Chiropractic spinal manipulative therapy for migraine

Dissertation for the degree philosophiae doctor (PhD) at the University of Oslo

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Oslo, 2016
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Acknowledgements

The work presented in this thesis was conducted at the Head and Neck Research Group, Research Centre, Akershus University Hospital, from 2012 to 2015.

First and foremost, I express sincere gratitude to my main supervisor, Michael Bjørn Russell, who believed in the project when I first contacted him in 2009. He has been a mentor and inspirational co-worker throughout this period. His high standards have kept me highly focused, efficient and motivated. The knowledge I have obtained on research methodology and headache disorders is mostly a result of his dedicated work and belief in me.

I also express gratitude to my co-supervisor, Peter J. Tuchin, for his in-depth knowledge of chiropractic research, invaluable advice on the subject and contributions to an improved thesis.

Furthermore, I extend special thanks to Jūratė Šaltytė Benth for her essential contributions to the statistical methods and interpretation of results. Despite the expected challenges, she kept me motivated. I have certainly acquired a different meaning of statistics after numerous meetings with her.

I also thank my scientific colleagues at the Research Centre, Kjersti Vetvik, Espen Saxhaug Kristoffersen and Kjersti Aarseth for their valuable input, discussion and companionship at scientific congresses around the world. My chiropractic colleagues deserve special thanks for their support and engagement in this project. A special thanks goes to my colleagues at Atlasklinikken who continuously offered assistance in all relevant and non-relevant matters. Furthermore, special thanks to the administrative office at the Research Centre, including Reidun Skårerhøgda, Nina Viksløkken Ødegård and Karin Anne Vassbakk for their invaluable experience in research organization and for welcoming me into the Research Centre. Gunn Seim Ekeland deserves special thanks for her contribution to the various questionnaires entered into SPSS and for her rapid responses.
A special thanks goes to Christofer Lundqvist, who proofread the thesis and provided invaluable feedback along with minor comments. This help has further improved the thesis.

Furthermore, the participants all deserve special thanks for willingly giving their time to participate in this research project; this study would, for obvious reasons, not have been possible without their contributions.

Financial support for this project was provided by Extrastiftelsen, the Norwegian Chiropractic Association, the Akershus University Hospital and the University of Oslo in Norway. Akershus University Hospital, Norway, kindly provided research facilities, and Chiropractor Clinic 1, Oslo, Norway, kindly performed the X-ray assessment.

My deepest thanks goes to my family. My parents deserve special thanks for always believing in me and for their unconditional support. My brother and his family deserve special thanks for being there for me and for elegantly distracting me from research when I undoubtedly needed it. Thanks also goes to my mother-in-law, who was both appointed and self-appointed herself as a nanny; she deserves more than one bottle of champagne.

Finally, my beloved cohabitant demonstrated unbelievable patience and support throughout the entire period, which was highly needed at times, particularly considering that during my PhD period, we managed to produce two fantastic and healthy children together. Without her unconditional support, it would have been difficult to complete my studies on time.

Oslo, 2016

Aleksander Chaibi
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>AE</td>
<td>Adverse event</td>
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<tr>
<td>CAD</td>
<td>Cervical artery dissection</td>
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<td>CSMT</td>
<td>Chiropractic spinal manipulative therapy</td>
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<td>GP</td>
<td>General Practitioner</td>
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<td>HVLA</td>
<td>High velocity low amplitude</td>
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<tr>
<td>ICHD-I</td>
<td>International Classification of Headache Disorders 1st ed.</td>
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<td>ICHD-II</td>
<td>International Classification of Headache Disorders 2nd ed.</td>
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<td>ICHD-III</td>
<td>International Classification of Headache Disorders 3rd ed.</td>
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<tr>
<td>IHS</td>
<td>International Headache Society</td>
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<tr>
<td>MA</td>
<td>Migraine with aura</td>
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<td>MO</td>
<td>Migraine without aura</td>
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<td>MOH</td>
<td>Medication overuse headache</td>
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<tr>
<td>NPE</td>
<td>Norwegian system of compensation to patients</td>
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<td>OR</td>
<td>Odds ratio</td>
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<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
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<td>REK</td>
<td>Regional Ethics Committee</td>
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<tr>
<td>SD</td>
<td>Standard deviation</td>
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<tr>
<td>SMT</td>
<td>Spinal manipulative therapy</td>
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<td>TTH</td>
<td>Tension-type headache</td>
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<td>WHO</td>
<td>World Health Organization</td>
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1 Summary

Migraine affects approximately 15% of the population and has substantial health and socioeconomic costs. In the recent Global Burden of Disease study, migraine was ranked as the 3\textsuperscript{rd} most common condition. Pharmacological management is usually the first treatment option. However, some patients do not tolerate acute and/or prophylactic medications because of side effects, have contraindications due to co-morbidities of other diseases, or wish to avoid medication for other reasons. Thus, non-pharmacological treatment options are warranted.

Three previous randomized controlled trials (RCTs) have assessed the efficacy of spinal manipulative therapy (SMT) for migraineurs, suggesting an effect on migraine frequency, migraine duration, migraine intensity and medicine consumption. The three pragmatic studies were limited by methodological shortcomings, including the lack of a placebo group to act as the control group. The lack of a proper placebo group is a major limitation in the majority of manual-therapy RCTs. Double-blinded studies is not possible because the interventional therapist cannot be blinded.

The purpose of the present study was to investigate the efficacy of chiropractic spinal manipulative therapy (CSMT) versus placebo and CSMT versus control in a triple-armed, single-blinded, placebo, randomized controlled trial over 17 months, with 12 intervention sessions over three months, with follow-up analysis at post-treatment, three, six and 12 months.

This thesis is based on four original research papers. Firstly, we developed a protocol in accordance with the guidelines for clinical trials of the International Headache Society’s (IHS). Second, this protocol was used to assess the efficacy of CSMT for migraineurs. Third, we developed a new, highly warranted, sham (placebo) intervention and validated the placebo procedure using a simple de-blinding questionnaire; finally, we reported on all adverse events (AEs).

Four hundred and eighty-six participants pre-diagnosed with migraine were contacted with information about the study and were invited to participate.
Thirty-five participants did not respond to the invitation letter, 182 did not fulfil the inclusion criteria, 23 were excluded, and 142 refrained from participation. Thus, a total of 104 participants were finally randomized into the study. The baseline and demographic characteristics were similar across the three groups. The majority of participants (92.3%) were recruited from secondary and tertiary health care.

There was a high compliance rate in the study, with 70.2% of our participants completing the entire study period with no missing values from the headache diaries.

The main results showed that the primary end-point measurement, migraine days, was significantly reduced within all three groups from baseline to post-treatment (p<0.001); the effect continued in the CSMT and placebo groups at all follow-up time points, whereas the control group returned to baseline. The reduction in migraine days was not significantly different between the groups, but the pairwise comparisons at individual time points showed significant differences in migraine days between the CSMT and control groups at all time points. Migraine duration and headache index were significantly more reduced in the CSMT than in the control group towards the end of follow-up. At 12 months of follow-up, the consumption of paracetamol was significantly lower in the CSMT group than in the placebo (p=0.04) and control (p=0.03) groups.

A total of 772 of the potential 840 interventions sessions were completed, and 68 (8.1%) were missed. The de-blinding questionnaire administered after each treatment session showed that >80% of the participants believed they had received CSMT regardless of group allocation. The odds ratio for believing that CSMT treatment was received was >10 at all treatment sessions in both groups (all p<0.001). Thus, blinding was strongly sustained throughout the trial.

A total of 703 of the potential 770 intervention sessions were assessed for AEs. Local tenderness was the most common AE reported by 11.3% (95% CI 8.4-15.0%) of patients in the CSMT group and 6.9% (95% CI 4.7-10.1%) of patients
in the placebo group, whereas tiredness on the intervention day and neck pain was reported by 8.5% and 2.0% (95% CI 6.0-11.8% and 1.0-4.0%) and 1.4% and 0.3% (95% CI 0.6-3.3% and 0.05-1.9%) of patients in the CSMT and placebo groups, respectively. The attributable risk was the highest for tiredness (7.0%, 95% CI 3.9-10.2%) with a relative risk of 5.9 (95% CI 2.3-15.0); the attributable risks for local tenderness and neck pain were 4.4 and 1.7%, respectively, (95% CI 0.1-8.6% and 0.1-3.2%), whereas the relative risks were 1.6 and 6.9, respectively, (95% CI 1.0-2.7 and 0.9-55.5). All other AEs were rare (<1%). The AEs were mild and transient, and no severe or serious AEs were reported.

Conclusion: Our data suggest within-group efficacy in migraine days, migraine duration and headache index for the CSMT and placebo groups at all time points, but there was no significant group difference. There was clear improvement in the active groups compared to no intervention. The study population consisted mostly of participants from tertiary health care; thus, replication of the study with a migraine population from the general population might change the results. Although there is no consensus on a placebo procedure in manual-therapy RCTs that mimics placebo in pharmacological RCTs, we managed to sustain blinding throughout the 12 intervention sessions over 3 months. Thus, our results suggest that it is possible to blind and sustain the blinding in the control group and thereby quantify the placebo effect. In accordance with the World Health Organization (WHO) guidelines on basic training and safety in CSMT, which consider CSMT to be an efficient and safe treatment modality, we demonstrated that the intervention is safe and has few, mild and transient AEs during the intervention period.
2 List of papers

This thesis is based on the following publications, referred to in the text by their Roman numerals. All articles are reproduced with permission.


**Paper IV:** Adverse events in a chiropractic spinal manipulative therapy single-blinded, placebo, randomized controlled trial for migraineurs. Submitted October 2016.
3 Introduction

3.1 International Classification of Headache Disorders

Headache disorders, specifically migraines, have been described as early as 1500 B.C. However, the first attempt to systematically classify migraines was conducted in 1962 by the ad hoc committee of the National Institute of Health in North America (1). The classification was partly recognized although the few headache disorders that were included lacked specificity and was widely open to interpretations. This classification was used until 1988 when the Headache Classification Committee of the International Headache Society (IHS) published the first comprehensive explicit diagnostic criteria, i.e., the International Classification of Headache Disorders (ICHD-I) (2). This classification received international recognition as the only accepted headache classification system. The IHS Headache Classification Committee has since published revised and updated versions, i.e., the 2nd edition in 2004, ICHD-II (3), and recently in 2013, a 3rd edition (ICHD-III β) (4). Currently, the number of headache disorders exceeds 300. This classification is now accepted as the reference for headache classification throughout the world and has been adopted by the World Health Organization (WHO).

The ICHD divides headache into primary and secondary diagnoses (4). The primary headaches are disorders in their own right and commonly include tension-type headaches (TTHs), migraines and cluster headaches, whereas secondary headaches typically relate to another disorder or injury or to a substance or withdrawal of a substance.

The ICHD-III β defines migraine as a usually unilateral headache with pulsating and moderate/severe pain that is aggravated by routine physical activity and is accompanied by photo- and phonophobia, nausea and sometimes vomiting, Appendix 1 (4).
Migraine exists in two major forms, migraine without aura (MO) and migraine with aura (MA) (4). Aura comprises reversible neurological disturbances of the vision, sensory, and/or speech functions, that occur prior to the headache. However, intra-individual variations may vary from attack to attack (5, 6).

Chronic migraine was introduced in the ICHD-II and is defined as headaches occurring on ≥15 days per month for at least 3 months with features of migraine in ≥8 days (3, 7).

There are no clear biomechanical or diagnostic markers for primary headaches; consequently, diagnoses are made upon diagnostic interviews with the patient. Thus, the IHS acknowledges the challenges in constructing diagnostic criteria for primary headache disorders, i.e., migraine, and introduced the term “probable migraine” in the ICHD-II version (3). The diagnostic criteria now allow for attacks to fulfil all but one of criteria A–D for MO and criteria A–C for MA, and the headache cannot be attributed to another disorder, Appendix 1 (3, 4).

Although the MO diagnosis has remained unchanged throughout the 1st, 2nd and 3rd versions, the MA diagnosis has been extensively updated to accommodate a higher inter-observer reliability and, hence, a higher sensitivity and specificity (8).

### 3.2 Epidemiology

In the Global Burden of Disease Survey 2010, migraine was ranked as the 3rd most prevalent disorder and 7th highest specific cause of disability worldwide (9). Currently, it is one of the leading causes of the disease burden for women aged 15–44 years (10). Nevertheless, the burden of headache is arguably underestimated and is believed to be universally under-recognized and undertreated (11).

Numerous prevalence studies have been conducted over the years and there is now a general consensus that the lifetime prevalence of migraine is approximately 15% in the general population with a male:female prevalence
varying from 1:2 to 1:3 (12, 13). Europeans and North Americans have an unknown higher prevalence than the African population (14). The most common age of onset for migraineurs is in the 2nd and 3rd decades of life, with a peak around the 4th decade for women and slightly earlier for men (11).

### 3.3 Costs

Migraine is a frequently disabling neurological disorder with substantial health and socioeconomic costs. Migraine causes the loss of 270 workdays per year per 1,000 persons in the general population (15). This value corresponds to approximately 3,700 work years lost annually in Norway because of migraine. It is estimated that migraineurs in the USA require 3.8 bed rest days for men and 5.6 bed rest days for women each year, resulting in a total of 112 million bedridden days (16). This value corresponds to 300,000 people staying in bed every 24 hours because of headaches (11). The annual economic cost per migraineur was estimated to be $5,761 in the USA and €1,222 in Europe (17, 18). Because of the high prevalence of migraine, the total annual cost for migraine was estimated to be $78 billion in the USA and €111 billion in Europe (17, 18). Migraine costs more than neurological disorders such as dementia, multiple sclerosis, Parkinson’s disease and stroke (19). Thus, based on growing scientific evidence, headache disorders are among the most prevalent, burdensome, and costly diseases in the world (20).

