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Complete List of Authors:	Chaibi, Aleksander; Research Centre, Head and Neck Research Group Šaltytė Benth, Jūratė; Akershus University Hospital, Head and Neck Research Group, Research Centre Tuchin, Peter; Macquarie University, Department of Chiropractic Russell, Michael; Akershus University Hospital, Head and Neck Research Group, Research Centre
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Chiropractic spinal manipulative therapy for migraine: A study protocol of a single-blinded placebo-controlled randomized clinical trial.

Aleksander Chaibi[1,2], BPT, MChiro, PhD stud; Jūratė Šaltytė Benth[2,3], MMathStat, PhD; Peter J. Tuchin[4], Associate professor, BSc, GradDipChiro, DipOHS, PhD, FACC; Michael Bjørn Russell[1,2], professor, MD, PhD, DrMedSci

[1]Head and Neck Research Group, Research Centre, Akershus University Hospital, 1478 Lørenskog, Norway, [2]Institute of Clinical Medicine, Akershus University Hospital, University of Oslo, 1474 Nordbyhagen, Norway, [3]HØKH, Research Centre, Akershus University Hospital, Lørenskog, Norway, [4]Department of Chiropractic, Macquarie University, NSW 2109, Australia

Correspondence:

Aleksander Chaibi

BPT, MChiro, PhD student

Head and Neck Research Group

Research Centre

Akershus University Hospital

1478 Lørenskog

Norway

aleksander.chaibi@medisin.uio.no

Key words

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Abstract

Introduction: Migraine affects 15% of the population, and has substantial health and socioeconomic costs. Pharmacological management is first-line treatment. However, acute and/or prophylactic medicine might not be tolerated due to side effects or contraindications. Thus, we aim to assess the efficacy of chiropractic spinal manipulative therapy (CSMT) for migraineurs in a single-blinded placebo-controlled randomized clinical trial (RCT).

Method and analysis: According to the power calculations, 90 participants are needed in the RCT. Participants will be randomized into one of three groups; CSMT, placebo (sham manipulation) and control (usual non-manual management). The RCT consists of three stages: 1 month run-in, 3 months intervention and follow-up analyses at the end of intervention and 3, 6 and 12 months. Primary end-point is headache frequency, while headache duration, headache intensity, headache index (frequency x duration x intensity) and medicine consumption are secondary end-points. Primary analysis will assess a change in headache frequency from baseline to the end of intervention and to follow-up, where the groups CSMT and placebo and CSMT and control will be compared. Due to two group-comparisons, p-values below 0.025 will be considered statistically significant. The results will be presented with the corresponding p-values and 95% confidence intervals (CI).

Ethics and dissemination: The RCT will follow the clinical trial guidelines from the International Headache Society. The Norwegian Regional Committee for Medical Research Ethics and the Norwegian Social Science Data Services has approved the project. Procedure will be conducted according to the declaration of Helsinki. The results will be published at scientific meetings and in peer-reviewed journals.

Trial registration: ClinicalTrials.gov identifier: NCT01741714, 2. December 2012.

Article summary

Strengths and limitations of the randomized controlled trial

- The study will be the first three-armed manual therapy RCT assessing the efficacy of chiropractic spinal manipulative therapy (CSMT) vs. placebo (sham manipulation) and control (usual non-manual management) for migraine.
- Strong internal validity, since a single chiropractor will conduct all interventions.
- The RCT has the potential to provide a non-pharmacological treatment option for migraine.
- Risk for drop-outs is increased due to strict exclusion criteria and 16 months duration of the RCT.
- A general accepted placebo has not been established for manual therapy, thus, there is a risk for unsuccessful blinding, while the investigator whom provides the interventions cannot be blinded for obvious reasons.

Background

Migraine is a common health problem with substantial health and socioeconomic costs. On the recent Global Burden of Disease study, migraine where ranked as the 3rd most common conditions.[1] About 15% of the general population have migraine.[2 3] Migraine is usually unilateral with pulsating and moderate/severe headache which is aggravated by routine physical activity, and is accompanied by photo- and phonophobia, nausea and sometimes vomiting.[4] Migraine exists in two major forms, migraine without aura (MO) and migraine with aura (MA) (Table 1). Aura is reversible neurological disturbances of the vision, sensory, and/or speech function, which occurring prior to the headache. However, intra-individual variations from attack to attack are common.[5 6] The origin of migraine is debated. The painful impulses may origin from the trigeminal nerve, central and/or peripheral mechanisms.[7 8] Extracranial pain sensitive structures include skin, muscles, arteries, periosteum and joints. The skin is sensitive to all usual forms of pain stimuli, while especially temporal and neck muscles may be sources for pain and tenderness in migraine.[9-11] Similarly, the frontal supraorbital, superficial temporal, posterior and occipital arteries are sensitive to pain.[9 12]

Pharmacological management is the first treatment option for migraine. However, some patients do not tolerate acute and/or prophylactic medicine, due to side effects or contraindications due to co-morbidity of other diseases or wish to avoid medication for other reasons. The risk of medication overuse due to frequent migraine attacks represents a major health hazard with both direct and indirect cost concerns. The prevalence of medication overuse headache (MOH) is 1-2% in the general population,[13-15] i.e. about half the population suffering chronic headache (15 headache days or more per month) have MOH.[16] Migraine causes loss of 270 workdays per year per 1,000 persons from the general population.[17] This corresponds to about 3,700 work years lost per year in Norway due to migraine. The economic cost per migraineur was estimated to be $655 in USA and €579 in Europe per year.[18 19] Due to the high prevalence of migraine, the total cost per year was estimated to be $14.4 billion in the USA and €27 billion in the EU countries, Iceland, Norway and Switzerland at that time. Migraine costs more than neurological disorders such as dementia, multiple sclerosis, Parkinson's disease and stroke.[20] Thus, non-pharmacological treatment options are warranted.

Diversified technique and Gonstead method are the two most used chiropractic manipulative treatment modalities, used by 91% and 59% respectively,[21 22] along with other manual and non-manual interventions, i.e. soft tissue techniques, spinal and peripheral mobilization, rehabilitation, postural corrections and exercises as well as general nutrition and dietetic advises.

