have introduced bias?
RISK: LOW / HIGH / UNCLEAR

B. Concerns regarding applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?
Do you feel the reference test itself or its manner of applying or interpreting the outcome (pos/ neg scoring) is too different so the review question cannot be answered from the result?
CONCERN: LOW / HIGH / UNCLEAR

DOMAIN 4: FLOW AND TIMING

A. Risk of Bias

Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram):

Describe the time interval and any interventions between index test(s) and reference standard:

From the answers to the signaling questions below, please derive a final score. The lowest score should determine the final score

- Was there an appropriate interval **(< 1week)** between index test(s) and reference standard? Yes /No /Unclear
- Did all patients receive a reference standard? Yes /No /Unclear
- Did patients receive the same reference standard? Yes /No /Unclear
- Were all patients included in the analysis? Yes /No /Unclear

Could the patient flow have introduced bias? RISK: LOW /HIGH/UNCLEAR

APPENDIX 3. Justification for downgrading the level of evidence for the different comparisons

Upper limb Neural tension tests (ULNT's)

Four combined Upper limb Neural tension tests (ULNT's)

- The level of evidence regarding the outcome measure sensitivity started as "high" and was downgraded by one level to "medium". There was no downgrading for risk of bias (0) as there was no inappropriate time between the reference and the index test in the one study of "unclear" quality [74] and the "high" quality of the other study [141]. The number of included patients however was low [74] (-1, imprecision).
- The level of evidence regarding the outcome measures specificity and PPV started as "high" and was downgraded by three levels to "very low". There was no downgrading for risk of bias (0) as there was no inappropriate time between the reference and the index test in the one study of "unclear" quality [74] and the "high" quality of the other study [141]. A low number of included patients and confidence intervals crossing the borders of clinical relevance (-2, imprecision) and strong inconsistency without 95% CI's overlapping (-1, inconsistency).
- The level of evidence regarding the outcome measures NPV started as "high" and was downgraded by two levels to "low" because of a low number of included patients and confidence intervals crossing the borders of clinical relevance in both studies (-2, imprecision).

ULNT1 median alone

- The level of evidence regarding the outcome measures sensitivity, PPV and NPV started as high and was downgraded by three levels to very low because

of inconsistency (-1, inconsistency) and confidence intervals crossing the borders of clinical relevance [74, 135, 141] (-2, imprecision). There was no downgrading for risk of bias (0) as there was no inappropriate time between the reference and the index test in the one study of "unclear" quality [74] and the "high" quality of two other study [135, 141].

- The level of evidence regarding the outcome measure specificity started as high and was downgraded by two levels to low because of a low number of included patients and confidence intervals crossing the borders of clinical relevance [74, 135, 141] (-2, imprecision). There was no downgrading for risk of bias (0) as there was no inappropriate time between the reference and the index test in the one study of "unclear" quality [74] and the "high" quality of two other study [135, 141].
- The level of evidence regarding the outcome measures NPV and PPV started as high and was downgraded by two levels to low because of a low number of included patients and confidence intervals crossing the borders of clinical relevance in both studies (-2, imprecision).

Arm squeeze test

- The level of evidence regarding the outcome measures sensitivity, specificity, NPV and PPV started as high and was downgraded by two levels to low because the sample had a case-control character (-2, risk of bias).

Spurling's test

- The level of evidence regarding the outcome measure sensitivity started as high and was downgraded by four levels to very low because of questionable overall risk of bias in one study [37], using different reference tests [37, 146, 148] and retrospective inclusion in on study [142] (-2, risk of bias), strong inconsistency without 95% CI's overlapping between [37, 148] (-1, inconsistency) and broad confidence intervals [135, 146] (-1, imprecision).
- The level of evidence regarding the outcome measure specificity started as high and was downgraded by two levels to low because of questionable overall risk of bias in [37], using different reference tests [37, 146, 148], retrospective inclusion [142] (-2, risk of bias), and confidence intervals crossing the borders of clinical relevance [135].
- The level of evidence regarding the outcome measure PPV started as high and was downgraded by three levels to very low because of questionable overall risk of bias in one study [37], using different reference tests [37, 146, 148] (-2, risk of bias) and broad confidence intervals crossing borders of clinical relevance [135, 148] (-1, imprecision).
- The level of evidence regarding the outcome measure NPV started as high and was downgraded by three levels to very low because of questionable overall risk of bias in [37], using different reference tests [37, 146, 148], retrospective inclusion [142] (-2, risk of bias) and strong inconsistency between all studies without 95% CI's overlapping between [146] and [37] (-1, inconsistency).

Axial traction test

- The level of evidence regarding the outcome measure sensitivity started as high and was downgraded by three levels to very low because of inappropriate exclusion criteria, and not all included patients received the same reference standard or index test, with no study of higher quality to compensate (-2, risk of bias) and a low number of included patients (-1, imprecision).
- The level of evidence regarding the outcome measures specificity, PPV and NPV started as high and was downgraded by three levels to very low because of inappropriate exclusion criteria, and not all included patients received the same reference standard or index test with no study of higher quality to compensate (-2, risk of bias) and crossing borders of clinical relevance (-1, imprecision).