### 3.4 Mechanisms of action of spinal manipulative therapy

For decades, migraine has been thought to be a vascular disorder for which extracranial arterial dilatation was hypothesized to be the cause of pain. However, a recent cross-sectional study assessing extracranial and intracranial arterial dilatation by magnetic resonance angiography during spontaneous unilateral migraine attack found that the attacks were not accompanied by extracranial arterial dilatation; instead, they were accompanied with only slight
intracranial dilatation (21). Thus, a possible neurological pathophysiological cause has been hypothesized (21).

One hypothesis is that migraine pain might be a result of complex of nociceptive afferent responses involving the upper cervical spine (C1, C2 and C3), leading to a hypersensitive state of the trigeminal pathway conveying sensory information for the face and much of the head (22, 23). However, the origin of migraine pain is still debatable because the origin of painful impulses in the trigeminal nerve remains uncertain. Some argue for central mechanisms whereas others argue for peripheral mechanisms (24). Extracranial pain-sensitive structures include the skin, muscles, arteries, periosteum and joints. The skin is sensitive to all usual forms of pain stimuli, whereas the temporal and neck muscles in particular may be sources for pain and tenderness in migraine (25-27). Similarly, the frontal supraorbital, superficial temporal, posterior and occipital arteries are sensitive to pain (25, 28).

Spinal manipulative therapy (SMT) might relieve migraine as a result of stimulation of different mechanoreceptors in the neck such as those in the zygapophyseal joints, intervertebral discs and neck muscles (29). Research has suggested that SMT may stimulate neural inhibitory systems at different spinal cord levels because it might activate various central descending inhibitory pathways (30-35). This hypothesis seems reasonable because muscle or joint dysfunctions have been suggested to act as triggers for migraine attacks (36).

Although it has been postulated that pain in different spinal regions should not be regarded as separate disorders but rather as a single entity (37), we also know that neck pain is highly prevalent in the general population and particularly in individuals with primary headaches (38). Regarding the proposed pain-sensitive structures inhibited by SMT, neck pain can arise from many of the same local structures, i.e., muscles, ligaments and facet joints through direct compression of upper cervical roots, or it can be referred (39). Thus, the growing body of evidence now points towards SMT as possibly resulting in plastic changes in sensorimotor integration within the central nervous system of humans (40), and
might affect altered sensory processing and influence corticospinal and spinal reflex excitability (41, 42).

However, the relevance of cervical pain or dysfunction during a migraine attack is subsequently unresolved, and there is no definitive conclusion to the influence of musculoskeletal dysfunctions in the pathogenesis of migraine (43). Nevertheless, although the hypothesized physiological mechanisms are not fully understood, there could be additional unexplored mechanisms that could explain the effect SMT has shown on mechanical pain sensitization.

### 3.5 Non-pharmacological management

Pharmacological management is usually the first treatment option for migraineurs (44), and to my knowledge, can acute migraine attack only be alleviated successfully with acute pharmacological treatment. Triptans, which were first made available for clinicians in 1991 (45), is regarded as the most effective pharmacological treatment for migraineurs. However, some patients (about 15%) do not tolerate acute and/or prophylactic medicine because of side effects, have contraindications due to co-morbidities of other diseases, or may wish to avoid medication for other reasons (46, 47).

The risk of medication overuse as a result of frequent migraine attacks represents a major health hazard with both direct and indirect cost concerns and is an important modifiable risk factors for developing chronic migraine (48). The prevalence of medication overuse headache (MOH) is 1-2% in the general population (11, 49-51), i.e., approximately half the population suffering chronic headache (≥15 headache days per month) have MOH (52). However, only 3% use prophylactic medication for their chronic migraine (44). Thus, non-pharmacological prophylactic treatment options are warranted.

The Diversified technique and the Gonstead method are the two most commonly used chiropractic spinal manipulative treatment (CSMT) modalities in the profession and are used by 91 and 59% of chiropractors, respectively (53, 54),
along with other manual and non-manual interventions, i.e., soft tissue techniques, spinal and peripheral mobilization, rehabilitation, postural corrections and exercises, general nutrition and dietetic advice, and other general lifestyle advice. A recent Norwegian questionnaire survey found SMT to be used by more than 90% of all chiropractors along with soft tissue techniques and exercise as equally commonly used treatment modalities (55).

SMT is defined as a passive controlled manoeuvre that uses directional high-velocity low amplitude (HVLA) thrusts directed at a specific joint past the physiological range of motion without exceeding the anatomical limit (56). The Diversified SMT technique includes a collections of procedures, hence the name diversified (54). It focuses on soft tissue pre-tension prior to the delivery of high velocity low amplitude (HVLA) adjustment (54). The Gonstead method differs from the Diversified technique by its minimal use of rotation (53). However, the application and duration of different manual treatments vary among those who perform the treatments. Thus, manual treatment is not necessarily as uniform as a specific treatment with a drug at a certain dose. For headache disorders, a recent Norwegian population study found that 52% had tried physiotherapy and 28% had tried CSMT for their headaches (44). This number appears to be equally high internationally, with one in three seeking these interventions for treating their headache (57).

Only three SMT randomized controlled trials (RCTs) using the Diversified technique have been conducted for migraine; the results suggest an effect on migraine frequency, migraine duration, migraine intensity and medicine consumption. (58-61). By contrast, no RCTs have applied the Gonstead method. The results from these three RCTs are comparable to the therapeutic gain of topiramate 100 mg/d and propranolol in the prophylactic management of migraine (62-64).

Several others non-pharmacological and non-manual prophylactic therapies such as psychological therapies, i.e., relaxation-training, cognitive therapy, and
biofeedback, aerobic exercise, and acupuncture, have also been proven safe and effective and are commonly used for migraneurs (65-68).

### 3.6 Methodological challenges in manual-therapy RCTs

The methodological quality of RCTs assessing manual therapies for headache disorders are frequently being criticized for being too low, occasionally rightly so; however, the methodological design of manual-therapy prevent such studies from reaching what is considered the gold standard in pharmacological RCTs. For example, a placebo intervention is difficult to establish because the investigator cannot be blinded to the applied treatment. Most studies are thus pragmatic or use “no treatment” as a control group. Conducting a manual-therapy RCT is furthermore, time-consuming and expensive, particularly when conducting large prospective manual-therapy RCTs, i.e., >100 participants in the smallest group.

Nearly all methodological checklists seem to be designed for pharmacological double-blinded studies, i.e., CONSORT, PEDro, Jadad and other validated checklists (69-73), were individual assessment points are given to each section of a particular study, i.e., the introduction, methods, results and discussion. Hence, comparing manual-therapy to pharmacological RCTs seems somewhat unfair, considering that manual-therapy RCTs then obviously begin with a handicap in relation to participant numbers and questions related to blinding.

Thus, despite the promising results in previous CSMT RCTs on migraine, acceptance by the scientific community is still lacking. Reasons for this lack of acceptance might include the methodological shortcomings mentioned and the following factors; inaccurate headache diagnosis, i.e., questionnaire diagnoses are imprecise compared to direct interviews (74); inadequate or lack of a randomization procedure; lack of a placebo group; and primary and secondary end-points not being pre-specified (64, 71, 75, 76). Specifically, the questionnaire-based diagnostic criteria, although designed according to the ICHD, leads to diagnostic uncertainty. A diagnostic interview is regarded as the
gold standard, whereas questionnaires and lay interviews are less precise diagnostic tools regarding headache disorders (74).

Because previous RCTs assessing CSMT for migraine were conducted prior to the clinical guidelines that were introduced by the IHS in 2008 (77, 78), criticism towards primary and secondary end-points in these RCTs should be extenuating. Nevertheless, it appears that many of the same shortcomings are also common in some of the SMT RCTs on headache disorders conducted after the introduction of the clinical guidelines (64, 76, 79).

Thus, RCTs with high methodological quality are warranted to scientifically confirm efficacy with certainty.

### 3.7 Adverse events in spinal manipulative therapy

Although there has been an increase in reporting adverse events (AEs) since the introduction of the 2010 CONSORT guidelines (80), manual-therapy RCTs do not always report AEs in prospective efficacy studies (81, 82), although it is well known that the benefit of any intervention should outweigh the potential harm (83). Furthermore, the few RCTs that provide information on AEs are often inadequate, i.e., lacking information on the type and severity of AEs or whether patient withdrawal is caused by AEs or not (73). Currently, there is no standardized reporting tool for examining AEs associated with SMT, which might be part of the explanation. However, monitoring AEs in RCTs is highly warranted and it is important to identify all AEs early on. In accordance with the recommendations by the CONSORT and the IHS Task Force on AEs in migraine trials, all AEs, related or not, should be reported in prospective RCTs (73, 84).

The WHO acknowledges chiropractic treatment to be a safe and effective treatment with few mild and transient AEs (85). The mild and transient AEs commonly include local tenderness and tiredness on the treatment day (86-92).

However, concerns have been raised with regards to serious AEs, including cervical artery dissection (CAD) and stroke in association with cervical SMT,
i.e., vertebral- and carotid artery dissection. The few serious AEs reported arise from case reports (93); thus, conclusions about whether there is a causal relationship between cervical SMT and CAD has not been established because of the methodological design and low level of evidence (94, 95). However, this lack of established causality may be related to the rarity of these events and low sample size, as well as the infrequent reporting of serious AEs in prospective manual-therapy RCTs (93).

Serious traumas, including neck fracture, spinal cord injuries and minor traumas to the neck from various sporting activities, whiplash and/or muscular tears, have also been associated with CAD (96). These minor traumas are often associated with hyperextension and/or rotational movements of the neck (96, 97).

Several retrospective cohort studies have investigated a possible association between SMT and CAD and stroke without finding a clinically significant causality (98-101). Similarly, retrospective cohort studies have not reported an association with traumatic injury to the head or neck after SMT for neuromusculoskeletal problems (102). Invasive studies have furthermore disproven any misconception of whether vertebral artery strains during head movements, including SMT, exceed published failure strains (103, 104). No changes in blood flow or velocity in the vertebral arteries of healthy young male adults were found in various head positions and during a cervical spine manipulation (105). Thus, these studies support the evidence suggesting very low risks for serious AEs following SMT (99, 106, 107).

Nevertheless, As unusual neck pain and/or headache are the most common initial physical symptoms, with Horner’s syndrome and lower cranial nerve palsy occasionally occurring in combination (97), it is of importance that manual therapists who utilize cervical manipulation and mobilization techniques are well informed of the possible red flags and capable of referring patients to essential medical examination and treatment before initiating manual-therapy treatment as recommended by the American Heart- and Stroke Association (108). Furthermore, when SMT is being conducted, one must be specific when
manipulating a single spinal segment, minimizing end-range in cervical techniques and minimizing force, all of which have been recommended to reduce the risk of serious AEs (109).
4 Aims of the thesis

The overall aim of this thesis was to investigate the efficacy of chiropractic spinal manipulative therapy for migraineurs. The more specific aims of the individual papers are listed below.

**Paper I:** To develop a protocol in accordance with the International Headache Society’s clinical guidelines for clinical trials in order increase the quality of chiropractic research in the future.

**Paper II:** To investigate the efficacy of chiropractic spinal manipulative therapy for migraineurs in a prospective triple-armed, single-blinded, placebo-controlled, randomized clinical trial of 17 months duration.

**Paper III:** To develop a new sham intervention and de-blinding questionnaire for manual-therapy RCTs, and similarly validate the placebo procedure in a prospective manual-therapy single-blinded, placebo-controlled, randomized clinical trial among migraineurs.

**Paper IV:** Report on all adverse events in a prospective chiropractic spinal manipulative therapy, single-blinded, placebo-controlled, randomized clinical trial.
5 Materials and Methods

The present study was established in 2008 in close cooperation between chiropractors and physicians. Strategically, this study aimed to stimulate cooperation between the University of Oslo and Macquarie University, Australia, making the study international. Between December 2008 and January 2012, several reviews (64, 76, 79), and fund applications, as well as necessary project approvals, i.e., ethical and social science data services approvals, were conducted to finalize and then commence the intended project. 1. January 2012, the author was formally enrolled in the PhD programme at the Faculty of Medicine, University of Oslo.

5.1 Study design

The present study was a triple-armed, single-blinded, placebo, randomized controlled trial in which the primary objective was to investigate the efficacy of CSMT vs. placebo (sham manipulation) and controls (continue their usual pharmacological management without receiving manual intervention) for migraineurs. To our knowledge, this study was the first prospective manual-therapy three-armed, single-blinded, placebo, RCT to be conducted for migraineurs. This study adhered to the recommended clinical trial guidelines from the IHS (77, 78), and the CONSORT guidelines (73). The RCT consisted of a one month run-in, three months intervention and outcome analyses at the end of the intervention and at three, six and 12 months follow-up, Figure 1 (110).

Figure 1. Study flow chart. CSMT = chiropractic spinal manipulative therapy; Placebo = sham manipulation; Control = usual pharmacological management.
5.2 Study population

From January to September 2013, 486 participants were invited to participate in the project primarily through Akershus University Hospital and secondarily through general practitioners and media advertisements in Akershus and Oslo counties in Norway. The participants received posted information about the project that was pre-approved by the ethical committee, followed by a short telephone interview. Potential participants were contacted by telephone on three different occasions in the cases when initial contact failed. When the potential participants had changed their address and consequently had not received the posted information, it was re-posted to the new address obtained. The participants recruited from general practitioners’ offices contacted the clinical investigator (AC), whose contact details had been provided on the poster, to obtain extensive information about the study. In response to the initial contact, the participants fulfilling the inclusion criteria were invited to a further assessment by the clinical investigator. Of the invited participants, 35 participants (7.2%) were unreachable, 182 (37.4%) did not meet the inclusion criteria, and 165 participants (34%) were excluded or refrained from participation with reasons explained in Figure 2. Thus, 104 participants (21.4%) were finally included in the study, Figure 2.

5.3 Eligibility criteria

Eligible participants were between 18 and 70 years of age and had at least one migraine attack per month. The majority of the participants were diagnosed by a neurologist, whereas a few were diagnosed by a physician alone. All participants were subsequently diagnosed by a chiropractor with experience in headache diagnostics at Akershus University Hospital during the interview and according to the ICHD-II (AC) (3). The participants were allowed to have a co-occurrence only of TTH.
Figure 2. Participant’s flow chart.