A few spinal manipulative therapy (SMT) randomized controlled trials (RCTs) using the Diversified technique have been conducted for migraine, suggesting an effect on headache frequency, headache

duration, headache intensity and medicine consumption.[23-26] However, common for previous RCTs are the methodological shortcomings such as; inaccurate headache diagnosis, i.e. questionnaire diagnoses used are imprecise,[27] inadequate or no randomization procedure, lack of placebo group, inadequate and no validation of blinding concealment of participants, and primary and secondary end-points not pre-specified.[28-31] In addition, previous RCTs did not consequently adhere to the recommended clinical guidelines from the International Headache Society (IHS).[32 33] At present, no RCTs have applied the Gonstead CSMT method. Thus, considering the methodological shortcomings in previous RCTs, a clinical placebo-controlled RCT with improved methodological quality remains to be conducted for migraine.

The SMT mechanism of action on migraine is unknown. It is argued that migraine might originate from a complexity of nociceptive afferent responses involving the upper cervical spine (C1, C2 and C3), leading to a hypersensitivity state of the trigeminal pathway conveying sensory information for the face and much of the head.[34 35] Research has thus, suggested that SMT may stimulate neural inhibitory systems at different spinal cord levels, as well as it might activates various central descending inhibitory pathways.[36-40] However, although the proposed physiological mechanisms are not fully understood, there are likely additional unexplored mechanisms which could explain the effect of SMT has on mechanical pain sensitisation.

The objective is to investigate the efficacy of CSMT vs. placebo (sham manipulation) and controls (usual non-manual management) for migraine in a RCT.

Method and design

This is a single-blinded placebo-controlled RCT with three parallel groups (CSMT, placebo and control). Our primary hypothesis is that CSMT gives at least 25% reduction in average number of headache days as compared to placebo and control from baseline to the end of intervention and we expect the reduction to be maintained at 3, 6 and 12 months follow-up. If the CSMT treatment is effective, it will be offered to participants whom received placebo or control after study completion. The study will adhere to the recommended clinical trial guidelines from the IHS,[32 33] and the methodological CONSORT and SPIRIT guidelines.[41 42]

Patient population

Participants will be recruited through Akershus University Hospital, through general practitioners and media advertisement in Akershus and Oslo County, Norway, in the period January to September 2013.

Contact will first be made through posted mail followed by a short telephone interview. Eligible participants are 18 to 70 years old and have at least one migraine attack per month. Participants are diagnosed according to the diagnostic criteria of the International Classification of Headache Disorders (ICHD-II) by a neurologist.[43]

Exclusion criteria are contraindication to SMT, radiculopathy, pregnancy, depression and CSMT within the previous 12 months. Participants whom during the RCT receive any manual interventions by physiotherapists, chiropractors, osteopaths or other health professionals to treat musculoskeletal pain and disability, and includes massage therapy, joint mobilization and manipulation,[44] changed their prophylactic headache medicine or pregnancy will be excluded from the time of the violation.

In response to initial contact, participants fulfilling the inclusion criteria will be invited to further assessment by the chiropractic investigator. The assessment includes an interview and a physical examination with special emphasis on the whole spinal column. Oral and written information about the project will be provided in advance and oral and written consent will be obtained from all accepted participants during the interview. In accordance with good clinical practice, all patients will be informed about the harms and benefits as well as possible adverse reaction of the intervention primarily including local tenderness and tiredness on the treatment day. No serious adverse events have been reported for the chiropractic Gonstead method.[45 46] Participants randomized into active or placebo interventions, will undergo a full spine radiographic examination and be scheduled for 12 intervention sessions. The control group which do not receive intervention will not be exposed to this assessment.

Clinical randomized controlled trial

The clinical RCT consist of 1 month run-in and 3 months intervention. Outcome analyses will be performed at the end of intervention and at 3, 6 and 12 months follow-up (Figure 1).

Run-in

One-month headache diary will be used as baseline data for all participants.[47 48] X-rays will be taken in standing position in the anterior-posterior and lateral planes of the entire spine. The x-rays will be assessed by the chiropractic investigator.

Randomization

Prepared sealed lots with the three interventions i.e. active treatment, placebo and the control group, will be subdivided into four subgroups by age and gender i.e. woman and men, 18-39 years and 40-70 years. Participants will be equally allocated to the three groups and the participant is only

allowed to draw one lot. The blocked randomization will be administrated by an external trained receptionist without the involvement from the chiropractic investigator.

Intervention

Active treatment is Gonstead CSMT.[21] A specific contact, high velocity, low amplitude, short lever, with no recoil post spinal adjustment directed to spinal biomechanical dysfunction diagnosed by standard chiropractic tests.

Placebo will be achieve through a sham manipulation, i.e. a broad non-specific contact, low velocity, low amplitude sham push manoeuvre in a non-directional line. All the non-intentional placebo contacts will be performed with adequate joint slack so no joint cavitations occur and outside the spinal column. Participant will lay either prone on a Zenith 2010 HYLO bench were the investigators left hand are placed on the participants right scapula with the other hand reinforced over, or the investigator place his right palm over the participants left scapula and left hand reinforced over, delivering a non-directional lateral push manoeuvre. Alternatively, the participant lay in the same side posture position as the active treatment group with the bottom leg straight and top leg flexed with top legs ankle resting on the bottom legs knee fold, preparing a side posture push move, delivering a non-directional push in the gluteal region. The sham manipulation alternatives will be systematically interchanged according to protocol during the 12 weeks treatment period to strengthen validity. Both the active and placebo group will receive the same structural and motion assessment prior to and after each intervention. No additional co-interventions or advises will be given to participants during the trial period. The treatment period will include 12 consultations, i.e. twice per week the first three weeks followed by once a week the next two and once every second week until 12 weeks are reached. Fifteen minutes will be allocated per consultation for each participant. All interventions will be administered by an experienced chiropractor (AC).

Blinding

Participants whom receive active or placebo will fill in a de-blinding questionnaire after each of the 12 treatment sessions administrated by an external trained independent receptionist with no involvement from the investigator. The first question regards whether active treatment was received ("yes" and "no"), while the second question regards how strongly the participant believe active treatment was received on numeric rating scale 0-10, where 0 represents absolutely uncertain and 10 represents absolutely certain. The control group and the investigator can for obvious reasons not be blinded.[49 50]

Follow-up

Follow-up analysis will be conducted on the end-points measured after the end of intervention and 3, 6 and 12 months follow-up. During this period all participants will continue to fill in a diagnostic headache diary. Participants will be contacted by phone to secure compliance.