Shoulder abduction test

- The level of evidence regarding the outcome measures sensitivity, specificity, NPV and PPV started as high and was downgraded by two levels to low because of inappropriate exclusion criteria, and not all included patients received the same reference standard or index test [148] (-1, risk of bias) and crossing borders of clinical relevance (-1, imprecision).
- The level of evidence regarding the outcome measures sensitivity, specificity, NPV and PPV started as high and was downgraded by three levels to very low because of inappropriate exclusion criteria, and not all included patients received the same reference standard or index test [148] (-1, risk of bias),

conflicting results (-1, inconsistency) and crossing borders of clinical relevance (-1, imprecision).

Neck tornado test (Choi's test)

- The level of evidence regarding the outcome measures sensitivity, specificity, NPV and PPV started as high and was downgraded by three levels to very low because risk of selection bias could not be ruled out due to the retrospective design [142] with no study of higher quality to compensate (-2, risk of bias) and crossing borders of clinical relevance (-1, imprecision).

APPENDIX 4: Ethical Review, Consent Forms and Patient Information Sheets for Chapter 3 (Median nerve study)

Erasmus Me
Universitair Medisch Centrum Rotterdam

Medische Ethische Toetsings Commissie
ErasmusMC
www.erasmusmc.nl/commissies/metc/

[redacted]

Doorkiesnummer [redacted]
Faxnummer
Kamernummer Z 744
E-mail [redacted]
Ons kenmerk NUsi/361575
Datum 8 augustus 2018

Betreft: MEC-2018-139, Besluit onderzoek is niet WMO-plichtig
Multicenter, Fysio-Experts initieert

Protocol titel:
'Excursions of the median nerve at the wrist and the elbow in patients with cervical radiculopathy and asymptomatic volunteers during a cervical contralateral lateral glide movement ("Elvey-glide")'

Protocol versie: zoals ontvangen d.d. 28 juni 2018

Geachte heer Thoomers,

De Medisch Ethische Toetsings Commissie Erasmus MC heeft het door u ingediende bovenvermeld onderzoeksvoorstel, volledig conform de eisen van de METC ontvangen op 28 juni 2018 ter beoordeling van de WMO-plichtigheid.

Het dagelijks bestuur van de commissie heeft beoordeeld of dit onderzoek al dan niet binnen de reikwijdte van de WMO valt. In verband hiermee is het dagelijks bestuur tot de conclusie gekomen dat:

> er wel sprake is van een medisch-wetenschappelijke vraagstelling in dit protocol;
> de proefpersonen niet aan een handeling worden onderworpen en er wordt hen geen gedragswijze opgelegd, beide zoals bedoeld in de **WMO**.

Omdat aan één van beide voorwaarden voor WMO-plichtigheid niet is voldaan, heeft het dagelijks bestuur van de commissie d.d. 31 juli 2018 besloten dat bovenvermeld onderzoek niet WMO-plichtig is. U mag dit onderzoek uitvoeren en u kunt de resultaten te zijner tijd voor publicatie aanbieden aan een wetenschappelijk tijdschrift.

De commissie attendeert u op de volgende punten

> De commissie heeft alleen de WMO-plichtigheid beoordeeld. Er heeft verder geen inhoudelijke toets van het onderzoek plaatsgevonden.
>
> U en uw afdeling zijn verantwoordelijk voor de correcte uitvoering van het onderzoek volgens de geldende wet- en regelgeving. Hierbij vestigen wij uw aandacht op het volgende:

Postadres
Postbus 2040
3000 CA Rotterdam

[redacted]
3015 CE Rotterdam

Voorzitters
Prof.dr. H.W. Tilanus
Prof.dr. H.J. Metselaar

Vice voorzitter
Dr. C.M. Zwaan

Secretarissen
Mw. mr. C.P. Bron-van Vliet
Mw.dr. F.M. Spoelstra
Mw.ing. W.C.M. Tielemans
Drs. H. van der Baan (a.i.)

Secretaresses
Mw. A. de Jong
Mw. S. Sneevliet
Mw. C.R.J. Laban-van der Velden

Adm. medewerker
Mw. A.E. van Huuksloot

Het secretariaat is geopend van maandag tot en met vrijdag van 08.30 tot 17.00 uur

De commissie verzoekt u haar op de hoogte te brengen van de volgende gegevens betreffende dit onderzoek:

- Startdatum (datum inclusie eerste proefpersoon) en/of start gegevens onderzoek
- einddatum (datum stop studie laatste proefpersoon) en/of stop gegevens onderzoek
- publicaties en/of eindrapport

Wanneer u vragen heeft over het opzetten, financieren, of uitvoeren van wetenschappelijk onderzoek, kunt u terecht bij het Consultatiecentrum Patiëntgebonden Onderzoek (CPO) voor advies en hulp. Het CPO organiseert ook meerdere keren per jaar de BROK cursus (Basiscursus Regelgeving en Organisatie van Klinisch Onderzoek), die door de commissie van harte wordt aanbevolen. Het volgen van de BROK cursus is, conform landelijke afspraken, alleen verplicht bij WMO-plichtig onderzoek. Voor informatie over de BROK-cursusdata kunt u contact opnemen met het Congresbureau, intern tel.nr. 43584.

Op de site van de METC kunt u links terugvinden naar de hierboven vermelde wet- en regelgeving. Wanneer u vragen heeft over dit METC besluit, kunt u contact opnemen met het secretariaat van de METC.