Potential participants informed and invited for screening (n=486)

Screened participants criteria (n=451)

Eligible participants (n=246)

Drop-out (n=2)
- 1 pregnancy
- 1 lost contact

Drop-out (n=1)
- 1 pregnancy
- 1 withdrawn due to control group
- 1 initiated physiotherapy

Randomized (n=104)

Chiropractic spinal manipulative therapy (CSMT) (n=35)

Sham manipulation (placebo) (n=35)

Control group (n=34)

Drop-out (n=1)
- 1 failed to return diary

Drop-out (n=1)
- 1 had exclusively attacks of cluster headache in the baseline period

Drop-out (n=5)
- 2 withdrew due to control group
- 1 personal reason
- 1 changed prophylactic medication

Baseline (n=34)

Baseline (n=34)

Baseline (n=29)

Drop-out (n=3)
- 1 pulmonary embolism
- 1 changed prophylactic medication
- 1 lost contact

Drop-out (n=6)
- 1 pregnancy
- 1 time concerns
- 4 lost contact

Drop-out (n=5)
- 2 refrained to keep diary
- 1 low back pain
- 1 pregnancy
- 1 time concerns

Post-treatment assessment (n=31)

Post-treatment assessment (n=28)

Post-treatment assessment (n=24)

Drop-out (n=2)
- 1 pregnancy
- 1 lost contact

Drop-out (n=1)
- 1 changed prophylactic medication

Drop-out (n=3)
- 2 changed prophylactic medication
- 1 pregnancy

3-months follow-up (n=29)

3-months follow-up (n=27)

3-months follow-up (n=21)

Drop-out (n=0)

Drop-out (n=0)

Drop-out (n=0)

6-months follow-up (n=29)

6-months follow-up (n=27)

6-months follow-up (n=21)

Drop-out (n=2)
- 2 changed prophylactic medication

Drop-out (n=1)
- 1 personal reason

Drop-out (n=1)
- 1 initiated physiotherapy

12-months follow-up (n=27)

12-months follow-up (n=26)

12-months follow-up (n=20)

No response after initial contact (n=35)

Not meeting inclusion criteria (n=182)

Excluded (n=23)
- 17 wished to continued manual therapy
- 4 wished to change prophylactic medicine
- 2 insufficient Norwegian language skills

Refrained to participate (n=142)
- 83 undisclosed reasons
- 57 time concerns
- 2 fear of chiropractic therapy

Potential participants informed and invited for screening (n=486)

Not meeting inclusion criteria (n=182)

Excluded (n=23)
- 17 wished to continued manual therapy
- 4 wished to change prophylactic medicine
- 2 insufficient Norwegian language skills

Refrained to participate (n=142)
- 83 undisclosed reasons
- 57 time concerns
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Drop-out (n=1)
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3-months follow-up (n=27)

3-months follow-up (n=21)

Drop-out (n=0)

Drop-out (n=0)

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6-months follow-up (n=27)

6-months follow-up (n=21)

Drop-out (n=2)
- 2 changed prophylactic medication

Drop-out (n=1)
- 1 personal reason

Drop-out (n=1)
- 1 initiated physiotherapy

12-months follow-up (n=27)

12-months follow-up (n=26)

12-months follow-up (n=20)
The exclusion criteria were contraindications to SMT, spinal radiculopathy, pregnancy, depression and CSMT within the previous 12 months. Participants who received any manual interventions by physiotherapists, chiropractors, osteopaths or other health professionals to treat musculoskeletal pain and disability, including massage therapy, joint mobilization and manipulation (111), or who changed their prophylactic headache medicine or became pregnant during the RCT were informed that they would be withdrawn from the study at that time and regarded as drop-outs. The participants were allowed to continue and change their usual acute migraine medication throughout the trial. Any such events were prospectively monitored throughout the trial period.

5.4 Clinical interview and examination

Potential eligible participants were invited to a thorough interview at the Research Centre, Akershus University Hospital, by the clinical investigator (AC). No telephone interviews were conducted. The semi-structured interview was specifically designed for diagnosing headache disorders and lasted approximately 60 minutes. The questions were all pre-defined, but the clinical investigator could adjust the order and change the formulation to obtain as much and as specific information as possible from the participant.

The questionnaire included a total of 135 questions with an extensive description of the headache history. Questions included the ICHD-II criteria for MA, MO, probable migraine and TTH (3), and a detailed history of headache frequency, duration and intensity. In addition, questions related to all health care contacts, including non-pharmacological contacts, were recorded. A detailed questionnaire regarding participants’ physical history was also recorded, Appendix 2.

After the interview, the participants underwent a thorough physical assessment by the clinical investigator, including a meticulous investigation of the spinal column. The physical examination included a neurological examination, a measurement of weight and height, and a visual range-of-motion test of the
cervical spine. All participants’ prescribed medications were recorded in the interview.

The participants who still fulfilled the inclusion criteria after the interview and examination went to a different location where the randomization was conducted. Prepared and sealed lots with the three interventions, i.e., active treatment, placebo and control groups, were subdivided into four subgroups by age and gender, i.e., 18-39 and 40-70 years of age and men and women, respectively. Block randomization was necessary to balance the arms by age and gender to reduce possible age- and/or gender-related biases. The participants were equally allocated to the three groups, and each participant was allowed to draw only one lot. Randomization was administered by a single external trained party with no involvement from the clinical investigator. Participants randomized to the CSMT or the placebo group had a full spine radiographic examination prior to their first intervention session.

All data were then entered into SPSS by an external trained party using a designed online transferring program with safe backup, i.e., Snap Survey (Snap Survey, London, UK), at Akershus University Hospital, Norway.

5.5 Prospective headache diary recordings

Following the clinical interview, all participants were explicitly instructed on how to complete the validated paper form diagnostic headache diary (112, 113). The diary included questions directly related to the primary and secondary endpoints and questions necessary to distinguish between MA, MO, probable migraine and TTH, Appendix 3. In accordance with IHS clinical guidelines, we considered one month prior to the intervention to be a sufficient time for baseline data recordings. The participants were instructed to continually fill in headache days immediately after a headache episode to minimize recall bias and to return the diaries on a monthly basis during the 17 months study period. In the case of unreturned diaries or missing values, the participants were contacted by the clinical investigator immediately upon detection to minimize recall bias. All
participants continuously received headache diaries and return pre-addressed and pre-paid envelopes by post and had the headache diaries e-mailed to them. If a participant moved abroad during the study period, he/she was allowed to e-mail the headache diary to the clinical investigator. All participants were also instructed to report relocations, and if not, they were contacted by telephone and/or e-mail by the clinical investigator to obtain their new address to secure future compliance.

A migraine day was defined as a day on which MA, MO, or probable migraine occurred. Migraine attacks lasting for >24 hours were calculated as one attack unless pain-free intervals of ≥48 hours had occurred (114). If a patient fell asleep during a migraine attack and woke up without a migraine, in accordance with the ICHD-III β, the duration of the attack was recorded as persisting until the time of awakening (4).

The following diagnostic hierarchy was decided on; (i) MA, (ii) MO, (iii) probable migraine and (iv) TTH. Thus, MA was considered superior for the entire attack from the time MA was fulfilled, i.e., in a four-day attack for a participant fulfilling MO criteria for the first two days and MA criteria for the following two days, the SPSS syntax would regard the headache episode as MO on days one and two and MA on days three and four. Similarly, if a four-day attack began with MA, it would be regarded as a continuous MA attack for the entire period independently of whether MO, probable migraine or TTH comprised the consecutive three days. Only participants pre-diagnosed with MA were considered for this diagnosis in the syntax.

If an attack fulfilled all but one ICHD-criterion for MO, the attack was classified as MO if symptomatic treatment was used; otherwise, it was classified as a probable migraine. The minimum duration of a migraine attack was 4 hours unless a triptan or drug containing ergotamine was used, in which case we specified no minimum duration. All other headache episodes not fulfilling MA, MO or probable migraine were classified as TTH.
All data from the headache diaries were entered into SPSS by the clinical investigator (AC) using a designed online transferring program with safe backup, i.e., Snap Survey, at Akershus University Hospital, Norway. The vertical VAS was calculated \((100 / \text{length of scale} \times \text{marked pain intensity by the participant})\) by an externally trained party.

5.6 End-points

The primary and secondary end-points adhered to the recommended IHS clinical trial guidelines (77, 78), and were all registered on ClinicalTrials.gov [identifier: NCT01741714]. Based on previous reviews of migraine, a 25% reduction in the primary end-point was considered a conservative estimate (64).

5.6.1 Primary end-point

We pre-defined the number of migraine days per month (30 days/month) as a primary end-point, and a 25% reduction was expected in the CSMT group from baseline to the end of the intervention, with the same level maintained at three, six and 12 months follow-up expected in the CSMT group. No change was expected in the placebo or the control groups.

5.6.2 Secondary end-points

Secondary end-points included migraine duration, migraine intensity and headache index (HI) with an expected improvement of 25% and expected reduction of 50% in medication use from baseline to post-treatment, with the same level maintained at three, six and 12 months follow-up in the CSMT group. No change was expected in the placebo or the control groups. Headache index was calculated as the mean days with migraine (30 days) \(\times\) mean migraine duration (hours per day) \(\times\) mean intensity (0-10 NRS).
5.7 Intervention

Because no clinical guidelines exist for treatment length and the number of treatment sessions for non-pharmacological clinical trials, we based our treatment regimen on those used in previous RCTs (58-61). These studies included 8 weeks of treatment with an average of 15 treatments. We decided to follow the IHS clinical guidelines of a three months intervention period but with 12 treatment sessions (77, 78). We believed the number of treatment sessions corresponded better to usual clinical practice.

Active treatment consisted of CSMT using the Gonstead method (53), i.e., a specific contact, high-velocity, low-amplitude, short-lever, spinal with no post-adjustment recoil directed to spinal biomechanical dysfunction (full spine approach) as diagnosed by standard chiropractic tests at each individual treatment session.

The placebo intervention consisted of sham manipulation, i.e., a broad non-specific contact, low-velocity, low-amplitude sham push manoeuvre in a non-intentional and non-therapeutic directional line. All the non-therapeutic contacts were performed outside the spinal column with adequate joint slack and without soft tissue pre-tension so that no joint cavitations occurred (115). In some sessions, the participant laid prone on a Zenith 2010 HYLO bench with the investigator standing at the participant’s right side with his left palm placed on the participant’s right lateral scapular edge with the other hand reinforcing. In other sessions, the investigator stood at the participant’s left side and placed his right palm over the participant’s left scapular edge with the left hand reinforcing, delivering a non-intentional lateral push manoeuvre. Alternatively, the participant laid in the same side posture position as the active treatment group with the bottom leg straight and the top leg flexed with the top leg’s ankle resting on the bottom leg’s knee fold in preparation for a side posture push move, which was delivered as a non-intentional push in the gluteal region. The sham manipulation alternatives were equally interchanged among the placebo
participants according to protocol during the 12 week treatment period to strengthen the study’s validity, Table 1.

Both the active and placebo groups received the same structural and motion assessment prior to and after each intervention. No additional co-interventions or advice were given to the participants during the trial period. The intervention period included 12 consultations, i.e., twice per week for the first three weeks followed by once a week for the next two weeks and once every second week until 12 weeks was reached. Fifteen minutes were allocated per consultation for each participant. All interventions were conducted at Akershus University Hospital and were administered by a single experienced chiropractor (AC).

The control group continued their usual pharmacological management without receiving manual intervention.

Table 1. Fixed intervention schedule for the placebo group.

<table>
<thead>
<tr>
<th>Week 1: two sessions</th>
<th>Week 2: two sessions</th>
<th>Week 3: two sessions</th>
<th>Week 4: one session</th>
<th>Week 5: one session</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reinforced left and right scapula push sequentially</td>
<td>Bilaterally scapula push and left gluteal push</td>
<td>Reinforced right and left scapula push sequentially</td>
<td>Reinforced right scapula and left gluteal push</td>
<td>Bilaterally scapula push</td>
</tr>
<tr>
<td>Week 7: one session</td>
<td>Week 9: one session</td>
<td>Week 11: one session</td>
<td>Week 12: one session</td>
<td></td>
</tr>
<tr>
<td>Bilaterally scapula push and right gluteal push</td>
<td>Bilaterally scapula push</td>
<td>Reinforced left scapula and right gluteal push</td>
<td>Bilaterally scapula and left gluteal push</td>
<td></td>
</tr>
</tbody>
</table>

5.8 Blinding

The participants who received active or placebo intervention completed a de-blinding questionnaire after each intervention session administered by an externally trained independent party with no involvement from the clinical investigator, i.e., providing a dichotomous “yes” or “no” answer as to whether active treatment was received. This response was followed by a second question regarding how certain they were that active treatment was received on a 0-10 numeric rating scale (NRS), in which where 0 represented absolutely uncertain
and 10 represents absolutely certainty, Appendix 4. The control group and the clinical investigator could not, for obvious reasons, be blinded (115-117).

All data from the de-blinding questionnaire were entered into SPSS by an externally trained independent party with no involvement from the clinical investigator using a designed online transferring program with safe backup, i.e., Snap Survey, at Akershus University Hospital, Norway.

5.9 Adverse events

A standardised recording scheme designed for pharmacological RCTs were used to collect AE data in the CSMT and placebo groups, Appendix 5 (118). The AE recording scheme was completed by the clinical investigator after each intervention session independently of whether or not the participant had experienced AE. Thus, the last intervention session was not included in the data set. The control group, not receiving intervention, did not report on AEs.