Primary and secondary end-points

The primary and secondary end-points are listed in Table 2. The end-points adhere to the recommended IHS clinical trial guidelines.[32 33] We define number of headache days to be a primary end-point and expect at least 25% reduction in average number of days from baseline to the end of intervention. In addition, we expect the reduction to maintain at follow-up. Based on previous reviews on migraine, a 25% reduction is considered to be a conservative estimate.[30] A 25% reduction is also expected in secondary end-points from baseline to the end of intervention and follow-up for headache duration, headache intensity, and headache index, where the index is calculated as mean days with headache (30 days) x mean headache duration (16 hours per day) x mean intensity (0-10 NRS), giving a maximum score of 4800 per month. While a 50% reduction in medication consumption from baseline to the end of intervention and to follow-up respectively is expected.

Data Processing

A flowchart of the participants is shown in Figure 2. Baseline demographic and clinical characteristics will be tabulated as means and standard deviations (SD) for continuous variables and proportions and percentages for categorical variables. Each of three groups will be described separately. Primary and secondary end-points will be presented by suitable descriptive statistics in each group and for each time point. Normality of end-points will be assessed graphically and log-transformation will be considered if necessary.

Change in primary and secondary end-points from baseline to the end of intervention and to follow-up will be compared between active and placebo and active and control group. Null-hypothesis is that there is no significant difference between the groups in average change from baseline to the end of intervention or to follow-up, while the alternative hypothesis states that a difference of at least 25% exists. Because of two group-comparisons in a primary end-point, p-values below 0.025 will be considered statistically significant.

The difference between the groups in change from baseline to the end of intervention will be assessed by a t-test for independent samples. Due to follow-up period, repeated recordings of primary and secondary end-points will be available, and trend analyses will be of primary interest. Intra-individual correlations (cluster effect) are likely to be present in data with repeated

measurements. Cluster effect will thus be assessed by calculating intra-class correlation coefficient (ICC) quantifying the proportion of total variation attributable to the intra-individual variations. Then, trend in primary and secondary end-points will be assessed by a linear regression model for longitudinal data (mixed model) to correctly account for cluster effect. Mixed model also handles unbalanced data, enabling information from all patients to be included, i.e. also drop outs. Regression models with random effects for patients and fixed effects for time component will be estimated by SAS PROC MIXED procedure. Regression coefficients for each time point will then be calculated with the corresponding p-values and 95% CI.

Per-protocol and intention-to-treat analyses will be conducted as drop-outs and loss to follow-up will likely be present. All analyses will be performed by a statistician, blinded for group allocation and participants. All adverse effects will also be registered and presented. Participants who experience any sort of adverse effects during the trial period will be entitled to call the prime investigator on the project cell phone. The data will be analyzed with SPSS 22 and SAS v9.3.

Power calculation

Sample size calculations are based on the results in a recently published group comparison study on topiramate.[51] We hypothesize that the mean difference in reduction of number of days with headache per month between active and the placebo group is 2.5 days corresponding to reduction by 25%. The same difference is assumed between active and the control group. Standard deviation for reduction in each group is assumed to be equal 2.5. As two group-comparisons will be performed as primary analysis, we set a significance level at 0.025. A sample size of 20 patients is required in each group to detect a mean difference in reduction of 25% with 80% power. The investigators plan to recruit at least 30 patients in each group to allow for drop-outs. Thus, at least 90 participants will be needed to achieve statistical significance in primary end-point given the assumed difference is present.

Discussion

Methodological considerations

Current SMT RCTs on migraine suggest efficacy regarding headache frequency, duration and intensity. However, a firm conclusion requires clinical single-blinded placebo-controlled RCTs with few methodological shortcomings.[30] Such studies should adhere to the recommended IHS clinical trial guidelines with headache frequency as primary end-point and headache duration, headache intensity, headache index and medication consumption as secondary end-point.[32 33] Headache index,

combination of 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, thus, we included this as a secondary outcome.[33 52 53] The primary and secondary end-points will be collected prospectively in a validated headache diary for all participants in order to minimize recalling bias.[47 48] To our knowledge, this is the first prospective manual therapy three-armed single-blinded placebo-controlled RCT to be conducted for migraine. The study design adheres to the recommendations for pharmacological RCTs as far as possible. RCTs that include a placebo and control group are advantageous to pragmatic RCTs that compare two active treatment arms. RCTs also provide the best approach for producing safety as well as efficacy data.

An unsuccessful blinding is a possible risk to the RCT. Blinding is often difficult as there is no single validated standardized chiropractic sham intervention which can be used as a control group to this date. It is however, necessary to include a placebo group in order to produce a true net effect of the active intervention. Consensus about an appropriate placebo for a clinical trial of SMT among experts representing both clinicians and academics has, however, not be reached.[54] No previous studies have to our knowledge, validated a successful blinding of a CSMT clinical trial with multiple treatment sessions. We intend to minimize this risk by following the proposed protocol for the placebo group. The placebo response is furthermore high in both pharmacological and non-pharmacological clinical studies and might be higher in manual therapy interventions were attention and physical contact is involved.[55] Similarly, a natural concern with regards to attention bias will be involved for the control group as they are not being seen by anyone or not seen as much as the other two groups.

There are always risks for drop-outs due to various reasons. As the trial duration is 16 months with a 12 months follow-up period, the risk for loss to follow-up is enhanced. Co-occurrence of other manual intervention during the trial period is another possible risk, as those whom receive manipulation or other manual physical treatments elsewhere during the trial period will be excluded at the time of violation. Participants are allowed to continue their usual medication throughout the trial.

The external validity of the RCT might be a weakness as there is only one investigator. However, we found that advantageous to multiple investigators, in order to provide similar information to participants in all three groups and manual intervention in the two active groups. Thus, we intend to eliminate inter-observer variability which can be present if there are two or more investigators. Although the Gonstead method is the second most used technique among chiropractors, we do not see an issue of concern when it comes to generalizability and external validity.