Met vriendelijke groet,
b Ethische Toetsings Commissie Erasmus MC,

Mw.drs. N. Loekabino
Secretaris

To whom it may concern,

The Daily Board of the Medical Ethics Committee Erasmus MC (hereafter the Committee) of Rotterdam, The Netherlands, has reviewed the above mentioned research proposal. As a result of this review, the Committee informs you that the rules laid down in the Medical Research Involving Human Subjects Act (also known by its Dutch abbreviation WMO), do not apply to this research proposal.

Please indicate the above MEC-number in every correspondence on this study

[redacted]
Yours sincerely,
On behalf of the Medical Ethics Committee Erasmus MC

Mrs. N. Loekabino, MSc
Secretary of the Committee

APPENDIX 5. Literature search strategy for effectiveness of neurodynamic mobilisations (Chapter 4)

Embase.com

No.	Query	Results
#14	#12 OR #13	311
#13	#9 AND #11 NOT #12 = RCT	150
#12	#9 AND #10 = SR	161
#11	'randomised controlled trial'/exp OR random*:ti,ab OR (((pragmatic OR practical) NEAR/1 'clinical trial*'):ti,ab) OR ((('non inferiority' OR noninferiority OR superiority OR equivalence) NEAR/3 trial*):ti,ab) OR rct:ti,ab,kw	1902585
#10	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	733409
#9	#7 AND #8 AND ([english]/lim OR [dutch]/lim) AND [2000-2022]/py NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	1350
#8	'physiotherapy'/exp OR physiotherap*:ti,ab,kw OR 'physio therap*':ti,ab,kw OR 'physical therap*':ti,ab,kw OR 'kinesiotherapy'/exp OR kinesiotherap*:ti,ab,kw OR kinesitherapeutic*:ti,ab,kw OR 'occupational therapy'/exp OR 'occupation* therap*':ti,ab,kw OR ergotherapy*:ti,ab,kw OR 'exercise'/exp OR exercise*:ti,ab,kw OR 'manipulative medicine'/exp OR chiropract*:ti,ab,kw OR manual*:ti,ab,kw OR manipulation*:ti,ab,kw OR collar:ti,ab,kw OR 'mobilisation'/exp OR mobili*ation:ti,ab,kw OR 'traction therapy'/exp OR traction:ti,ab,kw OR 'conservative treatment'/exp OR conservative:ti,ab,kw OR noninvasive:ti,ab,kw OR 'non invasive':ti,ab,kw OR nonsurg*:ti,ab,kw OR 'non surg*':ti,ab,kw OR nonoperati*:ti,ab,kw OR 'non operati*':ti,ab,kw	2266399

#7	'cervicobrachial neuralgia'/exp/mj OR cervicobrachialgia:ti,ab,kw OR ((radiculalgia:ti,ab,kw OR radiculitis:ti,ab,kw OR radiculitides:ti,ab,kw OR radiculopath*:ti,ab,kw OR polyradiculopath*:ti,ab,kw OR neuralgia:ti,ab,kw OR 'herniated disc*':ti,ab,kw OR hernia:ti,ab,kw OR ((radicular NEAR/3 (pain* OR neuralgia* OR symptom*)):ti,ab,kw) OR (('nerve root' NEAR/3 (pain* OR inflammation* OR disorder* OR compression* OR avulsion* OR impingement)):ti,ab,kw)) AND ('cervical spine'/exp OR 'neck'/exp OR cervical:ti,ab,kw OR cervico*:ti,ab,kw OR neck:ti,ab,kw)) OR (('radicular pain'/exp/mj OR 'radiculopathy'/exp/mj) AND ('cervical spine'/exp OR 'neck'/exp OR cervical:ti,ab,kw OR cervico*:ti,ab,kw OR neck:ti,ab,kw))	10643

Ovid/Medline

#	Searches	Results
9	7 or 8	238
8	(4 and 6) not 7 = RCT	114
7	4 and 5 = SR	124
6	(exp randomised controlled trial/ or randomised controlled trials as topic/ or random*.ti,ab. or rct?.ti,ab. or ((pragmatic or practical) adj "clinical trial*").ti,ab,kf. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab,kf.) not (animals/ not humans/)	1369026
5	(meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.) not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/))	560304
4	limit 3 to ((english language or dutch) and yr="2000 -Current")	906
3	1 and 2	1205

2	exp Physical Therapy Modalities/ or exp Occupational Therapy/ or physiotherap*.ti,ab,kf. or 'physio therap*'.ti,ab,kf. or 'physical therap*'.ti,ab,kf. or kinesiotherap*.ti,ab,kf. or kinesitherapeutic*.ti,ab,kf. or 'occupation* therap*'.ti,ab,kf. or ergotherapy*.ti,ab,kf. or exp Conservative Treatment/ or conservative.ti,ab,kf. or noninvasive.ti,ab,kf. or 'non invasive'.ti,ab,kf. or nonsurg*.ti,ab,kf. or 'non surg*'.ti,ab,kf. or nonoperati*.ti,ab,kf. or 'non operati*'.ti,ab,kf. or exp Exercise/ or exercise*.ti,ab,kf. or exp Musculoskeletal Manipulations/ or chiropract*.ti,ab,kf. or manual*.ti,ab,kf. or manipulation.ti,ab,kf. or collar.ti,ab,kf. or mobile*ation.ti,ab,kf. or exp Traction/ or traction.ti,ab,kf.	1227076
1	((exp Radiculopathy/ or radiculalgia.ti,ab,kf. or radiculitis.ti,ab,kf. or radiculitides.ti,ab,kf. or radiculopath*.ti,ab,kf. or polyradiculopath*.ti,ab,kf. or neuralgia.ti,ab,kf. or 'herniated disc*'.ti,ab,kf. or hernia.ti,ab,kf. or (radicular adj3 (pain* or neuralgia* or symptom*)).ti,ab,kf. or ('nerve root' adj3 (pain* or inflammation* or disorder* or compression* or avulsion* or impingement)).ti,ab,kf.) and (exp Cervical Vertebrae/ or exp Neck/ or cervical.ti,ab,kf. or cervico*.ti,ab,kf. or neck.ti,ab,kf.)) or cervicobrachialgia.ti,ab,kf.	6515