5.10 Statistical processing

All data from the interview, headache diary, de-blinding questionnaire and adverse event scheme were anonymous, including only participant number and initials in order to maintain anonymity. They were electronically transferred to SPSS using Snap Survey and analysed by a statistician blinded for group allocation with solely access to participant’s serial number and group code, A, B and C. The outcome analyses were calculated during the 30 days subsequently after the last intervention session and 30 days after the follow-up time points, i.e., three, six and 12 months, respectively. All statistical analyses were performed using SAS version 9.2, STATA version 14, or SPSS version 22, and for paper II, III and IV, respectively.
Paper II

For the migraine RCT (paper II), we based the calculation of sample size from a recent group comparison study of topiramate among migraine patients (119). We hypothesized that the average difference in reduction of number of days with migraine per month between the active and the placebo group was 2.5 days. The same difference was assumed between the active and the control group. Standard deviation for reduction in each group was assumed to be equal 2.5. Under the assumption of on average 10 migraine days per month at baseline in each group and no change in the placebo or control group during the study, 2.5 days reduction corresponds to a reduction by 25%. As primary analysis includes two group-comparisons, the Bonferroni correction was used to set the significance level to 0.025 (120). A sample size of 20 patients was required in each group to detect a statistically significant reduction by 25% with 80% power.

Demographic and clinical characteristics at baseline were presented as means and standard deviations (SD) or frequencies and percentages in each group. CSMT, placebo and control groups were compared by Independent samples t-test, $\chi^2$-test and z-test. Primary and secondary end-points within the group were described as means and SD at each time point.

Time profiles of all end-points were further compared between the groups. As all end-points were recorded at several time points, repeated measurements for each patient were available. To correctly account for the intra-individual correlations, linear mixed models were estimated for the primary end-point and migraine duration, migraine intensity and HI. Fixed effects for (first-, second-, and third-order) time components and group allocation were included together with the interaction between the two. As the residuals were skewed, the bootstrap inference based on 1000 cluster samples was used. Pairwise comparisons were performed by deriving individual time point contrasts within each group at each time point with the corresponding p-values and 95% confidence intervals.
All medications reported by patients were described as average number of doses with the corresponding SD, i.e., triptans and ergotamins (doses), paracetamol and paracetamol + codeine (1000mg), NSAIDs (tolfenamic acid, 200mg; diclofenac, 50mg; aspirin, 1000mg; ibuprofen, 600mg; and naproxen, 500mg) and morphinomimetics (tramadol 50mg). Differences in medication use between the CSMT and the placebo group, and the CSMT and the control group were assessed by Independent Samples Median test.

None of the patients changed the study arm and none of the drop-outs filled in headache diaries after withdrawal from the study. Hence, only per protocol analysis was relevant.

The results with p-values below 0.025 for primary end-point were considered statistically significant. In all other analyses, p-values below 0.05 indicated significant findings.

**Paper III**

For the validation of the placebo study (paper III), the rate of successful blinding and sureness in participants’ belief in both treatment groups, i.e., CSMT and placebo were outcome measures. The dichotomous “yes” and “no” data were presented as percentages with 95% confidence intervals (CIs), while the continuous 0-10 NRS outcome was presented as means with 95% CI. Time trend in both outcomes was assessed by regression models for repeated measurements correctly accounting for intra-individual correlations. The dichotomous outcome was analysed by a logistic regression model using SAS GLIMMIX procedure, while linear mixed model was estimated (SAS MIXED) for continuous outcome. In both models, fixed effects for treatment group and treatment number were specified. An interaction between the two fixed effects was included into the model to quantify possible differences in trend in the placebo and the active groups. Random intercept accounting for within-subject variability was also included into the model. The analyses were in addition stratified by believers vs. non-believers by including a fixed effect for a dummy identifying those two
subgroups. The odds ratio (OR) and estimated mean NRS scores with 95% CI for each treatment session were calculated and presented graphically. P-values below 0.05 were considered statistically significant.

**Paper IV**

All AE registered during the intervention period were described as percentages and frequencies within each group. The 95% CI for percentages (absolute risk) of AE in each group were calculated when possible. Attributable risk (%) and relative risk were calculated with the corresponding 95% CI. The analyses were also stratified by those who had and had not previously received CSMT.

### 5.11 Ethical considerations

Good clinical practice guidelines were followed (121). Oral and written information about the project was provided in advance of inclusion and group allocation, i.e., active or placebo intervention, including benefits and possible AEs. All data were anonymized, and written consent was obtained from all participants. The Declaration of Helsinki was otherwise followed. If the CSMT treatment was to be effective, it would be offered to participants who received placebo or control after study completion, i.e., after 12 months of follow-up and completion of the analysis.

Insurance was provided through the Norwegian System of Compensation to Patients (NPE), an independent national body that compensates patients injured by treatments provided by the Norwegian health service. A stopping rule was defined for withdrawing participants from this study in accordance with the recommendations in the CONSORT extension for Better Reporting of Harms (73).

All AEs were registered in accordance with the recommendations of CONSORT and the IHS Task Force on AEs in migraine trials (73, 84). The clinical investigator (AC) was available on the study mobile phone at any time throughout the trial period to monitor any AEs occurring between the
intervention sessions. Severe AEs would result in withdrawal from the study and referral to the general practitioner (GP) or hospital emergency department depending on the event.

The Norwegian Regional Committee for Medical Research Ethics (REK) and the Norwegian Social Science Data Services approved the project. All methods were carried out in accordance with the approved guidelines and regulations. The study was registered on 2. December 2012 at ClinicalTrials.gov (ID no. NCT01741714).

None of the funding sources had any influence on the protocol or the studies involved. All data collection, data analysis, data interpretation, and writing of the article were conducted by the authors alone. Only the first author (AC), the blinded statistician (JSB) and the principal investigator (MBR) had access to all data in this study. The corresponding author of all four papers (AC) had final responsibility for the decision to submit for publication.
6 Main results

6.1 Paper I

Because paper I was a protocol, no results are presented (110). Nevertheless, to the best of our knowledge, this was the first prospective manual-therapy three-armed, single-blinded, placebo RCT protocol to be conducted for migraineurs. The study design adhered to the recommendations for pharmacological RCTs as much as possible and followed the recommended clinical trial guidelines from IHS and the CONSORT and SPIRIT guidelines. It is generally accepted that RCTs that include a placebo and control group are advantageous to pragmatic RCTs that compare two active treatment arms considering that the placebo response can be high. However, a generally accepted placebo intervention had not previously been established for manual therapy (122). The protocol therefore had the potential to increase the methodological quality in future prospective chiropractic and other manual-therapy RCTs on headaches and for other musculoskeletal spinal disorders.

6.2 Paper II

A total of 104 migraineurs were included in this study, Figure 2. The baseline and demographic characteristics were similar across the three groups, Table 2. The response rate to the prospective headache diaries during the full 17 months study period was 70.2%. The results of the primary and secondary end-points are presented descriptively in Table 3, while results adjusted for intra-individual correlations can be found in Figure 2a-d in paper II (123).
### Table 2. Baseline demographic and clinical characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Chiropractic spinal manipulative therapy (CSMT)</th>
<th>Sham manipulation (placebo)</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
<td>34</td>
<td>34</td>
<td>29</td>
</tr>
<tr>
<td>Males</td>
<td>6 (18%)</td>
<td>5 (15%)</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Females</td>
<td>28 (82%)</td>
<td>29 (85%)</td>
<td>26 (90%)</td>
</tr>
<tr>
<td>Age ± SD (range)</td>
<td>41.0 ± 11.3 (19-63)</td>
<td>39.6 ± 9.8 (18-65)</td>
<td>38.7 ± 11.1 (20-58)</td>
</tr>
<tr>
<td>Migraine without aura</td>
<td>32 (94%)</td>
<td>30 (88%)</td>
<td>26 (90%)</td>
</tr>
<tr>
<td>Migraine with aura</td>
<td>9 (26%)</td>
<td>12 (35%)</td>
<td>6 (21%)</td>
</tr>
<tr>
<td>Duration (years with migraine ± SD)</td>
<td>21.9 ± 13.2</td>
<td>21.4 ± 11.2</td>
<td>20.8 ± 10.5</td>
</tr>
<tr>
<td>Migraine days (30 days/month) in the run-in period ± SD</td>
<td>6.5 ± 3.3</td>
<td>8.3 ± 5.6</td>
<td>7.8 ± 6.0</td>
</tr>
<tr>
<td>Co-morbid tension-type headache (%)</td>
<td>24 (71%)</td>
<td>26 (76%)</td>
<td>22 (76%)</td>
</tr>
<tr>
<td>Tension-type headache days (30 days/month) in the run-in period ± SD</td>
<td>1.0 ± 2.0</td>
<td>2.1 ± 3.5</td>
<td>0.9 ± 1.8</td>
</tr>
<tr>
<td>On prophylactic migraine medicine</td>
<td>8 (24%)</td>
<td>8 (24%)</td>
<td>7 (24%)</td>
</tr>
<tr>
<td>Diagnosed at hospital by a neurologist</td>
<td>26 (76%)</td>
<td>26 (76%)</td>
<td>21 (72%)</td>
</tr>
<tr>
<td>Diagnosed by neurologist</td>
<td>5 (15%)</td>
<td>7 (21%)</td>
<td>4 (14%)</td>
</tr>
<tr>
<td>Diagnosed by general practitioner alone</td>
<td>3 (9%)</td>
<td>1 (3%)</td>
<td>4 (14%)</td>
</tr>
<tr>
<td>Previously received CSMT (%)</td>
<td>11 (32%)</td>
<td>13 (38%)</td>
<td>16 (55%)</td>
</tr>
<tr>
<td>Previously experienced cervical pain</td>
<td>29 (85%)</td>
<td>28 (82%)</td>
<td>20 (69%)</td>
</tr>
<tr>
<td>Previously experienced thoracic pain</td>
<td>24 (71%)</td>
<td>26 (76%)</td>
<td>16 (55%)</td>
</tr>
<tr>
<td>Previously experienced lumbar pain</td>
<td>24 (71%)</td>
<td>26 (76%)</td>
<td>18 (62%)</td>
</tr>
</tbody>
</table>

\*Data are presented as means and standard deviations or frequencies and percentages in each group and compared by \(^1\)Independent Samples t-test, \(^2\)χ²-test and \(^3\)z-test. No significant group difference were seen between CSMT versus placebo and CSMT versus control (all p>0.05). The primary end-point, migraine days, was significantly reduced within all three groups from baseline to post-treatment (p<0.001). The effect continued in the CSMT and placebo groups at three, six and 12 months follow-up, whereas migraine days returned to baseline levels in the control group, Figure 2a in paper II. According to the linear mixed model, there were no overall significant differences in migraine days change between the CSMT and placebo groups (p=0.039 for interaction) or between the CSMT and control groups (p=0.060 for interaction), Table 3. However, the pairwise comparisons at individual time points showed significant differences between the CSMT and control groups at all time points beginning at post-treatment, Table 3.
Table 3. Means and standard deviations (SD), not adjusted for intra-patient correlations, at baseline and follow-up for all end-points by group. P-values are based on linear mixed model analysis. P-values <0.025 for change from baseline (BL) to Post-treatment in primary end-point, migraine days, and <0.05 for secondary end-points denotes significant finding.

<table>
<thead>
<tr>
<th></th>
<th>Chiropractic spinal manipulative therapy (CSMT)</th>
<th>Sham manipulation (placebo)</th>
<th>Control group</th>
<th>CSMT vs. Placebo</th>
<th>CSMT vs. Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Migraine days</strong></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>p-values</td>
<td>p-values</td>
</tr>
<tr>
<td>Baseline</td>
<td>6.5 (3.3)</td>
<td>8.3 (5.6)</td>
<td>7.8 (6.0)</td>
<td>0.073</td>
<td>0.116</td>
</tr>
<tr>
<td>Post-treatment</td>
<td>3.9 (3.1)</td>
<td>4.1 (5.7)</td>
<td>6.1 (5.9)</td>
<td>0.204</td>
<td>0.018</td>
</tr>
<tr>
<td>3-months follow-up</td>
<td>4.5 (3.6)</td>
<td>4.6 (5.7)</td>
<td>6.2 (5.6)</td>
<td>0.394</td>
<td>0.005</td>
</tr>
<tr>
<td>6-months follow-up</td>
<td>4.1 (3.9)</td>
<td>5.1 (6.4)</td>
<td>6.8 (6.3)</td>
<td>0.648</td>
<td>0.003</td>
</tr>
<tr>
<td>12-months follow-up</td>
<td>4.4 (4.2)</td>
<td>4.1 (6.0)</td>
<td>8.0 (8.2)</td>
<td>0.853</td>
<td>0.002</td>
</tr>
<tr>
<td>BL to Post-treatment</td>
<td>2.6 (0.4)</td>
<td>3.0 (0.4)</td>
<td>2.0 (0.4)</td>
<td>0.039</td>
<td>0.060</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>p-values</td>
<td>p-values</td>
</tr>
<tr>
<td>Baseline</td>
<td>11.7 (5.9)</td>
<td>14.0 (4.7)</td>
<td>11.1 (6.1)</td>
<td>0.036</td>
<td>0.621</td>
</tr>
<tr>
<td>Post-treatment</td>
<td>9.2 (5.8)</td>
<td>10.4 (7.0)</td>
<td>13.1 (6.5)</td>
<td>0.036</td>
<td>0.196</td>
</tr>
<tr>
<td>3-months follow-up</td>
<td>9.5 (6.9)</td>
<td>10.6 (7.2)</td>
<td>10.8 (6.9)</td>
<td>0.058</td>
<td>0.069</td>
</tr>
<tr>
<td>6-months follow-up</td>
<td>7.3 (7.1)</td>
<td>11.6 (7.4)</td>
<td>11.3 (6.7)</td>
<td>0.116</td>
<td>0.028</td>
</tr>
<tr>
<td>12-months follow-up</td>
<td>8.1 (7.3)</td>
<td>8.9 (7.7)</td>
<td>11.8 (5.9)</td>
<td>0.335</td>
<td>0.010</td>
</tr>
<tr>
<td>BL to Post-treatment</td>
<td>1.7 (0.6)</td>
<td>1.9 (0.6)</td>
<td>0.9 (0.6)</td>
<td>0.609</td>
<td>0.009</td>
</tr>
<tr>
<td><strong>Intensity</strong></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>p-values</td>
<td>p-values</td>
</tr>
<tr>
<td>Baseline</td>
<td>5.7 (1.7)</td>
<td>6.1 (1.7)</td>
<td>5.6 (2.0)</td>
<td>0.158</td>
<td>0.636</td>
</tr>
<tr>
<td>Post-treatment</td>
<td>4.7 (2.8)</td>
<td>5.0 (3.0)</td>
<td>5.7 (2.5)</td>
<td>0.269</td>
<td>0.259</td>
</tr>
<tr>
<td>3-months follow-up</td>
<td>5.0 (3.0)</td>
<td>4.9 (2.8)</td>
<td>5.4 (2.8)</td>
<td>0.462</td>
<td>0.134</td>
</tr>
<tr>
<td>6-months follow-up</td>
<td>4.4 (3.6)</td>
<td>5.2 (2.9)</td>
<td>5.7 (2.5)</td>
<td>0.693</td>
<td>0.085</td>
</tr>
<tr>
<td>12-months follow-up</td>
<td>5.1 (3.5)</td>
<td>4.4 (3.2)</td>
<td>6.1 (2.4)</td>
<td>0.965</td>
<td>0.061</td>
</tr>
<tr>
<td>BL to Post-treatment</td>
<td>0.7 (0.2)</td>
<td>0.8 (0.2)</td>
<td>0.4 (0.2)</td>
<td>0.414</td>
<td>0.105</td>
</tr>
<tr>
<td><strong>Headache index</strong></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>p-values</td>
<td>p-values</td>
</tr>
<tr>
<td>Baseline</td>
<td>557.5 (458.2)</td>
<td>762.5 (639.0)</td>
<td>581.6 (635.0)</td>
<td>0.058</td>
<td>0.678</td>
</tr>
<tr>
<td>Post-treatment</td>
<td>295.5 (348.1)</td>
<td>330.1 (602.3)</td>
<td>547.6 (649.7)</td>
<td>0.157</td>
<td>0.098</td>
</tr>
<tr>
<td>3-months follow-up</td>
<td>338.0 (350.8)</td>
<td>399.6 (582.0)</td>
<td>526.8 (641.1)</td>
<td>0.319</td>
<td>0.019</td>
</tr>
<tr>
<td>6-months follow-up</td>
<td>313.0 (395.6)</td>
<td>402.8 (595.1)</td>
<td>562.6 (740.1)</td>
<td>0.559</td>
<td>0.009</td>
</tr>
<tr>
<td>12-months follow-up</td>
<td>350.8 (451.6)</td>
<td>322.9 (668.8)</td>
<td>872.0 (1475.6)</td>
<td>0.921</td>
<td>0.009</td>
</tr>
<tr>
<td>BL to Post-treatment</td>
<td>229.7 (42.7)</td>
<td>276.9 (50.9)</td>
<td>118.2 (55.1)</td>
<td>0.051</td>
<td>0.045</td>
</tr>
</tbody>
</table>