The internal validity is however strong by having one investigator. It reduces the risk of potential selection, information and experimental biases. Furthermore, the diagnosis of all participants is

performed by experienced neurologists and not by questionnaires. A direct interview has higher sensitivity and specificity as compared to questionnaire.[27] Individual motivational factors which can influence participant's perception as well as personal preferences when treating are both reduced by having one investigator. In addition, the internal validity is further strengthened by a concealed validated randomization procedure. As age and genders may play a role in migraine, block randomization was found necessary to balances arms by age and gender in order to reduce possibly age and gender biases.

Conducting x-rays prior to the active and placebo interventions was found applicable in order to visualize posture, joint and disc integrity.[56 57] As the total x-ray radiation dose varies from 0.2-0.8 mSv, the radiation exposure was considered low.[58 59]

As we are unaware of the mechanisms of possible efficacy, and both spinal cord and central descending inhibitory pathways has been postulated, we found no reasons to exclude a full spine treatment approach for the intervention group. It has furthermore been postulated that pain in different spinal regions should not be regarded as separate disorders but rather a single entity.[60] Similarly, including a full spine approach limits the differentiations between the two active intervention groups. Thus, strengthen the likelihood of successful blinding in the placebo group being achieved. Similarly, all the placebo contacts will be performed outside the spinal column, thus, minimizing a possible spinal cord afferent input.

Innovative and scientific value

The RCT will highlight and validate the Gonstead CSMT for migraine which has not previously been studied. If CSMT proves to be efficient, it will provide a non-pharmacological treatment option. This is especially important as some migraineurs do not have efficacy of prescript acute and/or prophylactic medications, while others have non-tolerable side-effects or co-morbidity of other diseases that contradict medication while others wish to avoid medication for various reasons. Thus, if CSMT works, it can really have an impact on migraine. The study also bridge cooperation between chiropractors and physicians, which is important in order to make the healthcare more efficient. Finally, our method might be applied in future chiropractic and other manual therapy RCTs on headache.

Ethics and dissemination

Ethics

The study has been approved by the Norwegian Regional Committee for Medical Research Ethics (REK) (2010/1639/REK) and the Norwegian Social Science Data Services (11-77). The declaration of Helsinki is otherwise followed. All data will be anonymised while participants must give oral and written informed consent. Insurance is provided through "The Norwegian System of Compensation to Patients" (NPE) which is an independent national body, set up to process compensation claims from patients who have suffered an injury as a result of treatment under the Norwegian health service. A stopping rule was defined for withdrawing participants from this study in accordance with recommendations in the CONSORT extension for Better Reporting of Harms.[61] If a participant reports to their chiropractor or research staff a severe adverse event, he or she will be withdrawn from the study and referred to their General Practitioner or hospital emergency department depending on the nature of the event. The final dataset will be available to the primary investigator (AC), the independent and blinded statistician (JSB) and Study Director (MBR). Data will be stored in a locked cabinet at the Research Centre, Akershus University Hospital, Norway, for five years.

Dissemination

This project is due for completion three years after the start. Results will be published in peer-reviewed international scientific journals in accordance with the CONSORT 2010 Statement. Positive, negative, as well as inconclusive results will be published. In addition, a written lay summary of the results will be available to study participants on request. All authors should qualify for authorship according to the International Committee of Medical Journal Editors, 1997. Each author should have participated sufficiently in the work to take public responsibility for the content. The final decision on the order of authorship will be decided when the project has been finalised. The results from the study may, moreover, be presented as posters or oral presentations at national and/or international conferences.

Author Affiliations:

[1]Head and Neck Research Group, Research Centre, Akershus University Hospital, 1478 Lørenskog, Oslo, Norway (AC and MBR);

[2]Institute of Clinical Medicine, Akershus University Hospital, University of Oslo, 1474 Nordbyhagen, Oslo, Norway (AC, JSB, MBR);

[3]HØKH, Research Centre, Akershus University Hospital, 1478 Lørenskog, Oslo, Norway (JSB);

[4]Department of Chiropractic, Macquarie University, NSW 2109, Australia (PJT);

Authors' Contribution: AC and PJT had the original idea of the study. AC and MBR obtained funding. MBR planned the overall design. AC prepared the initial draft and PJT commented on the final version of the research protocol. JSB performed all the statistical analysis. AC, JSB, PJT and MBR was involved in the interpretation and assisted in revision and preparation of the manuscript. All authors have read and approved the final manuscript.

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Conflicts of Interests: All authors have completed the ICMJE uniform disclosure form and no conflicts of interest were reported for this study.

Ethical Approval: The Norwegian Regional Committee for Medical Research Ethics approved the project (ID of the approval: 2010/1639/REK).

Patient Consent: Obtained.

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Data Sharing Statement: The majority of data collected will be published. Any unpublished, de-identified data will be made available on request.

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Table 1.

Diagnostic criteria for migraine without aura by the International Classification of Headache Disorders-II
A. At least 5 attacks fulfilling criteria B-D
B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)
C. Headache has at least two of the following characteristics:
1. Unilateral location
2. Pulsating quality
3. Moderate or severe pain intensity
4. Aggravated by or causing avoidance of routine physical activity
D. During headache at least one of the following:
1. Nausea and/or vomiting
2. Photophobia and phonophobia
E. Not attributed to another disorder

Diagnostic criteria for migraine with aura by the International Classification of Headache Disorders-II
A. At least 2 attacks fulfilling criteria B-D
B. Aura consisting of at least one of the following, but no motor weakness:
1. fully reversible visual symptoms including positive features (i.e. flickering lights, spots or lines) and/or negative features (i.e. loss of vision)Moderate or severe pain intensity
2. fully reversible sensory symptoms including positive features (i.e. pins and needles) and/or negative features (i.e. numbness)
3. fully reversible dysphasic speech disturbance
C. At least two of the following:
1. Homonymous visual symptoms and/or unilateral sensory symptoms
2. At least one aura symptom develops gradually over ≥5 minutes and/or different aura symptoms occur in succession over ≥5 minutes
3. Each symptom lasts ≥5 and ≤60 minute
D. Headache fulfilling criteria B-D for 1.1 Migraine without aura begins during the aura or follows aura within 60 minutes
E. Not attributed to another disorder