APPENDIX 6. Table of excluded studies

Reference	Reason for exclusion
Akkan 2018	Wrong comparator
Allison 2002	<15 patients per treatment arm
Alshami 2021	<15 patients per treatment arm
Anwar 2015	Wrong outcome
Aydin 2012	<15 patients per treatment arm
Borrella-Andrés 2021	Wrong intervention
Boyles 2011	Wrong study type included
Cheng 2015	Wrong patient population
Colombo 2020	Too broad PICO
Coppieters 2003(a)	Wrong outcome
Coppieters 2003(b)	Duplicate study population (Coppieters)
Costello 2016	<15 patients per treatment arm
Elnaggar 2009	Insufficient reporting of outcome of interest
Graham 2008	Wrong patient population
Gross 2015	Wrong patient population
Gross 2016	wrong study type
Halvorsen 2016	Duplicate study population (Dedering), wrong study design
Jellad 2009	<15 patients per treatment arm
Kuligowski 2021	wrong intervention, wrong outcome presentation (narrative)
Langevin 2015	wrong intervention
Leininger 2011	Incomplete study inclusion, not up to date
Liang 2019	wrong intervention, wrong language
Marks 2011	Wrong intervention
Ojoawo 2016	Possible duplicate patient population with Ojoawo 2018 (included in analysis)

Pandey 2021	Unclear presentation of outcome
Rajalaxmi 2020	Wrong intervention/unclear intervention
Rodine 2012	wrong study type included
Rodríguez-Sanz 2018	Duplicate patient population with 2017
Romeo 2018	More recent SR available
Salt 2011	Wrong intervention
Thoomes 2016	Wrong study type included
Thoomes 2013	Wrong controls (including surgery)
Xiao 2021	Insufficient reporting of outcome of interest
Yadav 2020	No full text available
Zhu 2016	Foreign language
Zronek 2016	Wrong patient population

APPENDIX 7: Ethical Review, Consent Forms and Patient Information Sheets for Chapter 5 (Delphi study)

UNIVERSITY OF BIRMINGHAM

Application for Ethics Review Form

Guidance Notes:

What is the purpose of this form?
This form should be completed to seek ethics review for research projects to be undertaken by University of Birmingham staff, PGR students or visiting/emeritus researchers who will be carrying out research which will be attributed to the University.

Who should complete it?
For a staff project – the lead researcher/Principal Investigator on the project.
For a PGR student project – the student's academic supervisor, in discussion with the student.
Students undertaking undergraduate projects and taught postgraduate (PGT) students should refer to their Department/School for advice

When should it be completed?
After you have completed the University's online ethics self-assessment form (SAF), **IF** the SAF indicates that ethics review is required. You should apply in good time to ensure that you receive a favourable ethics opinion prior to the commencement of the project and it is recommended that you allow at least 60 working days for the ethics process to be completed.

How should it be submitted?
An electronic version of the completed form should be submitted to the Research Ethics Officer, at the following email address: aer-ethics@contacts.bham.ac.uk.

What should be included with it?
Copies of any relevant supporting information and participant documentation, research tools (e.g. interview topic guides, questionnaires, etc) and where appropriate a health & safety risk assessment for the project (see section 10 of this form for further information about risk assessments).

What should applicants read before submitting this form?
Before submitting, you should ensure that you have read and understood the following information and guidance and that you have taken it into account when completing your application:

- The information and guidance provided on the University's ethics webpages (https://intranet.birmingham.ac.uk/finance/accounting/Research-Support-Group/Research-Ethics/Ethical-Review-of-Research.aspx)
- The University's Code of Practice for Research (https://www.birmingham.ac.uk/Documents/university/legal/research.pdf)

- The guidance on Data Protection for researchers provided by the University's Legal Services team at https://intranet.birmingham.ac.uk/legal-services/What-we-do/Data-Protection/resources.aspx.
-

Section 1: Basic Project Details

Project Title: Timing of evidence based non-surgical interventions as part of multi-modal treatment guideline: a Delphi study

Is this project a:

University of Birmingham Staff Research project ☐
University of Birmingham Postgraduate Research (PGR) Student project ☒
Other (Please specify below) ☐

Details of the Principal Investigator or Lead Supervisor (for PGR student projects):

Title: Professor
First name: Deborah
Last name: Falla

Position held: Lead Supervisor
School/Department: Centre of Precision Rehabilitation for Spinal Pain, School of Sport, Exercise and Rehabilitation Sciences, College of Life and Environmental Sciences ,University of Birmingham

Telephone:
Email address:

Details of any Co-Investigators or Co-Supervisors (for PGR student projects):

Title: Dr
First name: Marloes
Last name: Thoomes-de Graaf
Position held: Co-investigator
School/Department Fysio-Experts, Research department, Hazerswoude, The NetherlandsTelephone:
Email address:

Title: Dr
First name: Joshua
Last name: Cleland
Position held: Co-investigator
School/Department Doctor of Physical Therapy Program, Department of Public Health and Community Medicine, Tufts University School of Medicine, Boston, Mass. USA
Telephone: Click or tap here to enter text.
Email address:

Title: Dr
First name: Alessio
Last name: Gallina
Position held: Co-supervisor
School/Department Centre of Precision Rehabilitation for Spinal Pain, School of Sport, Exercise and Rehabilitation Sciences, College of Life and Environmental Sciences ,University of Birmingham
Telephone: Click or tap here to enter text.
Email address:

Details of the student for PGR student projects:
Title: Mr
First name: Erik
Last name: Thoomes
Course of study: PGR
Email address:

Project start and end dates:
Estimated start date of project: 01/10/2020
Estimated end date of project: 31/01/2021

Funding:
Sources of funding: None

Section 2: Summary of Project
Conservative management is a preferred first treatment option for patients with cervical radiculopathy, since the risk-benefit ratio for surgery is less favourable. Several systematic reviews (SRs) and treatment guidelines suggest effective non-surgical management strategies. However, SRs traditionally include outcomes from randomised controlled trials (RCTs) and RCTs have a limitation in that management is not tailored to the individual. Evidence based practice (EBP) requires the clinician to be aware of outcomes of research. But at the same time to take the individual patient preference in to account as well as the clinical expertise of the individual clinician, combined with clinical expertise of peers across the health care provider's profession. Practice based evidence (PBE) emphasizes the combined experience of both professional and client. EBP and PBE are not opposites but

complimentary. Delphi studies are often used to combine clinical expertise and achieve consensus on what preferred management options should or could include and are well suited to add PBE to established EBP management as outlined in SRs or guidelines. The aim of this study is to establish a consensus on suitable non-surgical treatment modalities for patients in different stages of CR. *Experts within the field of cervical radiculopathy will be recruited for this study.*

Section 3: Conduct and location of Project
Modified Delphi methodology

Geographic location of project
The study will be conducted electronically and therefore no travel will be needed.

Section 4: Research Participants and Recruitment
Does the project involve human participants?
Yes ☒
No ☐

If you have answered NO please go on to Section 8 of this form. If you have answered YES please complete the rest of this section and then continue on to section 5.

Who will the participants be?
Participant number are expected to be approximately 20. All participants will be considered experts within the field of cervical radiculopathy or spinal entrapment neuropathy and may consist of Physiotherapists, Allied Health Care Professionals, Doctors and Academics.

- Eligibility criteria: ≥ 1 peer-reviewed publications on CR or spinal entrapment neuropathies within the past 10 years OR
- ≥ 10 years' experience working in a pain/musculoskeletal outpatient service with patients with CR or spinal entrapment neuropathies
- Sufficient English literacy skills judged by language of authored publications
- Sufficient computer literacy skills judged by availability of e-mail address on affiliated websites or contact details on authored articles

How will the participants be recruited?
Electronic libraries (PubMed, Embase, CINAHL, Google Scholar) will be searched for individuals meeting the 'expert' criteria. A snowballing strategy will be adopted by the recruiting author (ET), requesting contacted panellists to recommend peers who satisfy the eligibility criteria. Members of the steering committee will also be eligible to recommend potential panellists from their professional network. Publicly available contact details from research papers will be used to contact potential panellists. A copy of the recruitment message is attached.

Section 5: Consent

What process will be used to obtain consent?
The Participant Information Sheet will provide a description of the study. Consent will be obtained via a completed and returned consent form, which will be signed and dated.

Use of deception?

Will the participants be deceived in any way about the purpose of the study?

Yes ☐
No ☒

Section 6: Participant compensation, withdrawal and feedback to participants

What, if any, feedback will be provided to participants?
Participants will be acknowledged in the final manuscript as a contributor and panellist.

What arrangements will be in place for participant withdrawal?
The Participant Information Sheet will lay out the withdrawal process with assurance on anonymity and no consequences upon withdrawal from the study.
Participants will be able to withdraw within two weeks after each of the Delphi rounds.

What arrangements will be in place for participant compensation?

Yes ☐
No ☒

Section 7: Confidentiality/anonymity

Will the identity of the participants be known to the researcher?

Yes ☒
No ☒

In what format will data be stored?
Each participant will be assigned an ID code and a key will kept allowing the researcher to identify a participant's data.

Will participants' data be treated as confidential?
Yes ☒
No ☐

Section 8: Storage, access and disposal of data

How and where will the data (both paper and electronic) be stored, what arrangements will be in place to keep it secure and who will have access to it?

All data will be stored offline on a password encrypted computer in a locked office with access only available to the researchers. In accordance with university guidelines, data will be destroyed ten years after completion of the study.

Data retention and disposal

Yes ☒

No ☐

The data will be disposed of securely after 10 years.

Section 9: Other approvals required

Are you aware of any other national or local approvals required to carry out this research?

No

For projects involving NHS staff, is approval from the Health Research Authority (HRA) needed in addition to University ethics approval?

Yes ☐

No ☒

Section 10: Risks and benefits/significance

Benefits/significance of the research

This study will provide an expert consensus on non-surgical treatment modalities of the three identified stages (acute, sub-acute & chronic) patients with cervical radiculopathy. *This is important because currently guidelines are not tailored to the individual not to the individual and clinically different stages of cervical radiculopathy*

Risks of the research

Nil risk identified.