For the secondary end-points, there was a significant reduction from baseline to post-treatment in migraine duration, intensity and HI in the CSMT group (p=0.003, p=0.002 and p<0.001, respectively) and the placebo group (p<0.001, p=0.001 and p<0.001, respectively), and the effect continued at three, six and 12 months follow-up.

According to the linear mixed model, there were significant differences only between the CSMT and control groups in changes in migraine duration (p=0.019 for interaction) and in HI (p=0.045 for interaction), Table 3.

At 12 months follow-up, the consumption of paracetamol was significantly lower in the CSMT group than in the placebo (p=0.04) and control (p=0.03) groups. No
other significant differences in acute migraine medication were observed between the groups at any of the follow-up time points; see Table 4 in paper II for details. Two participants in the CSMT group developed MOH by overusing triptans during the 17 months trial period.

### 6.3 Paper III

The placebo RCT included all 70 participants, i.e., six men and 29 women in both the CSMT and placebo groups (115). In total, 772 intervention sessions were completed (390 and 382 in the CSMT and placebo groups, respectively), and 68 (8.1%) intervention sessions were missed (30 and 38 in the CSMT and placebo groups, respectively).

At each intervention session, more than 80% of the participants believed they had received active treatment regardless of whether they had received CSMT or placebo intervention throughout the RCT, Figure 3a. Thus, blinding was strongly sustained throughout the entire RCT period.

**Figure 3.** (A) The percentages with 95% confidence intervals (CI) of participants believing they had active treatment at each treatment session. (B) Mean numeric rating scale (NRS) score with 95% CI for how certain participants were that they received active treatment on a NRS (0–10).

There was no significant difference between those who had and those who had not received SMT previously (p=0.149). Similarly, there were no significant
differences between the intervention groups with respect to having previously received SMT (p=0.588), and this result was consistently observed throughout the RCT, Figure 3b.

The odds for believing that CSMT was received at baseline were approximately 10 times higher than the odds for not believing placebo was received (p<0.001). In the CSMT treatment group, these same odds were 73 times higher (p<0.001). The odds continued to increase in the placebo group for each intervention session, whereas the opposite effect was observed in the CSMT group, Figure 4.

**Figure 4.** The odd ratios (OR) with 95% confidence intervals (CI) for believing active treatment was received for each consecutive treatment session.

6.4 Paper IV

The AE RCT included 70 participants, i.e., six men and 29 women in both the CSMT and placebo groups. A total of 703 of the potential 770 intervention sessions were assessed for AEs, i.e., 355 in the CSMT group and 348 in the placebo group. Reasons for missing AE assessment included dropping out and missed intervention session appointments (124).

*Adverse events related to the intervention*

AEs were reported in significantly more of the CSMT intervention sessions than the placebo intervention sessions (73/355 vs. 29/348, respectively; p<0.001). In
the majority of the intervention sessions, only a single AE was reported, i.e., 63 times in the CSMT group and 26 times in the placebo group, whereas two AEs were reported 10 times in the CSMT group and three times in the placebo group. No participants reported three or more AEs at a single intervention session. Ten participants in the CSMT group and 17 participants in the placebo group did not experience AEs in any of the intervention sessions, whereas the remaining participants experienced AEs in at least one intervention session.

Local tenderness, tiredness and neck pain were the most common AEs, whereas other AEs were rare (<1%), Table 4.

The attributable risk was the highest for tiredness (7.0%, 95% CI 3.9-10.2%) with a relative risk of 5.9 (95% CI 2.3-15.0); the attributable risks for local tenderness and neck pain were 4.4 and 1.7%, respectively, (95% CI 0.1-8.6% and 0.1-3.2%), whereas the relative risks were 1.6 and 6.9, respectively, (95% CI 1.0-2.7 and 0.9-55.5).

The attributable risks and relative risk for local tenderness, tiredness and neck pain in the CSMT group were not influenced by having previously received CSMT or not (attributable risk 3.6% (95% CI -3.4-10.9%); 2.7% (95% CI -3.7-9.1%) and 4.7% (95% CI 0.6-8.8%), respectively; relative risk 1.4 (95% CI 0.8-2.5), 1.4 (95% CI 0.7-2.7) and 12.2 (95% CI 1.5-100.2), respectively, Table 4.

All AEs were mild and transient, except for a single case of a moderate AE, i.e., a possible provoked migraine attack. No severe or serious AEs were reported.

Adverse events unrelated to the intervention

AEs not related to the intervention were rare (<1%), except for neck and lower back pain, i.e., 0.8% and 1.1% and 1.4% and 2.3% in the CSMT and placebo group, respectively, see Table 3 in paper IV for details. Two participants in the CSMT group reported lower back pain as an AE; one participant after two intervention sessions and the other participant after three intervention sessions.
This pain was regarded as non-related to CSMT because both participants received CSMT only at the cervical spine and not at the lumbar spine.

Table 4. Adverse events related to the intervention stratified by ± previously received CSMT. N is total number of interventions.

<table>
<thead>
<tr>
<th>Type</th>
<th>Chiropractic spinal manipulative therapy (CSMT) (N = 355)</th>
<th>Placebo (N = 348)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%, [95% CI] (n)</td>
<td></td>
</tr>
<tr>
<td>Previously received CSMT</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>Total number of intervention sessions</td>
<td>134 [2-8] (5)</td>
<td>134 [2-8] (5)</td>
</tr>
<tr>
<td>Local tenderness</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>YES</td>
<td>14 [6-17] (12)</td>
<td>14 [6-17] (12)</td>
</tr>
<tr>
<td>NO</td>
<td>10 [5-12] (18)</td>
<td>10 [5-12] (18)</td>
</tr>
<tr>
<td>Total</td>
<td>24 [6-12] (30)</td>
<td>24 [6-12] (30)</td>
</tr>
<tr>
<td>Tiredness on treatment day</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>YES</td>
<td>10 [6-17] (12)</td>
<td>10 [6-17] (12)</td>
</tr>
<tr>
<td>NO</td>
<td>8 [5-12] (18)</td>
<td>8 [5-12] (18)</td>
</tr>
<tr>
<td>Total</td>
<td>18 [6-12] (30)</td>
<td>18 [6-12] (30)</td>
</tr>
<tr>
<td>Neck pain</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>NO</td>
<td>1 [0-2] (1)</td>
<td>1 [0-2] (1)</td>
</tr>
<tr>
<td>Total</td>
<td>6 [1-4] (7)</td>
<td>6 [1-4] (7)</td>
</tr>
<tr>
<td>Low back pain</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>YES</td>
<td>&lt;1 [0-2] (1)</td>
<td>&lt;1 [0-2] (1)</td>
</tr>
<tr>
<td>NO</td>
<td>&lt;1 [0-2] (1)</td>
<td>&lt;1 [0-2] (1)</td>
</tr>
<tr>
<td>Total</td>
<td>&lt;2 [1-4] (2)</td>
<td>&lt;2 [1-4] (2)</td>
</tr>
<tr>
<td>Face numbness</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>YES</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>NO</td>
<td>&lt;1 (1)</td>
<td>&lt;1 (1)</td>
</tr>
<tr>
<td>Total</td>
<td>&lt;1 (1)</td>
<td>&lt;1 (1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>YES</td>
<td>&lt;1 (1)</td>
<td>&lt;1 (1)</td>
</tr>
<tr>
<td>NO</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Total</td>
<td>&lt;1 (1)</td>
<td>&lt;1 (1)</td>
</tr>
<tr>
<td>Provoked migraine attack</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>YES</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>NO</td>
<td>&lt;1 (1)</td>
<td>&lt;1 (1)</td>
</tr>
<tr>
<td>Total</td>
<td>&lt;1 (1)</td>
<td>&lt;1 (1)</td>
</tr>
<tr>
<td>Fatigue in arms</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>YES</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>NO</td>
<td>&lt;1 (1)</td>
<td>&lt;1 (1)</td>
</tr>
<tr>
<td>Total</td>
<td>&lt;1 (1)</td>
<td>&lt;1 (1)</td>
</tr>
<tr>
<td>Total % of adverse events</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>YES</td>
<td>31 (36)</td>
<td>31 (36)</td>
</tr>
<tr>
<td>NO</td>
<td>20 (47)</td>
<td>20 (47)</td>
</tr>
<tr>
<td>Total</td>
<td>23 (83)</td>
<td>23 (83)</td>
</tr>
</tbody>
</table>

Furthermore, both participants had lower back pain at study inclusion and experienced daily lower back pain after strenuous activities. Two participants in the CSMT group reported neck pain; one participant 6 days after the intervention session and the other participant 7 days after the intervention session.
7 Discussion and Interpretation

To our knowledge, this was the first prospective manual-therapy, three-armed, single-blinded, placebo RCT to be conducted for migraineurs (64, 76). The results showed that migraine days were significantly reduced within all three groups from baseline to post-treatment; the effect continued in the CSMT and placebo groups at all follow-up time points, whereas the control group returned to baseline. The reduction in migraine days was not significantly different between the groups. Migraine duration and headache index were significantly reduced in the CSMT group compared with the control group towards the end of follow-up. This RCT is also the first manual-therapy RCT for migraineurs with documented successful blinding; moreover, AEs were few mild and transient and demonstrated safe.

7.1 Methodological considerations

7.1.1 Design

The study design, which included a placebo group in addition to active intervention and a control group, adhered to the recommendations for pharmacological RCTs as much as possible. The end-points adhered to the recommended IHS clinical trial guidelines with migraine days as the primary end-point and migraine duration, migraine intensity, headache index and medication consumption as secondary end-points (78, 114). Adhering to the recommended end-points allows manual-therapy RCTs to be compared in future meta-analyses. The study protocol which has been published (paper I) follows closely the primary and secondary end-points pre-specified at ClinicalTrial.gov which strengthen the quality and validity of the study.

Furthermore, placebo-controlled RCTs also provide the best approach for efficacy and safety data. This approach is important, considering that no studies have validated blinding and quantified the placebo effect for migraineurs
receiving SMT over a full treatment course, whereas manual-therapy RCTs have generally not reported AEs (81, 82).

Currently, there is no standardized AE reporting tool for manual-therapy RCTs. Thus, we applied a standardized reporting tool used in pharmacological RCTs to monitor AEs and safety (118). This scheme was found to be easy to apply in our CSMT RCT, and we adhered to the CONSORT and the IHS Task Force on AEs in migraine RCT recommendations for reporting all AEs (73, 84).

Thus, considering these previous methodological shortcomings, we conducted a prospective, clinical, three-armed, placebo, RCT with improved methodological quality in order to assess efficacy of CSMT for migraineurs with certainty.

7.1.2 Patient population

The majority of the participants were recruited through Akershus University Hospital and were diagnosed at the hospital by a neurologist with experience in headache diagnostics through clinical interviews, whereas a few participants were diagnosed by a physician alone. All participants were subsequently also diagnosed by a chiropractor (AC) with experience in headache diagnostics during the interview. Clinical interviews are considered a more valid method than questionnaires for establishing a precise headache diagnosis (74). Thus, diagnostic certainty accounts for one of our primary strengths.

Of the 486 participants who were initially contacted and invited for screening, 21.4% (n=104) of the 55.3% eligible participants accepted participation. Reasons for refraining included stress and time concerns; not wanting to risk being allocated to the control group, which consequently prohibited them from attending regular manual therapy; wanting to change their prophylactic medication; and, interestingly, a fear of CSMT intervention.