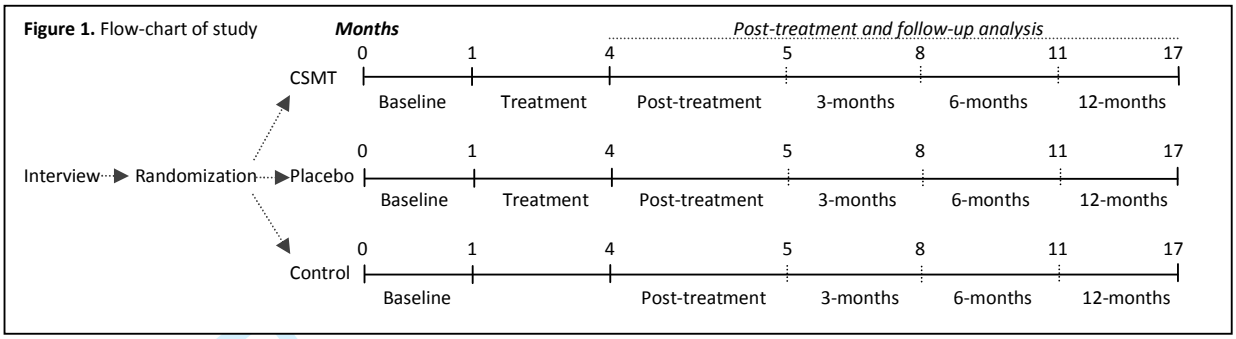
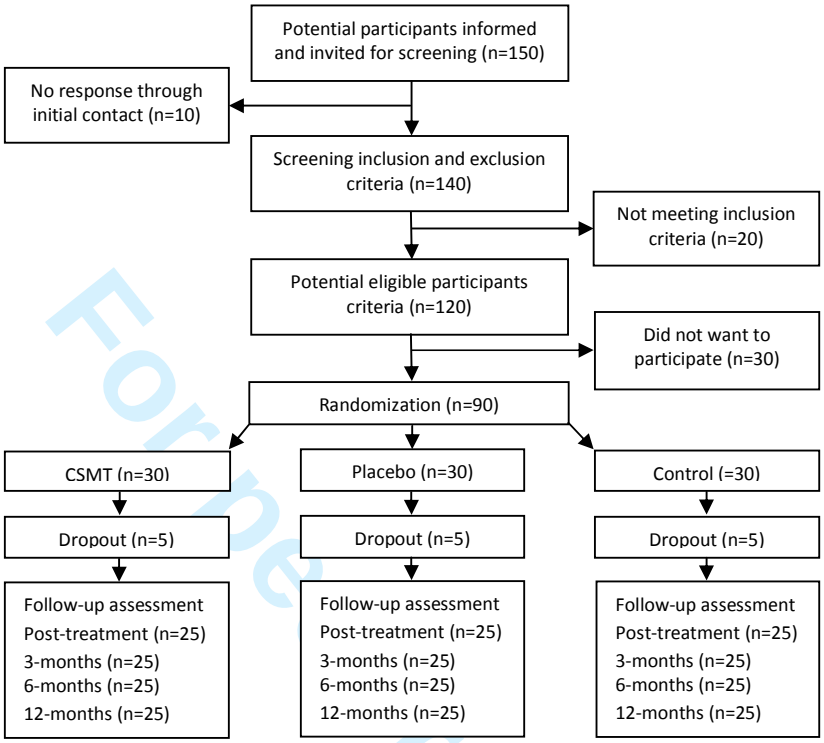


Figure 1. Flow-chart of study

Table 2. Primary and secondary end-points
Primary end-points
1. Number of headache days in active treatment vs. placebo group.
2. Number of headache days in active treatment vs. control group.
Secondary end-points
3. Headache duration in hours in active treatment vs. placebo group.
4. Headache duration in hours in active treatment vs. control group.
5. Self-reported VAS in active treatment vs. placebo group.
6. Self-reported VAS in active treatment vs. control group.
7. Headache index (frequency x duration x intensity) in active treatment vs. placebo group.
8. Headache index in active treatment vs. control group.
9. Headache medication dosage in active treatment vs. placebo group.
10. Headache medication dosage in active treatment vs. control group.

* The data analysis is based on the run-in period vs. end of intervention. Point 11-40 is a duplicate of point 1-10 above at respectively 3, 6 and 12 months follow-up.

Figure 2. Expected participants flow diagram



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Reported on page NO
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	14
	5b	Name and contact information for the trial sponsor	Supplied in ICMJE form by AC
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Supplied in ICMJE form by AC
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5,6

	6b	Explanation for choice of comparators	6
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7, Figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10, Figure 2
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6,7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7,8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7,8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7,8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	8
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9,10

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9,10,13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9,10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9,10
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9,10
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Supplied in ICMJE form by AC
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	13
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10,13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	All minor changes have been reported and approved by the Norwegian ethics committee prior to trial commenced.
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	14, Supplied in ICMJE form by AC
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	13
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13
	31b	Authorship eligibility guidelines and any intended use of professional writers	13

	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	13
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Chiropractic spinal manipulative therapy for migraine: A study protocol of a single-blinded placebo-controlled randomized clinical trial.

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Chiropractic spinal manipulative therapy for migraine: A study protocol of a single-blinded placebo-controlled randomized clinical trial.

Aleksander Chaibi[1,2], BPT, MChiro, PhD stud; Jūratė Šaltytė Benth[2,3], MMathStat, PhD; Peter J. Tuchin[4], Associate professor, BSc, GradDipChiro, DipOHS, PhD, FACC; Michael Bjørn Russell[1,2], professor, MD, PhD, DrMedSci

[1]Head and Neck Research Group, Research Centre, Akershus University Hospital, 1478 Lørenskog, Norway, [2]Institute of Clinical Medicine, Akershus University Hospital, University of Oslo, 1474 Nordbyhagen, Norway, [3]HØKH, Research Centre, Akershus University Hospital, Lørenskog, Norway, [4]Department of Chiropractic, Macquarie University, NSW 2109, Australia

Correspondence:

Aleksander Chaibi

BPT, MChiro, PhD student

Head and Neck Research Group

Research Centre

Akershus University Hospital

1478 Lørenskog

Norway

aleksander.chaibi@medisin.uio.no

Key words

Migraine, Headache, Randomized Controlled Trial, Chiropractic, Spinal Manipulation, Protocol

Abstract

Introduction: Migraine affects 15% of the population, and has substantial health and socioeconomic costs. Pharmacological management is first-line treatment. However, acute and/or prophylactic medicine might not be tolerated due to side effects or contraindications. Thus, we aim to assess the efficacy of chiropractic spinal manipulative therapy (CSMT) for migraineurs in a single-blinded placebo-controlled randomized clinical trial (RCT).