University Health & Safety (H&S) risk assessment

Section 11: Any other issues

Does the research raise any ethical issues not dealt with elsewhere in this form?

No

Do you wish to provide any other information about this research not already provided, or to seek the opinion of the Ethics Committee on any particular issue?

No

Section 12: Peer review

Has your project received scientific peer review?

Yes ☒
No ☐

From both supervisors as well as co-investigators as part of a post graduate research project.

Section 13: Nominate an expert reviewer

Section 14: Document checklist
Please check that the following documents, where applicable, are attached to your application:

Recruitment advertisement ☒
Participant information sheet ☒
Consent form ☒
Questionnaire ☐
Interview/focus group topic guide ☐

Section 15: Applicant declaration

I submit this application on the basis that the information it contains is confidential and will be used by the University of Birmingham for the purposes of ethical review and monitoring of the research project described herein, and to satisfy reporting requirements to regulatory bodies. The information will not be used for any other purpose without my prior consent. ☒

The information in this form together with any accompanying information is complete and correct to the best of my knowledge and belief and I take full responsibility for it. ☒

I undertake to abide by University Code of Practice for Research (https://www.birmingham.ac.uk/Documents/university/legal/research.pdf) alongside any other relevant professional bodies' codes of conduct and/or ethical guidelines. ☒

I will report any changes affecting the ethical aspects of the project to the University of Birmingham Research Ethics Officer. ☒

I will report any adverse or unforeseen events which occur to the relevant Ethics Committee via the University of Birmingham Research Ethics Officer. ☒

Copy of the recruitment message that will be sent to potential panelists

INVITATION TO PARTICIPATE IN AN E-DELPHI STUDY

Dear xxxx,

I hope you are well under the current COVID-19 pandemic.

You have been identified by our research team as an expert within the field of management of patients with cervical radiculopathy or spinal entrapment neuropathies and we would like to invite you to participate in our e-Delphi study.

Details of the study are included in the attached document. Our research protocol is submitted to a peer reviewed journal and currently under review. Please take the time to read through the document and feel free to ask any questions regarding the study.

We would also like to you nominate individuals who you determine to be eligible for this study, using the criteria stated within the attached document.
Recruitment process will last up to two weeks from today and depending on the number of recruitments, may extend another week or two.

We appreciate your time and hope to hear back from you soon.

On behalf of the research team,

Erik Thoomes (Lead investigator, PhD candidate at University of Birmingham, UK)

Supervisory team:
Lead supervisor:
- Prof. Deborah Falla, University of Birmingham, UK

Co-supervisor:
- Dr. Alessio Gallina, University of Birmingham, UK

Co-investigators:
- Dr. Josh Cleland, Tufts University School of Medicine, Boston, USA;
- Dr. Marloes Thoomes-de Graaf, Fysio-Experts, Hazerswoude, The Netherlands

Participant Information Sheet

Lead Investigator: Erik Thoomes
Co-investigators: Deborah Falla, Alessio Gallina, Marloes Thoomes-de Graaf, Joshua Cleland

Study title
Timing of evidence based non-surgical interventions as part of multi-modal treatment guidelines for the management of cervical radiculopathy: a Delphi study protocol.

Invitation paragraph
It is our pleasure to invite you to participate in our study.
This information sheet will provide you with the background, purpose and methodology of this study.
Please read carefully before considering to participate and feel free to contact the lead investigator via email for any queries.

What is the purpose of the study?

The aim of this study is to establish a consensus on effective non-surgical treatment modalities for patients in different stages (acute, sub-acute and chronic) of cervical radiculopathy by using the Delphi method approach.

Non-surgical management is a preferred first treatment option for patients with cervical radiculopathy, since the risk-benefit ratio for surgery is less favourable. Several systematic reviews (SRs) and treatment guidelines suggest effective non-surgical management strategies. However, SRs traditionally include outcomes from randomised controlled trials (RCTs) and RCTs have a limitation in that management is not tailored to the individual. Additionally, RCTs in general do not relate the management strategy under scrutiny to the different stages of the studied condition. Instead they manage all participants identically, regardless of the stage of the studied condition being acute, sub-acute or chronic. Rehabilitation programs however, are based on the logical assumption that some treatment modalities might potentially be better suited in the early acute stage of the disorder, while others might be better for the management during the subacute or chronic phases. Current evidence on the effectiveness of non-surgical management of patients with CR report a lack of consensus on the optimal timing and dosage of treatment modalities

Why have I been chosen?
You have been chosen to participate as you are identified as a potential expert in the field of cervical radiculopathy or spinal entrapment neuropathies and that you should fulfil the below criteria:

- Author of ≥ 1 peer-reviewed publications on cervical radiculopathy or cervical spinal entrapment neuropathies within the past 10 years OR
- ≥ 10 years' experience working in a pain/musculoskeletal outpatient service with patients with cervical radiculopathy or cervical spinal entrapment neuropathies.