However, our rigorous exclusion criteria were necessary in order to mitigate two known confounders for migraine, i.e., depression and pregnancy, while dispensing with chiropractic treatment within the previous 12 months was
necessary to obtain a homogenous sample population, avoid encountering type-II errors and enable successful blinding in the placebo group. Finally, by not allowing participants in the three groups to attend non-pharmacological management during the trial period, i.e., manual and non-manual interventions, was considered important to maintain strong internal validity and avoid what is sometimes known as contamination bias.

Although headache accounts for 4% of the GP consultations, 2–4% of these cases are referred to specialists or hospitals (44, 125, 126). In contrast to the three previous chiropractic RCTs on migraine in which participants were recruited through media, i.e., newspapers and radio advertisements (58-61), more than 2/3 (76%) of our included patients were contacted and invited through Akershus University Hospital’s databases, whereas 92.3% of the total sample had been in contact with and been diagnosed by a neurologist. In general, patients referred to secondary and tertiary health care and neurologists are often regarded as more complex because these patients are thought to consult more frequently, attribute more symptoms in relation to their headache, have stronger emotional distress and are generally more worried and anxious regarding their headache symptoms (126). Considering that migraine was not successfully treated by the GP and/or practicing neurologist, resulting in referral to the hospital, it is reasonable to believe that our patient group might have suffered some of the same efficacy resistance with our intervention. The majority of our patients had also had several additional prior healthcare contacts; thus, their expectations might have been low at baseline. These factors are reflected in the high numbers of participants who had previously received CSMT.

The majority of participants had also been experiencing cervical, thoracic and/or lumbar pain, which could have contributed to an altered central and/or peripheral de-sensitization derangement (41, 42). The high percentage of spinal pain in our study is comparable to a recent Danish population-based study that found a one-year prevalence of neck pain to be as high as 76.2% for migraineurs (38).
These factors might have influenced the results and might not be generalized to chiropractic clinical practice where patients often have less frequent monthly migraine attacks. Thus, a replication of the trial with participants from the general population and primary care alone might have changed the results.

### 7.1.3 Primary and secondary end-points

The primary and secondary end-points were collected prospectively in a validated diagnostic headache diary and adhered to the recommended IHS clinical trial guidelines with migraine frequency as the primary end-point and migraine duration, migraine intensity, headache index and medication consumption as secondary end-points (77, 78).

There is a significant difference in number of migraine days and migraine attacks set to be primary end-point. We decided to use migraine days as the end-point, which consequently can help us better detect a possible difference. At the time of conception of this study, few trials had been done to identify the optimal responder rate for use in clinical manual-therapy studies, and therefore the optimal cut off was not known at this time point. In the guideline from 2008 (78), a 25% improvement could be considered and was also decided upon after discussion with several headache experts.

In 2012 a new and updated 3rd edition of the guidelines for controlled trials of drugs in migraine was published (114). This guideline recommends 2-8 migraine attacks as compared to the minimum of one attack per month which we sat as an inclusion criterion.

Migraine duration was used as a secondary end-point because of its importance in assessing the history and because the participants suffered discrete headache episodes with start and stop times and with complete pain-free periods in between. Some participants have a continuous background headache that never disappear completely and are consequently not candidates for such a clinical trial. However, the new guideline does not recommend migraine duration as a
secondary end-point measures (114), due to the use of acute treatment which cannot be standardized among patients and the uncertainty of duration in patients who fall asleep with their migraine which consequently will create difficulty in accurately timing the end of an attack. This was however, corrected for in our study in accordance with the ICHD-III β, were duration of the attack was recorded as persisting until the time of awakening (4).

Migraine intensity was used to rate each headache on a VAS scale, i.e., mild, moderate, or severe. The participants were instructed to record the maximum intensity for each migraine day/episode and/or each calendar day.

Headache index, combined with frequency, duration and intensity gives an indication of the total level of suffering. Headache index has, despite the lack of consensus, been recommended as an accepted standard secondary end-point (78, 127, 128). In the new guideline however, headache index is now not recommended as an secondary end-point (114).

Medication use was chosen as a secondary end-point, not only to track medication, which likely will decline if the number of migraine days is reduced, but also because it is important in diagnosing migraine attacks because migraines relieved by a triptans are by definition migraine attacks (4). Follow-up by a physician was not monitored in the three groups which might have introduced a bias. However, the triptans has been on the marked for >20 years and our participants had on average suffered from migraine for >20 years, thus, it is not likely that they changed their acute pharmacological treatment; furthermore the different triptans have quite similar efficacy. More than 70% of the included participants in each of the three groups were also recruited from tertiary health care, whereby neither of those participants was followed-up at the hospital during the RCT period. Given their many years with migraine, it is also unlikely that those remaining participants consulted their physician due to migraine during the RCT period. Thus, all in all, the effect of this anticipated bias should be considered to be minor, especially since the control group did not change from
baseline, and that this group would probably be a little more prone to consultations with their physician than the two other groups.

Another secondary end-point which was not included in our study relates to the responder rate in which the proportion of participants with ≥50% improvement in number of migraine days as compared to baseline values is now being considered as an important secondary efficacy outcome in the updated guidelines (114).

### 7.1.4 Data collection

A prospective diagnostic headache diary was used to record outcome measures because it is less likely to be subject to recall bias than a retrospective headache history (112, 113). Thus, questionnaire-based outcomes with mean values calculated for each outcome measure for each assessment period give near exact data and precise measurements.

To our knowledge, no manual-therapy RCTs has assessed the long-term efficacy of CSMT for migraineurs beyond 2 months of follow-up (64, 76). We decided to follow the recommended IHS clinical trial guidelines with a minimum of 12 months of follow-up (77, 78).

We decided that one month of headache diary recordings would be sufficient for baseline recordings (78); however, because migraine frequency tends to be intermittent, a three-month baseline period might in retrospect have been preferable (114).

To save time and reduce the risk of backfilling typo errors when transferring diaries into SNAP and thereby SPSS (129), an electronic headache diary would also have saved significant time. These diaries can be set up so the participants are unable to submit their diaries until all required fields are filled in, minimizing the risk for missing values. However, technical challenges might occur, and we do not know whether such a diary would result in lower or higher compliance because some participants prefer paper diaries and others prefer digital diaries (130). Non-compliance is a known challenge, and it may be more pronounced at
the end of the study (131). However, frequent contact between the participants and the investigator, including monthly contact when the participants did not return complete diaries, likely maintained the high compliance in our study. Of our participants, 70.2% completed the entire study period with no missing values. Modern society, however, allows visible and applicable diaries to be used on smartphones either by entering a desired URL or even by downloading a simple smartphone application that could have simplified the process even further.

7.1.5 Blinding

Blinding was a challenge because there was no single validated standardized chiropractic sham intervention that could be used as a control group at the time the study commenced. Furthermore, there was no consensus on an appropriate placebo for a clinical trial of SMT among experts representing both clinicians and academics (122). Thus, several challenges arose when we discovered that no previous studies had, to our knowledge, validated a successful blinding of a CSMT clinical trial with multiple treatment sessions. Because it has been recommended that RCTs should include a placebo group (132), and to adhere to the recommendations for pharmacological RCTs as much as possible, we developed a new sham procedure.

Previous RCTs were naturally comparative and/or pragmatic, and no treatment was used for the control group (64). RCTs that include a placebo group and a control group are advantageous to pragmatic RCTs that compare two active treatment arms to produce a true net effect (133). It is also important to quantify a likely placebo response in a given manual intervention. Double-blinded studies are not possible because the investigator cannot be blinded for obvious reasons (134); thus, our method accounted for the best possible design.

Regarding methods for monitoring blinding, video recordings and a clinical investigator questioning participants were considered; however, both methods were rejected, primarily because of possible biases in relation to the interpretation of the videos and to avoid bias induced by the clinical investigator.
In addition to investigating the literature (135-141), we discussed the challenge with international researchers at international congresses. Some of the scientific experts we consulted proposed sham manoeuvres in the cervical spine, whereas others proposed sham contacts close to, and even in contact with, the spinal column. We believed that the placebo contacts should be performed outside the spinal column, minimizing a possible spinal cord afferent input (142-144).

The placebo response often observed has been described for decades (145), and refers to a positive clinical outcome given to a control group without a specific target for the condition being treated (146). While there is no single explanation for the placebo effect, research argues that several psychological and neurobiological factors contribute to the effect observed (147). Favourable neurobiological effects have also been demonstrated by positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) (148-150). It is well known that the placebo effect in both pharmacological and non-pharmacological clinical trials is high, and likely higher in manual-therapy RCTs where attention and physical contact is involved (151).

Because we are unaware of the mechanisms of possible efficacy, and because both spinal cord and central descending inhibitory pathways had been postulated, we saw no reason to exclude a full spine treatment approach for the active treatment group. Because it has been postulated that pain in different spinal regions should not be regarded as separate disorders but rather as a single entity (37), it seemed reasonable not to direct focus entirely to the cervical spine. Similarly, including a full spine approach limits the differentiations between the CSMT and the placebo group. We believed the minimal differentiation between the groups strengthens the likelihood of blinding the placebo group successfully.

The placebo intervention should resemble active treatment in terms of procedure, treatment frequency and time spent with the investigator to allow for similar expectations in both groups (152). Thus, the elimination of inter-observer variability by having one investigator and by including random participant numbers is of high importance to achieve successful blinding (153), in addition
to strengthening the internal validity of the study. However, the external validity of the RCT might be weakened because there was only one investigator.

The second concern was in relation to the validation procedures. Some researchers argued that the de-blinding questionnaire could be completed after the first sessions, whereas others argued that it would be sufficient to complete it after the last session. However, we decided to conduct the de-blinding questionnaire in the participants after each session and to assess how strongly they believed active treatment was being received. We believed that participant beliefs could change during the intervention period and that having as much data as possible would allow us to present the results as precisely as possible during the full treatment course, i.e., 12 intervention sessions over 3 months, on an issue that clearly lacked consensus (122).

A brief questionnaire administered by an externally trained assistant after each intervention session was therefore decided upon because we considered it less biased and highly applicable for this and future RCTs.

7.1.6 Adverse events

The advantage of collecting AEs in house with the participant is related to the common view difference on AE between participants and clinical investigator (154). The participants reported the type, severity and duration of AE, and the clinical investigator interpret the reported AEs in relation to onset and region affected. Thus, AEs that occurred several days after an intervention session and were of non-musculoskeletal character were deemed to be unrelated to the intervention session. However, as this was at the discretion of the clinical investigator, it could be viewed as a limitation of the study (84). Furthermore, the study methodology was limited due to the interpretation of AEs by the clinical investigator. A warranted question therefore relates to the objectivity of the clinical investigator in terms of communication and reporting of AEs.
Although a single clinical investigator eliminates inter-observer variability (134), the AEs reported in this study might not necessarily be representative for all CSMT, since AEs may not be similar whether one applies the Gonstead or the Diversified technique and similarly when there are several investigators applying the same intervention. Finally, and probably the most important limitation relates to the sample size; although the RCT was sufficiently powered, the sample size was too small to detect uncommon AE even though we had a total of 703 AEs recordings. However, this study will alongside future large scale studies contribute to pooled meta-analysis which may better establish uncommon AEs from manual-therapy and estimate the incidence rates for AEs.

7.2 Discussion of the Results

7.2.1 Paper II

Three pragmatic chiropractic manual-therapy RCTs using the diversified technique have previously been conducted for migraineurs (58-61, 64). An Australian RCT showed a within-group reduction in migraine frequency, duration and intensity of 40, 43 and 36%, respectively, at two months follow-up (58, 59). An American study found a within-group reduction of migraine frequency and intensity of 33 and 42%, respectively, at one month follow-up (60). A 2nd Australian study that was the only RCT including a control group, i.e., detuned ultrasound, found a within-group reduction of migraine frequency and duration of 35 and 40%, respectively, at two months follow-up in the CSMT group, compared with a within-group reduction of 17 and 20% in the control group, respectively (61). The reduction in migraine days are comparable to those seen in our study (mean 40%) in the CSMT group from baseline to three months follow-up, whereas the migraine duration and intensity were less reduced at three months follow-up, i.e., mean 21 and 14%, respectively (123).

As compared to our study, all previous manual-therapy studies on headache, whether by RCT or not, lack a placebo arm which naturally should be conceived
as an inert treatment, and a control group which continued usual management (64). This limitation should be eliminated in order to be able to calculate the net effect of an active intervention and similarly quantify the placebo response (155).

Two of the three RCTs included several investigators which introduce inter-observer variability (58-60). This naturally also questions the enthusiasm, known as allegiance bias, which commonly relates to RCTs with multiple investigators and thus, affects the internal validity and consequently the comparative treatment effects (156, 157). In comparison, our enthusiasm was enforced to be neutral as we in addition to monitoring efficacy, we similarly validated blinding. Thus, if skewed patient-provider interaction was present, it would result in disclosing the blinding.

The two participants in the CSMT group who developed MOH during the trial period might have affected the results negatively as MOH patients tend to be resistant to therapy (158).

Therefore, considering our study design, diagnostic certainty, long term follow-up period and strong internal validity, it allows us to interpret the effects observed in the CSMT and placebo groups for this patient group, with reasonable certainty, as a placebo response.

7.2.2 Paper III

Although most manual-therapy RCTs are pragmatic, a few manual-therapy studies have included a placebo intervention as a control (141), i.e., for mechanical neck pain (159, 160), lower back pain (161-165), and primary dysmenorrhoea (166, 167). However, all these studies omitted validation of the blinding. Thus, whether the placebo group was concealed throughout the trial remains unknown.

Two previous manual-therapy RCTs that included participants with headache have applied placebo but in a single treatment session (139, 140). The first study included children naive to SMT who either received an HVLA manipulation by a
general practitioner without rotation or alternatively, a light touch, i.e., placebo, at the affected specific spinal segment (139). Approximately 20% of the children in both groups were unable to tell whether they had received active treatment or placebo, with the remainder guessing the correct treatment 50% of the time in both groups. Thus, blinding was ascertained. The second experimental study applied active treatment followed by placebo (sham intervention) and placebo followed by a placebo intervention (140). Both interventions were given in a single treatment session. The active treatment was applied on the side of the lesion, followed by placebo applied on the other side, i.e., a touch near the target region with positioning of the head and neck, movement and sound timed with treatment delivery that mimicked the active treatment. Correct intervention was anticipated by approximately 50% of the participants in each of the two groups. Thus, blinding was ascertained.