Method and analysis: According to the power calculations, 90 participants are needed in the RCT. Participants will be randomized into one of three groups; CSMT, placebo (sham manipulation) and control (usual non-manual management). The RCT consists of three stages: 1 month run-in, 3 months intervention and follow-up analyses at the end of intervention and 3, 6 and 12 months. Primary end-point is headache frequency, while headache duration, headache intensity, headache index (frequency x duration x intensity) and medicine consumption are secondary end-points. Primary analysis will assess a change in headache frequency from baseline to the end of intervention where the groups CSMT and placebo and CSMT and control will be compared. Due to two group-comparisons, p-values below 0.025 will be considered statistically significant. For all secondary end-points and analyses, p-value below 0.05 will be used. The results will be presented with the corresponding p-values and 95% confidence intervals (CI).

Ethics and dissemination: The RCT will follow the clinical trial guidelines from the International Headache Society. The Norwegian Regional Committee for Medical Research Ethics and the Norwegian Social Science Data Services has approved the project. Procedure will be conducted according to the declaration of Helsinki. The results will be published at scientific meetings and in peer-reviewed journals.

Trial registration: ClinicalTrials.gov identifier: NCT01741714, 2. December 2012.

Article summary

Strengths and limitations of the randomized controlled trial

- The study will be the first three-armed manual therapy RCT assessing the efficacy of chiropractic spinal manipulative therapy (CSMT) vs. placebo (sham manipulation) and control (continue usual pharmacological management without receiving manual intervention) for migraineurs.
- Strong internal validity, since a single chiropractor will conduct all interventions.
- The RCT has the potential to provide a non-pharmacological treatment option for migraine.
- Risk for drop-outs is increased due to strict exclusion criteria and 17 months duration of the RCT.
- A general accepted placebo has not been established for manual therapy, thus, there is a risk for unsuccessful blinding, while the investigator whom provides the interventions cannot be blinded for obvious reasons.

Background

Migraine is a common health problem with substantial health and socioeconomic costs. On the recent Global Burden of Disease study, migraine where ranked as the 3rd most common conditions.[1] About 15% of the general population have migraine.[2 3] Migraine is usually unilateral with pulsating and moderate/severe headache which is aggravated by routine physical activity, and is accompanied by photo- and phonophobia, nausea and sometimes vomiting.[4] Migraine exists in two major forms, migraine without aura (MO) and migraine with aura (MA) (Table 1). Aura is reversible neurological disturbances of the vision, sensory, and/or speech function, which occurring prior to the headache. However, intra-individual variations from attack to attack are common.[5 6] The origin of migraine is debated. The painful impulses may origin from the trigeminal nerve, central and/or peripheral mechanisms.[7 8] Extracranial pain sensitive structures include skin, muscles, arteries, periosteum and joints. The skin is sensitive to all usual forms of pain stimuli, while especially temporal and neck muscles may be sources for pain and tenderness in migraine.[9-11] Similarly, the frontal supraorbital, superficial temporal, posterior and occipital arteries are sensitive to pain.[9 12]

Pharmacological management is the first treatment option for migraine. However, some patients do not tolerate acute and/or prophylactic medicine, due to side effects or contraindications due to co-morbidity of other diseases or wish to avoid medication for other reasons. The risk of medication overuse due to frequent migraine attacks represents a major health hazard with both direct and indirect cost concerns. The prevalence of medication overuse headache (MOH) is 1-2% in the general population,[13-15] i.e. about half the population suffering chronic headache (15 headache days or more per month) have MOH.[16] Migraine causes loss of 270 workdays per year per 1,000 persons from the general population.[17] This corresponds to about 3,700 work years lost per year in Norway due to migraine. The economic cost per migraineur was estimated to be $655 in USA and €579 in Europe per year.[18 19] Due to the high prevalence of migraine, the total cost per year was estimated to be $14.4 billion in the USA and €27 billion in the EU countries, Iceland, Norway and Switzerland at that time. Migraine costs more than neurological disorders such as dementia, multiple sclerosis, Parkinson's disease and stroke.[20] Thus, non-pharmacological treatment options are warranted. Diversified technique and Gonstead method are the two most commonly used chiropractic manipulative treatment modalities in the profession, used by 91% and 59% respectively,[21 22] along with other manual and non-manual interventions, i.e. soft tissue techniques, spinal and peripheral mobilization, rehabilitation, postural corrections and exercises as well as general nutrition and dietetic advises.

A few spinal manipulative therapy (SMT) randomized controlled trials (RCTs) using the Diversified technique have been conducted for migraine, suggesting an effect on headache frequency, headache duration, headache intensity and medicine consumption.[23-26] However, common for previous RCTs are the methodological shortcomings such as; inaccurate headache diagnosis, i.e. questionnaire diagnoses used are imprecise,[27] inadequate or no randomization procedure, lack of placebo group, inadequate and no validation of blinding concealment of participants, and primary and secondary end-points not pre-specified.[28-31] In addition, previous RCTs did not consequently adhere to the recommended clinical guidelines from the International Headache Society (IHS).[32 33] At present, no RCTs have applied the Gonstead CSMT method. Thus, considering the methodological shortcomings in previous RCTs, a clinical placebo-controlled RCT with improved methodological quality remains to be conducted for migraine.

The SMT mechanism of action on migraine is unknown. It is argued that migraine might originate from a complexity of nociceptive afferent responses involving the upper cervical spine (C1, C2 and C3), leading to a hypersensitivity state of the trigeminal pathway conveying sensory information for the face and much of the head.[34 35] Research has thus, suggested that SMT may stimulate neural inhibitory systems at different spinal cord levels, as well as it might activates various central descending inhibitory pathways.[36-40] However, although the proposed physiological mechanisms are not fully understood, there are likely additional unexplored mechanisms which could explain the effect SMT has on mechanical pain sensitisation.