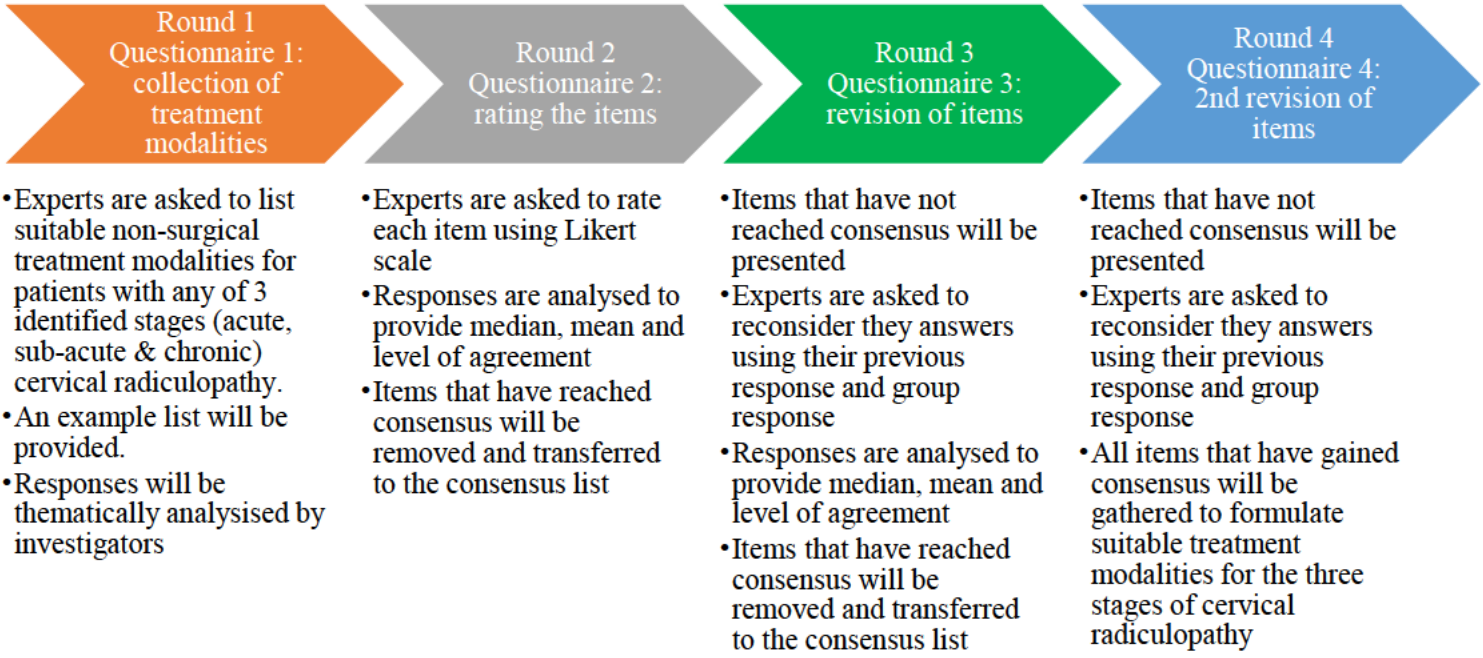
Do I have to take part?

Participation is voluntary and if you're eligible, your participation is much appreciated and valued. You will be able to withdraw within two weeks after each of the Delphi rounds without provision of reason(s).
If you wish to withdraw, you must contact lead investigator in writing via email. A confirmation of withdrawal will subsequently be returned.

What will happen if I decide to take part?

You will be required to complete a "participant consent form", a "conflict of interest form" and a "participants' professional background form" and return these to lead investigator via email. We will confirm your eligibility prior sending you a conformational email.

Once participation is confirmed, you will be invited to complete a three-round online questionnaire. Questionnaires will take approximately half an hour to complete.



What are the potential benefits and risks of taking part?

There are no risks associated with taking part in this Delphi study.
Findings from the study will be published in a peer-reviewed journal and presented at relevant conferences. You will be acknowledged in the final manuscript as a contributor.

Will my participation be confidential?

Your participation may remain confidential if desired. However, it is the investigators intention to recognise participants' contribution within the published paper. The data provided during every stage of the Delphi will however be anonymised via ID code generation.

The data obtained in the study will be stored in a password encrypted electronic device which will only be accessible to the investigators involved in the study and all data will be backed up on a server and kept securely for 10 years after completion of the Delphi study in the School of Sport, Exercise and Rehabilitation Sciences, University of Birmingham, United Kingdom before being securely destroyed, in accordance with University guidelines.

This study will comply with General Data Protection Regulation 2018 (GDPR, 2018). GDPR. 2018. General Data Protection Regulation. Online available at: https://gdpr-info.eu. [Accessed 18 Apr 2020].

What will happen at the end of the research study?
Participants will be sent an email of thanks on completion of the study with an estimated timeframe for study publication. Participants will also be sent the full article once completed.

For further information regarding the study please contact Erik Thoomes the Lead Investigator:
Email:
Or the Supervisor:
Professor Deborah Falla
Email:

Thank you for taking time to read this Participant Information Sheet

Participant Consent Form

Study Title	*Timing of evidence based non-surgical interventions as part of multi-modal treatment guidelines for the management of cervical radiculopathy: a Delphi study protocol.*		
Participant Name:	Click here to enter the text.	**Date:**	Click here to enter the text.
Researcher Name:	Erik Thoomes Deborah Falla Alessio Gallina Joshua Cleland Marloes Thoomes-de Graaf	**Ethics Number:**	ERN

This section to be completed by the participant:
Please tick the box at the end of each statement if you agree with it.