Although it has been suggested that only 50% of subjects believe that they have received active treatment in each group if the blinding is perfect in a pharmacological double-blinded placebo-controlled RCT (116), this belief may not hold true in manual-therapy RCTs because the physical stimulus may be more convincing than a tablet (151, 168). Furthermore, to truly validate the blinding, one must monitor the participant’s belief throughout a full intervention period to eliminate the possibility of blinding occurring by chance.

In both previously mentioned studies, the light touch was directed to the affected area, which might have generated an afferent input because the intervention was placed near the target area (142-144). Thus, the placebo intervention might not constitute a true placebo because placebo is usually conceived as an inert treatment. Applying both active and placebo treatments during the same treatment session is far from ideal in an RCT because such a design does not provide meaning in a pharmacological RCT. If the participants were to receive both treatments during a pharmacological RCT, each treatment would be given separately at different time periods, i.e., a cross-over RCT. One disadvantage of
cross-over RCTs is the carryover effect that may also play a role in manual-therapy studies (140).

Similarly, our placebo intervention could be criticized because it is natural to consider the palpatory procedures and the placebo sham contacts to elicit sensory stimulus to an anatomical area which give rise to an afferent signal (169, 170). However, although this is true, this assumption similarly appears to be unreasonable, considering that all of the placebo sham contacts were made outside the spinal column. One recent study reported increased stimulation of afferents with increased duration and amplitude of a spinal manipulation intervention compared with mobilization (143). Another study found no neurophysiological changes when grade-III mobilization was utilize in asymptomatic participants, i.e., the use of a large-amplitude rhythmic oscillating mobilization technique to the point of limitation in range of movement (144). While another study only found reflex surface electromyographic activity to occur after high-velocity low-amplitude SMT as compared to lower-velocity mobilization (142). Thus, we do not believe that our placebo intervention by itself had any effect other than a placebo effect.

The fact that we obtained significant success in blinding the participants might have occurred because we used interchangeable placebo contacts, but standardized for all participants at each intervention session, throughout the intervention period, but, similarly, we provided equal manual and oral interaction in terms of palpatory procedures and communication with the participants (115). Furthermore, our full-spine approach as performed in the CSMT group resembled the placebo intervention in terms of anatomical locations. Thus, it reduced the risk of disclosing the blinding if the participants were to exchange individual experiences (153).

### 7.2.3 Paper IV

Generally, few RCTs report AEs during a full treatment period (81). The few RCTs reporting AEs were all using the Diversified technique as a modality.
Hence, although few prospective RCTs have used the Gonstead technique, none have, to our knowledge, reported AEs. The fact that different AEs may occur with different interventions is similar to the fact that different pharmacological medications often have different AE profiles. Thus, in the absence AEs profiles in RCTs using the Gonstead method, it becomes difficult to compare AE profiles for the two most commonly used manual SMT interventions, i.e., Diversified and Gonstead. Furthermore, when the different RCTs that report AEs also lack consistency in terms of when and how they report AEs (73), it becomes clear that few RCTs are comparable in terms of AEs profile.

To our knowledge, only one previous RCT is comparable to ours that reported AEs after each intervention session and during the entire intervention period (92). The RCT reported mild and transient local tenderness (38%), muscle soreness (13%) and headache (11%), whereas tiredness was not recorded as an AE.

Two studies have reported AEs from treatment conducted on the entire spine, but they reported AEs only after one and two intervention sessions (86, 91). Five studies were conducted exclusively on the cervical spine (87-90, 92), whereas the remaining studies reporting AEs included two observational cohort studies (89, 90), and one prospective survey (88).

Our RCT reported fewer AEs than previous studies but with similar transient and mild characteristics (86-92). Common AEs from previous studies included local tenderness (mean 26.4%; 95% CI 26.2-26.6) (86-92), and tiredness on the treatment day (mean 10.5%; 95% CI 10.4-10.6) (86, 87, 89, 90). Headache was interestingly reported as a common AE (mean 10.3%; 95% CI 10.2-10.4), likely because the previous CSMT studies primarily investigated neck pain and not headache (86-92).

This study and previous CSMT studies suggest that AEs are usually mild and transient and that severe and serious AEs are rare (106, 107). This AE rate is in accordance with WHO guidelines on basic training and safety in CSMT that
consider it to be an safe treatment modality (85). However, it is certain that this and previous prospective manual-therapy RCTs have been underpowered to detect uncommon AEs.

The risk for AEs in manual therapy appears furthermore to be substantially lower than what is accepted in any medical context for both acute and prophylactic migraine medication (171, 172). A previous RCT, assessing AEs after a pharmacological intervention, topiramate, reported paraesthesias (49%), fatigue (22%), anorexia (18%), diarrhoea (13%), nausea (13%), difficulty with memory (12%), weight loss (10%) and hypaesthesia (11%) (63). For metoprolol, AEs were drowsiness/sedation (28%), gastrointestinal symptoms (13%), sleep disturbances (13%), muscle fatigability (13%), weight gain (12%), dizziness (5%), depression (3%) (173), and for candesartan, AEs were respiratory tract infections (36%), dizziness (36%), bodily pain (20%), sleep problems (17%), tiredness (17%), bowel infection/diarrhoea (14%), reduced physical capacity (8%), nausea (8%), and skin problems/itching (6%) (174).

Thus, migraine prophylactic medication seems to cause many AEs that cannot be classified as mild and transient, while non-pharmacological management has also the advantage of no pharmacological interaction/AEs (175).
8 Innovative and scientific value

The socio-economic costs of migraine are enormous because of the high prevalence and disability during attacks reflected by the recent Global Burden of Disease study that ranked migraine as the 3rd most common condition (9). Our RCT did not provide evidence of CSMT’s superiority to placebo. The effects observed at post-treatment in all three groups continued in the CSMT and the placebo groups at three, six and 12 months follow-up, whereas migraine days returned to the baseline level in the control group. Although there was no significant difference between the three groups, the pairwise comparisons at individual time points showed significant differences between the CSMT and the control group at all time points beginning at post-treatment.

This finding is of importance because some migraineurs do not tolerate medication because of AEs or co-morbid disorders, whereas other migraineurs wish to avoid medication. Headache caused by the overuse of medication, i.e., medication-overused headache, is also important to alleviate. Thus, as primary care musculoskeletal experts, chiropractors can have an impact on this headache disorder therapeutically but can also function as advisors in close cooperation with the patient’s GP. Such multidisciplinary cooperation between these two professions is highly important in making today’s healthcare more efficient.

Strategically, this study could stimulate further scientific cooperation to confirm or dismiss uncertainties within musculoskeletal and headache disorders so as to provide the best available evidence for clinical practice. Such cooperation is highly warranted, considering that the Global Burden of Disease study ranks musculoskeletal problems and migraine among the top ten disabilities worldwide (9). A knowledge-sharing cooperation could eventually lead to a non-pharmacological management guideline that is highly necessary to sufficiently handle the common methodological challenges found in manual-therapy RCTs. Such a guideline should certainly follow the IHS clinical guidelines for headache disorders to obtain scientific acceptance across professional disciplines.
Furthermore, this doctoral thesis has managed to validate a placebo intervention in a prospective manual-therapy RCT. Many manual therapies, i.e., physiotherapy, chiropractic, and osteopathy, along with other practices, utilize spinal joint mobilization and manipulation in treating musculoskeletal pain and disability; thus, they all have the same common limitation; they lack a three-armed, single-blinded, placebo-controlled trial design. Our placebo procedure, including a brief de-blinding questionnaire, should therefore add to the methodological quality of future manual-therapy RCTs and may easily be replicated in future RCTs.

Finally, we have reported all AEs in a chiropractic SMT RCT. The results should contribute to confirm common AEs. Our results support the fact that the risk of common AEs in SMT RCTs appears to be substantially lower than what is accepted as common AEs in any medical context.
9 Conclusions

To our knowledge, this was the first prospective manual-therapy three-armed single-blinded placebo, RCT to be conducted for migraine. The RCT closely followed the recommendations from the International Headache Society and CONSORT, while the study design, which should be considered gold standard in manual-therapy RCTs, adhered to the recommendations for pharmacological RCTs as far as possible.

Our data suggest within-group efficacy for migraine days, migraine duration and headache index for the CSMT and placebo groups at all time points but with no significant group differences. Compared to groups with no intervention, there was clear improvement in the active groups. The study population consisted mostly of participants from tertiary health care; thus, replication of the study with a migraine population from primary health care and the general population that is naive to secondary and tertiary health care might change the results.

We managed to sustain blinding in the placebo group throughout the trial, which indicates that it is possible to have a valid placebo group. The de-blinding questionnaire was also found to be applicable, and we therefore believe that the sham procedure can easily be replicated in future manual-therapy RCTs to improve the methodological quality to the level of pharmacological RCTs.

The intervention was demonstrated to be safe with few mild and transient AEs, but similarly underpowered to detect uncommon serious AEs.

Although we conclude that the efficacy was likely caused by a placebo response, it might be considered in situations when other therapeutic options are either ineffective or poorly tolerated.
10 Errata

Correction added is marked in bold.

Page 32, section 5.10: CSMT, placebo and control groups were compared by Independent samples t-test, $\chi^2$-test and $z$-test.
References


86. Cagnie B, Vinck E, Beernaert A, Cambier D. How common are side effects of spinal manipulation and can these side effects be predicted? Man Ther. 2004;9(3):151-6.


133. Tramer MR, Reynolds DJ, Moore RA, McQuay HJ. When placebo controlled trials are essential and equivalence trials are inadequate. BMJ. 1998;317(7162):875-80.


156. Luborsky L, Singer B, Luborsky L. Comparative studies of psychotherapies: is it true that "everybody has won and all must have prizes"? Proceedings of the annual meeting of the American Psychopathological Association. 1976(64):3-22.


Appendix 1: ICHD-III diagnostic criteria

<table>
<thead>
<tr>
<th>Diagnostic criteria by the International Classification of Headache Disorders III β</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Migraine without aura</strong></td>
</tr>
<tr>
<td>A. At least 5 attacks fulfilling criteria B-D</td>
</tr>
<tr>
<td>B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)</td>
</tr>
<tr>
<td>C. Headache has at least two of the following four characteristics:</td>
</tr>
<tr>
<td>1. Unilateral location</td>
</tr>
<tr>
<td>2. Pulsating quality</td>
</tr>
<tr>
<td>3. Moderate or severe pain intensity</td>
</tr>
<tr>
<td>4. Aggravated by or causing avoidance of routine physical activity</td>
</tr>
<tr>
<td>D. During headache at least one of the following:</td>
</tr>
<tr>
<td>1. Nausea and/or vomiting</td>
</tr>
<tr>
<td>2. Photophobia and phonophobia</td>
</tr>
<tr>
<td>E. Not better accounted for by another ICHD-3 diagnosis</td>
</tr>
<tr>
<td><strong>Probable migraine without aura</strong></td>
</tr>
<tr>
<td>A. Attacks fulfilling all but one of criteria A–D for 1.1 Migraine without aura</td>
</tr>
<tr>
<td>B. Not fulfilling ICHD-3 criteria for any other headache disorder</td>
</tr>
<tr>
<td>C. Not better accounted for by another ICHD-3 diagnosis</td>
</tr>
<tr>
<td><strong>Migraine with aura</strong></td>
</tr>
<tr>
<td>A. At least 2 attacks fulfilling criteria B and C</td>
</tr>
<tr>
<td>B. One or more of the following fully reversible aura symptoms:</td>
</tr>
<tr>
<td>1. Visual</td>
</tr>
<tr>
<td>2. Sensory</td>
</tr>
<tr>
<td>3. Speech and/or language</td>
</tr>
<tr>
<td>4. Motor</td>
</tr>
<tr>
<td>5. Brainstem</td>
</tr>
<tr>
<td>6. Retinal</td>
</tr>
<tr>
<td>C. At least two of the following four characteristics:</td>
</tr>
<tr>
<td>1. At least one aura symptom spreads gradually over ≥5 minutes, and/or two or more symptoms occur in succession</td>
</tr>
<tr>
<td>2. Each individual aura symptom last 5-60 minutes</td>
</tr>
<tr>
<td>3. At least one aura symptom is unilateral</td>
</tr>
<tr>
<td>4. The aura is accompanied, or followed within 60 minutes, by headache</td>
</tr>
<tr>
<td>D. Not better accounted for by another ICHD-3 diagnosis, and transient ischaemic attack has been excluded</td>
</tr>
<tr>
<td><strong>Probable migraine with aura</strong></td>
</tr>
<tr>
<td>A. Attacks fulfilling all but one of criteria A–C for 1.2 Migraine with aura or any of its subforms</td>
</tr>
<tr>
<td>B. Not fulfilling ICHD-3 criteria for any other headache disorder</td>
</tr>
<tr>
<td>C. Not better accounted for by another ICHD-3 diagnosis</td>
</tr>
</tbody>
</table>
Appendix 2: The semi-structured interview

<table>
<thead>
<tr>
<th>INTERVIEW</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Serial number</td>
</tr>
<tr>
<td>2. Initials</td>
</tr>
<tr>
<td>3. Assessment date/day/month/year</td>
</tr>
<tr>
<td>4. Time</td>
</tr>
</tbody>
</table>

**INFORMATION ABOUT THE STUDY**

| 5. Written and oral information about the study has been given |
| 6. The headache diary has been explicitly gone through |