The objective is to investigate the efficacy of CSMT vs. placebo (sham manipulation) and controls (continue usual pharmacological management without receiving manual intervention) for migraineurs in a RCT.

Method and design

This is a single-blinded placebo-controlled RCT with three parallel groups (CSMT, placebo and control). Our primary hypothesis is that CSMT gives at least 25% reduction in average number of headache days per month (30 days/month) as compared to placebo and control from baseline to the end of intervention. We expect the same reduction to maintain at 3, 6 and 12 months follow-up. If the CSMT treatment is effective, it will be offered to participants whom received placebo or control after study completion, i.e. after 12 months follow-up. The study will adhere to the recommended clinical trial guidelines from the IHS,[32 33] and the methodological CONSORT and SPIRIT guidelines.[41 42]

Patient population

Participants will be recruited in the period January to September 2013 through Akershus University Hospital, through general practitioners and media advertisement, i.e. poster with general information will be put up at general practitioners offices along with oral information, in Akershus and Oslo counties, Norway. Participants will receive posted information about the project followed by a short telephone interview. Participants recruited from the general practitioners offices will have to contact the clinical investigator whose contact details have been provided on the poster on order to obtain extensive information about the study.

Eligible participants are between 18 and 70 years of age and have at least one migraine attack per month. Participants are diagnosed according to the diagnostic criteria of the International Classification of Headache Disorders (ICHD-II) by a neurologist at Akershus University Hospital.[43] Participants are only allowed to have co-occurrence of tension-type headache and not other primary headaches.

Exclusion criteria are contraindication to SMT, spinal radiculopathy, pregnancy, depression and CSMT within the previous 12 months. Participants whom during the RCT receive any manual interventions by physiotherapists, chiropractors, osteopaths or other health professionals to treat musculoskeletal pain and disability, and includes massage therapy, joint mobilization and manipulation,[44] changed their prophylactic headache medicine or pregnancy will be excluded from the time of the violation. Participants are allowed to continue and change their usual acute migraine medication throughout the trial.

In response to initial contact, participants fulfilling the inclusion criteria will be invited to further assessment by the chiropractic investigator. The assessment includes an interview and a physical examination with special emphasis on the whole spinal column. Oral and written information about the project will be provided in advance and oral and written consent will be obtained from all accepted participants during the interview and by the clinical investigator. In accordance with good clinical practice, all patients will be informed about the harms and benefits as well as possible adverse reaction of the intervention primarily including local tenderness and tiredness on the treatment day. No serious adverse events have been reported for the chiropractic Gonstead method.[45 46] Participants randomized into active or placebo interventions, will undergo a full spine radiographic examination and be scheduled for 12 intervention sessions. The control group which do not receive intervention will not be exposed to this assessment.

Clinical randomized controlled trial

The clinical RCT consist of 1 month run-in and 3 months intervention. Outcome analyses will be performed at the end of intervention and at 3, 6 and 12 months follow-up (Figure 1).

Run-in

The participants will fill in a validated paper headache diary one month prior to intervention which will be used as baseline data for all participants.[47 48] The validated diary includes questions directly related to the primary and secondary end-points. X-rays will be taken in standing position in the anterior-posterior and lateral planes of the entire spine. The x-rays will be assessed by the chiropractic investigator.

Randomization

Prepared sealed lots with the three interventions i.e. active treatment, placebo and the control group, will be subdivided into four subgroups by age and gender i.e. 18-39 and 40-70 years of age and men and women, respectively. Participants will be equally allocated to the three groups and the participant is only allowed to draw one lot. The blocked randomization will be administrated by an external trained party with no involvement from the clinical investigator.

Intervention

Active treatment consist of CSMT using the Gonstead method,[21] 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.

The placebo intervention consist 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 will be performed outside the spinal column with adequate joint slack and without soft tissue pre-tension so no joint cavitations occur. In some sessions, the participant lay either 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 will stand at the participant's left side and place 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 lay in the same side posture position as the active treatment group with the bottom leg straight and top leg flexed with top legs ankle resting on the bottom leg's knee fold, in preparation for a side posture push move, which will be delivered as an a non-intentional push in the gluteal region. The sham manipulation alternatives will be equally interchanged among the placebo participant's according to protocol during the 12-week treatment period to strengthen the study validity. Both the active and the placebo group will receive the same structural and motion assessment prior to and after each

intervention. No additional co-interventions or advises will be given to participants during the trial period. The treatment period will include 12 consultations, i.e. twice per week the first three weeks followed by once a week the next two and once every second week until 12 weeks are reached. Fifteen minutes will be allocated per consultation for each participant. All interventions will be conducted at Akershus University Hospital and administered by an experienced chiropractor (AC). The control group will continue usual care, i.e. pharmacological management without receiving manual intervention by the clinical investigator. The same exclusion criteria apply for the control group during the whole study period.

Blinding

After each treatment session, the participants whom receive active or placebo will complete a de-blinding questionnaire administrated by an external 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), where 0 represents absolutely uncertain and 10 represents absolutely certainty. The control group and the clinical investigator can for obvious reasons not be blinded.[49 50]

Follow-up

Follow-up analysis will be conducted on the end-points measured after the end of intervention and 3, 6 and 12 months follow-up. During this period all participants will continue to fill in a diagnostic paper headache diary and return it on a monthly basis. Missing values will be obtained by contacting the participants immediately upon detection to minimize recalling bias. Participants will be contacted by phone to secure compliance.

Primary and secondary end-points

The primary and secondary end-points are listed in Table 2. The end-points adhere to the recommended IHS clinical trial guidelines.[32 33] We define number of headache days to be a primary end-point and expect at least 25% reduction in average number of days from baseline to the end of intervention. In addition, we expect the reduction to maintain at follow-up. Based on previous reviews on migraine, a 25% reduction is considered to be a conservative estimate.[30] A 25% reduction is also expected in secondary end-points from baseline to the end of intervention and follow-up for headache duration, headache intensity, and headache index, where the index is calculated as mean days with headache (30 days) x mean headache duration (hours per day) x mean intensity (0-10 NRS).