I confirm that I have read and understood the Participant Information Sheet for the above study. I have had the opportunity to ask questions and these have all been answered satisfactorily.	☐
I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, up to two weeks after my last visit to the lab.	☐
I agree to the storage and use of my data for the purposes of this research study.	☐
I agree to be named as a contributor in the final manuscript which will be submitted for publication and dissemination.	☐
Based on the above, I agree to take part in this research study.	☐
Signed: Click here to enter the text.	
Name in capitals: Click here to enter the text.	
Date: Click here to enter the text.	

This section to be completed by the researcher

I certify that this participant has read, properly completed and signed the screening and consent forms: Signed: Click here to enter the text. Date: Click here to enter the text.

By supplying this information you are consenting to the University storing your information for the purposes of the stated research study. The information will be processed by the University of Birmingham in accordance with the provisions of the Data Protection Act 2018. No identifiable personal data will be published.

Conflict of Interest Form

Project title: *Timing of evidence based non-surgical interventions as part of multi-modal treatment guidelines for the management of cervical radiculopathy: a Delphi study protocol.*

Researchers: Erik Thoomes, Deborah Falla, Alessio Gallina, Marloes Thoomes-de Graaf, Joshua Cleland
Email:

I, Click here to enter the text. declare that I have no conflict of interest to participate in the above study.

Name of participant	Click here to enter the text.
Date	Click here to enter the text.
Signature	Click here to enter the text.

Please return the consent form, conflict of interest and participants' professional background to:

Participants Professional Background

Project title: *Timing of evidence based non-surgical interventions as part of multi-modal treatment guidelines for the management of cervical radiculopathy: a Delphi study protocol.*

Researchers: Erik Thoomes, Deborah Falla, Alessio Gallina, Marloes Thoomes-de Graaf, Joshua Cleland
Email:

Participant details

Name:	Click here to enter the text.
Age:	Click here to enter the text.
Gender:	Click here to enter the text.
Country of origin:	Click here to enter the text.
Country of current employment(s):	Click here to enter the text.
Academic qualification(s):	Click here to enter the text.
Occupation(s):	Click here to enter the text.
Peer reviewed publications related to cervical radiculopathy or spinal entrapment neuropathy:	Click here to enter the text.

Please return the consent form, conflict of interest and participants' professional background to:

APPENDIX 8: List of Questions for Round 1 of the Delphi Questionnaire

Participant Characteristics

- What is your age (in years)?
- What is your country of origin?
- In which country do you currently live / work?
- What is your highest professional qualification (e.g. PhD, MSc, etc.)?
- What is your professional background? (multiple answers possible)
- What is your current main occupation?

Eligibility criteria

- Do you have:≥ 1 peer-reviewed publications on cervical radiculopathy or cervical spinal entrapment neuropathies within the past 10 years?
- Can you list 1 or 2 of your (most relevant) publication(s)?
- Do you have ≥ 10 years' experience working in a pain/musculoskeletal outpatient service with patients with cervical radiculopathy or cervical spinal entrapment neuropathies?

ROUND 1 QUESTIONNAIRE

In this section you will find a list of treatment modalities that have been proposed to be effective for patients with cervical radiculopathy.
Some modalities might be more relevant to a particular stage of the process of recovery i.e. the first 6 weeks = "acute"; from 6-12 weeks = "sub-acute"; > 12 weeks = "chronic".
In this section please rate the relevance of each individual treatment modality for each of the different stages (acute, sub-acute, chronic).
Later on in the questionnaire you can add treatment modalities you feel have not yet been mentioned.

List of proposed effective treatment modalities

Counseling

- Information / patient education
- Pain education
- Behavioral therapy
- Physiotherapy
-

General Physiotherapy

- General aerobic exercise
- General strength training
- Focused / targeted strength training
- Individualized physical activity
- Supervised exercise
- Motor control exercise
- Directional preference exercise
-

Spinal Manipulative Therapy

- Spinal manipulative therapy as a stand-alone treatment

- Cervical manipulation
- Cervical mobilization
- Thoracic manipulation
- Thoracic mobilization
- Chiropractic treatment
- Neurodynamic mobilization
- Spinal manipulative therapy combined with (specific) exercise
- Spinal manipulative therapy combined with neurodynamic mobilization
- Spinal manipulative therapy combined with neurodynamic mobilization and (specific) exercise

Traction

- Mechanical “over the door” traction
- Continuous mechanical traction
- Intermittent mechanical traction
- Manual traction
-

Miscellaneous

- Hard collar
- Soft collar
- Massage
- Acupuncture
- Dry Needling
- Medical Tape / Kinesiotape
- Transcutaneous electrical nerve stimulation (TENS)
-

Medication

- Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) e.g. Ibuprofen, Diclofenac, Meloxicam, Naproxen, Celecoxib, Indomethacin, etc.
- Opioids (e.g. Codeine, Hydrocodone, Vicodin, Morphine, Oxycodone, Percocet, Fentanyl, etc.)
- Combination of NSAIDs and Opioids
- Anti-epileptic drugs (e.g. Pregabalin, Gabapentin, Lyrica, etc.)
- Combination of NSAIDs and Anti-epileptic drugs
- Combination of Opioids and Anti-epileptic drugs
- Combination of NSAIDs and Opioids and Anti-epileptic drugs

Additions

In this final section you can add treatment modalities you feel have not been mentioned in the previous section. Please rate them also for each individual stage of CR (acute, sub-acute, chronic)

APPENDIX 9: Copyright permissions

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- Musculoskeletal Science and Practice

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