**MIGRAINE**

| 7. Migraine without aura (MO) |
| 8. Debut age of MO in years |
| 9. Average number days/months with MO the last 3 months |
| 10. Precisely, how many days/month have you had MO on average the last 3 months, |
| 11. Number of days with MO during the last year |
| 12. Precisely, how many days have you had MO the last year, |
| 13. Number of attacks with MO during the last year |
| 14. Precisely, how many MO attacks have you had the last year |
| 15. Average duration per MO attack |
| 16. How painful is the MO on a VAS |
| 17. Unilateral |
| 18. Pulsating |
| 19. Moderate/severe |
| 20. Provoked by physical activity |
| 21. Nausea |
| 22. Vomiting |
| 23. Photophobia |
| 24. Phonophobia |
| 25. Side location Left Right Shifting |

**Migraine with aura (MA)**

| 26. Debut age of MA in years |
| 27. Average number days/months with MA the last 3 months |
| 29. Precisely, how many days/month have you had MA on average the last 3 months, |
| 30. Number of days with MA during the last year |
| 31. Precisely, how many days have you had MA the last year, |

*Translated from the Norwegian original version*
### Number of attacks with MA during the last year

- 1 attack
- 2-4 attacks
- 5-9 attacks
- 10-49 attacks
- 50-99 attacks
- ≥ 100 attacks

### Average duration per MA attack

- < 30 min
- 30 min - <4 hours
- 4 - <24 hours
- 1 - <3 days
- 3 - <7 days
- ≥ 7 days

### Painful MA on a VAS

- 0-10

### Unilateral

- Yes
- No

### Pulsting

- Yes
- No

### Moderate/severe

- Yes
- No

### Provoked by physical activity

- Yes
- No

### Nausea

- Yes
- No

### Photophobia

- Yes
- No

### Phonophobia

- Yes
- No

### Side location location

- Left
- Right
- Shifting

### AURA

- Yes
- No

### Migraine aura without headache

- Yes
- No

### Migraine Disability Assessment (MIDAS)

#### MO

- 1a
- 1b
- 0

#### MA

- 2a
- 2b
- 1-5

- 3a
- 3b
- 6-10

- 4a
- 4b
- 11-20

- 5a
- 5b
- ≥ 21

### How many days the last

- 1a
- 1b
- 0

- 2a
- 2b
- 1-5

- 3a
- 3b
- 6-10

- 4a
- 4b
- 11-20

### Do not include days from Q1

- 5a
- 5b
- ≥ 21

### How many days the last

- 1a
- 1b
- 0

- 2a
- 2b
- 1-5

- 3a
- 3b
- 6-10

- 4a
- 4b
- 11-20

### Housekeeping due to headache

- 5a
- 5b
- ≥ 21

### How many days the last

- 1a
- 1b
- 0

- 2a
- 2b
- 1-5

- 3a
- 3b
- 6-10

- 4a
- 4b
- 11-20

### (Do not include days from Q3)

- 5a
- 5b
- ≥ 21

### How many days the last

- 1a
- 1b
- 0

- 2a
- 2b
- 1-5

- 3a
- 3b
- 6-10

- 4a
- 4b
- 11-20

### Activities due to headache

- 5a
- 5b
- ≥ 21

### TENSION-TYPE HEADACHE (TTH)

- Yes
- No

### Debut age of TTH in years

- Age

### Average number days/months with TTH the last 3 months

- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9
- ≥ 21

### Days

### Precisely, how many days/month have you had TTH on average the last 3 months

- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9
- ≥ 21

### Number of days with TTH during the last year

- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9
- ≥ 21

### Days

### Precisely, how many days have you had TTH the last year

- Days

*Translated from the Norwegian original version*
61. Average duration per TTH

<table>
<thead>
<tr>
<th></th>
<th>&lt; 30min.</th>
<th>30 min~&lt;4 hours</th>
<th>4~&lt;24 hours</th>
<th>1~&lt;3 days</th>
<th>3~7 days</th>
<th>≥ 7 days</th>
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62. How painful is the TTH on a VAS

<table>
<thead>
<tr>
<th></th>
<th>0~10</th>
<th>11~20</th>
<th>21~30</th>
<th>31~40</th>
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63. Bilateral

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64. If no, side location?

<table>
<thead>
<tr>
<th></th>
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65. Pressing/tightening

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66. Mild/moderate pain

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67. Daily activity not inhibited

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68. Nausea

<table>
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69. Vomiting

<table>
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70. Photophobia

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<tr>
<th></th>
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<th>No</th>
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</thead>
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<tr>
<td>1</td>
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</table>

71. Phonophobia

<table>
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<tr>
<th></th>
<th>Yes</th>
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**HEALTH CARE CONTACT AND TREATMENT EFFECT**

72. Have you had contact with:

<table>
<thead>
<tr>
<th>MO</th>
<th>Effected treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>No</td>
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</tbody>
</table>

73. Physician

<table>
<thead>
<tr>
<th>1a</th>
<th>1b</th>
<th>2a</th>
<th>2b</th>
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</thead>
<tbody>
<tr>
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</table>

74. Neurologist

<table>
<thead>
<tr>
<th>1a</th>
<th>1b</th>
<th>2a</th>
<th>2b</th>
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<tbody>
<tr>
<td>☐</td>
<td>☐</td>
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</table>

75. Other secondary professionals

If yes to Q75, please specify:

76. Hospital

<table>
<thead>
<tr>
<th>1a</th>
<th>1b</th>
<th>2a</th>
<th>2b</th>
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<tbody>
<tr>
<td>☐</td>
<td>☐</td>
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**OTHER TREATMENT MODALITIES**

84. Hospital

<table>
<thead>
<tr>
<th>la</th>
<th>1b</th>
<th>2a</th>
<th>2b</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
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</table>

**PHYSICAL ANAMNESIS**

112. Have you now or previously been experiencing pain in:

<table>
<thead>
<tr>
<th></th>
<th>Neck</th>
<th>Mid back</th>
<th>Low back</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
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</tbody>
</table>

113. Have you now or previously been experiencing radiating pain in arms?

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

114. Have you now or previously been experiencing radiating pain in legs?

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

*Translated from the Norwegian original version*
115. Have you ever been exposed for whiplash injury? (quick acceleration followed by de-acceleration)  
Yes ☐ No ☐

If yes:
116. Did you experience headache within the following 7 days?  ☐ Yes ☐ No ☐

117. When was you exposed for whiplash? Age

118. Has the headache persisted in more than 3 months?  ☐ Yes ☐ No ☐

119. Do you use insole for leg length discrepancy?  ☐ Yes ☐ No ☐

120. Do you use insole for flatfoot?  ☐ Yes ☐ No ☐

121. If yes, do you use insole in all your shoes?  ☐ Yes ☐ No ☐

**PHYSICAL ASSESSMENT**

122. Normal somatic assessment  ☐ Yes ☐ No ☐

123. Normal neurological assessment  ☐ Yes ☐ No ☐

124. Weight kg

125. Height cm

**Passive range of motion in neck**

126. Flexion ☐°

127. Extension ☐°

128. Lateral flexion sin. ☐°

129. Lateral flexion dxt. ☐°

130. Rotation sin. ☐°

131. Rotation dxt. ☐°

**RELEVANT HEADACHE MEDICATION**

<table>
<thead>
<tr>
<th>NSAIDs</th>
<th>Name</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>a.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c.</td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Acute</th>
<th>Name</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>a.</td>
<td></td>
<td></td>
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<tr>
<td>b.</td>
<td></td>
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<tr>
<td>c.</td>
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<table>
<thead>
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<td></td>
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<tr>
<td>b.</td>
<td></td>
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<tr>
<td>c.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Other</th>
<th>Name</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>a.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b.</td>
<td></td>
<td></td>
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<tr>
<td>c.</td>
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</tbody>
</table>

*Translated from the Norwegian original version*
# Appendix 3: Headache diary

<table>
<thead>
<tr>
<th>Serial number:</th>
<th>Initials:</th>
<th>Date:</th>
<th>/</th>
<th>/</th>
<th>/</th>
<th>/</th>
<th>/</th>
<th>/</th>
</tr>
</thead>
<tbody>
<tr>
<td>When did the headache start? Indicate nearest hour:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Prior to the headache commenced</td>
<td>vision:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>any disturbances of:</td>
<td>numbness/tingling in skin:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>other disturbances:</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was the headache:</td>
<td>right sided:</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>left sided:</td>
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<td></td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>on both sides:</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Was the headache:</td>
<td>pulsating/throbbing:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>tightening/pressing:</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>worst imaginable pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>How intense was the headache?</td>
<td>(Please mark with an straight line)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did the headache change by routine physical activity?</td>
<td>aggravated:</td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td>unchanged:</td>
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<tr>
<td></td>
<td>improved:</td>
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<td></td>
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</tr>
<tr>
<td>Was the headache accompanied with nausea?</td>
<td>no:</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>mild:</td>
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<td></td>
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<tr>
<td></td>
<td>moderate:</td>
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<td></td>
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<tr>
<td></td>
<td>severe:</td>
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</tr>
<tr>
<td>Was the headache accompanied with light sensitivity?</td>
<td>no:</td>
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<tr>
<td></td>
<td>mild:</td>
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<tr>
<td></td>
<td>moderate:</td>
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<td></td>
<td>severe:</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Was the headache accompanied with sound sensitivity?</td>
<td>no:</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>mild:</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>moderate:</td>
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<td></td>
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<tr>
<td></td>
<td>severe:</td>
<td></td>
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</tr>
<tr>
<td>When did the headache stop? Indicate nearest hour:</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>How many hours did you have headache this day?</td>
<td></td>
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</tr>
<tr>
<td>Were there any triggers for the headache?</td>
<td>what:</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>name:</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>dose:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did you take any medications?</td>
<td>time:</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Please record name, dose and time.</td>
<td>name:</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>dose:</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>time:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Sick leave</td>
<td>yes/no:</td>
<td></td>
<td></td>
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*Translated from the Norwegian original version*
Appendix 4: De-blinding questionnaire

De-blinding questionnaire

Serial number: □□□□□□
Initials: □□□□□□
Date of questioning: □□□□□□
Time: □□□□□□

1. Do you believe you received active treatment? Yes □ No □

2. How certain are you that active treatment was received on a 0-10 numeric rating scale (NRS), where 0 represents absolutely uncertain and 10 represents absolutely certainty □□ 0-10

*Translated from the Norwegian original version
## Appendix 5: Adverse event scheme

### Part I – Adverse event (AE) form - Chiropractic spinal manipulative therapy for migraines

<table>
<thead>
<tr>
<th>Serial number</th>
<th>Initials</th>
<th>Date of questions</th>
<th>Time:</th>
</tr>
</thead>
</table>

Has the participant had any AEs since last treatment?  
[ ] Yes  [ ] No  
(If yes, please list all AEs below)

<table>
<thead>
<tr>
<th>Severity</th>
<th>Study Intervention Relationship</th>
<th>Action Taken Regarding Study Intervention</th>
<th>Outcome of AE</th>
<th>Expected</th>
<th>Serious</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 = Mild</td>
<td>1 = Definitely related</td>
<td>1 = None</td>
<td>1 = Resolved, No Sequel</td>
<td>1 = Yes</td>
<td>1 = Yes</td>
</tr>
<tr>
<td>2 = Moderate</td>
<td>2 = Possibly related</td>
<td>2 = Discontinued permanently</td>
<td>2 = AE still present- no treatment</td>
<td>2 = No</td>
<td>2 = No</td>
</tr>
<tr>
<td>3 = Severe</td>
<td>3 = Not related</td>
<td>3 = Discontinued temporarily</td>
<td>3 = AE still present-being treated</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 = Reduced Dose</td>
<td>4 = Residual effects present-not treated</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 = Increased Dose</td>
<td>5 = Residual effects present- treated</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 = Delayed Dose</td>
<td>6 = Death</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7 = Unknown</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Start Date</th>
<th>Stop Date</th>
<th>Severity</th>
<th>Relationship to Study Treatment</th>
<th>Action Taken</th>
<th>Outcome of AE</th>
<th>Expected</th>
<th>Serious Adverse Event?</th>
<th>Initials</th>
</tr>
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<tbody>
<tr>
<td>1.</td>
<td></td>
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<td>2.</td>
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<td>3.</td>
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<tr>
<td>Part II – Serious adverse event (SAE) form - chiropractic spinal manipulative therapy for migraineurs</td>
<td></td>
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<tr>
<td>Serial number:</td>
<td>Initials:</td>
<td>Date of questions:</td>
<td>Time:</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>1. SAE Onset Date: ______________________ (dd/mm/yyyy)</td>
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<tr>
<td>2. SAE Stop Date: ______________________  (dd/mm/yyyy)</td>
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</tr>
<tr>
<td>3. Location of serious adverse event: __________________________</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>4. Was this an unexpected adverse event?  Yes</td>
<td>NO</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Brief description of participant(s) with no personal identifiers:  Sex:  F</td>
<td>M</td>
<td>Age: ______</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>6. Brief description of the nature of the serious adverse event (attach description if more space needed):</td>
<td></td>
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<tr>
<td>7. Category of the serious adverse event:</td>
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<tr>
<td>death – date ______ (dd/mm/yyyy)</td>
<td>congenital anomaly / birth defect</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>life-threatening</td>
<td>required intervention to prevent permanent injury</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>hospitalization-initial or prolonged</td>
<td>other</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>disability / incapacity</td>
<td></td>
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<tr>
<td>8. Intervention type:</td>
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<tr>
<td>Medication or Nutritional Supplement: specify ______</td>
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<tr>
<td>Devices: Specify:</td>
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<td>Surgery: Specify:</td>
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<td>Behavior/Self Care: Specify:</td>
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<td>9. Relationship of event to intervention:</td>
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<td>Unrelated (clearly not related to the intervention)</td>
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<td>Possible (may be related to intervention)</td>
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<td>Definite (clearly related to intervention)</td>
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<td>10. Was study intervention discontinued due to event?  Yes</td>
<td>No</td>
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<td>11. What medications or other steps were taken to treat serious adverse event?</td>
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<td>12. List any relevant tests, laboratory data, history, including preexisting medical conditions</td>
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<td>13. Type of report:</td>
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<td>Initial</td>
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<td>Follow-up</td>
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<td>Final</td>
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<td>Signature of Principal Investigator: ______________________ Date: ______</td>
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