While a 50% reduction in medication consumption from baseline to the end of intervention and to follow-up respectively is expected.

Data Processing

A flowchart of the participants is shown in Figure 2. Baseline demographic and clinical characteristics will be tabulated as means and standard deviations (SD) for continuous variables and proportions and percentages for categorical variables. Each of three groups will be described separately. Primary and secondary end-points will be presented by suitable descriptive statistics in each group and for each time point. Normality of end-points will be assessed graphically and log-transformation will be considered if necessary.

Change in primary and secondary end-points from baseline to the end of intervention and to follow-up will be compared between active and placebo and active and control group. Null-hypothesis is that there is no significant difference between the groups in average change from baseline to the end of intervention, While the alternative hypothesis states that a difference of at least 25% exists. Because of two group-comparisons in the primary end-point, p-values below 0.025 will be considered statistically significant. For all secondary end-points and analyses, p-value below 0.05 will be used. The difference in change from baseline to the end of intervention between the groups will be assessed by a t-test for independent samples. Due to follow-up period, repeated recordings of primary and secondary end-points will be available, and analyses of trend in primary and secondary end-points will be of interest. Intra-individual correlations (cluster effect) are likely to be present in data with repeated measurements. Cluster effect will thus be assessed by calculating intra-class correlation coefficient (ICC) quantifying the proportion of total variation attributable to the intra-individual variations. Then, trend in end-points will be assessed by a linear regression model for longitudinal data (mixed model) to correctly account for cluster effect. Mixed model also handles unbalanced data, enabling information from all patients to be included, i.e. also drop outs. Regression models with fixed effects for time component and group allocation as well as the interaction between the two will be estimated. The interaction will quantify possible differences between groups regarding time trend in the end-points. Random effects for patients will be included to adjust the estimates for intra-individual correlations. The model will be estimated by SAS PROC MIXED procedure. Regression coefficients for each time point will then be calculated with the corresponding p-values and 95% CI.

No multivariate regression models will be estimated as there are no known confounders for migraine.

Per-protocol and intention-to-treat analyses will be conducted as drop-outs and loss to follow-up will likely be present. All analyses will be performed by a statistician, blinded for group allocation and participants. All adverse effects will also be registered and presented. Participants who experience any sort of adverse effects during the trial period will be entitled to call the clinical investigator on the project cell phone. The data will be analyzed with SPSS v22 and SAS v9.3.

Power calculation

Sample size calculations are based on the results in a recently published group comparison study on topiramate.[51] We hypothesize that the mean difference in reduction of number of days with headache per month between active and the placebo group is 2.5 days corresponding to reduction by 25%. The same difference is assumed between active and the control group. Standard deviation for reduction in each group is assumed to be equal 2.5. As two group-comparisons will be performed as primary analysis, we set a significance level at 0.025. A sample size of 20 patients is required in each group to detect a mean difference in reduction of 25% with 80% power. The investigators plan to recruit at least 30 patients in each group to allow for drop-outs. Thus, at least 90 participants will be needed to achieve statistical significance in primary end-point given the assumed difference is present.

Discussion

Methodological considerations

Current SMT RCTs on migraine suggest efficacy regarding headache frequency, duration and intensity. However, a firm conclusion requires clinical single-blinded placebo-controlled RCTs with few methodological shortcomings.[30] Such studies should adhere to the recommended IHS clinical trial guidelines with headache frequency as primary end-point and headache duration, headache intensity, headache index and medication consumption as secondary end-point.[32 33] Headache index, combination of 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, thus, we included this as a secondary outcome.[33 52 53] The primary and secondary end-points will be collected prospectively in a validated headache diary for all participants in order to minimize recalling bias.[47 48] To our knowledge, this is the first prospective manual therapy three-armed single-blinded placebo-controlled RCT to be conducted for migraine. The study design adheres to the recommendations for pharmacological RCTs as far as possible. RCTs that include a

placebo and control group are advantageous to pragmatic RCTs that compare two active treatment arms. RCTs also provide the best approach for producing safety as well as efficacy data.

An unsuccessful blinding is a possible risk to the RCT. Blinding is often difficult as there is no single validated standardized chiropractic sham intervention which can be used as a control group to this date. It is however, necessary to include a placebo group in order to produce a true net effect of the active intervention. Consensus about an appropriate placebo for a clinical trial of SMT among experts representing both clinicians and academics has, however, not be reached.[54] No previous studies have to our knowledge, validated a successful blinding of a CSMT clinical trial with multiple treatment sessions. We intend to minimize this risk by following the proposed protocol for the placebo group. The placebo response is furthermore high in pharmacological and assumed similar high for non-pharmacological clinical studies and might be higher in manual therapy interventions were attention and physical contact is involved.[55] Similarly, a natural concern with regards to attention bias will be involved for the control group as they are not being seen by anyone or not seen as much by the clinical investigator as the other two groups.

There are always risks for drop-outs due to various reasons. As the trial duration is 17 months with a 12 months follow-up period, the risk for loss to follow-up is enhanced. Co-occurrence of other manual intervention during the trial period is another possible risk, as those whom receive manipulation or other manual physical treatments elsewhere during the trial period will be excluded at the time of violation.

The external validity of the RCT might be a weakness as there is only one investigator. However, we found that advantageous to multiple investigators, in order to provide similar information to participants in all three groups and manual intervention in the two active groups. Thus, we intend to eliminate inter-observer variability which can be present if there are two or more investigators. Although the Gonstead method is the second most commonly used technique among chiropractors, we do not see an issue of concern when it comes to generalizability and external validity. As the majority of included participants are expected to be enrolled in the study from the Akershus Hospital, generalizability should not be an issue of concern. Furthermore, the blocked randomization procedure will provide for a homogenous sample size across the three groups.

The internal validity is however strong by having one treating clinician. It reduces the risk of potential selection, information and experimental biases. Furthermore, the diagnosis of all participants is performed by experienced neurologists and not by questionnaires. A direct interview has higher sensitivity and specificity as compared to questionnaire.[27] Individual motivational factors which can influence participant's perception as well as personal preferences when treating are both reduced by having one investigator. In addition, the internal validity is further strengthened by a concealed

validated randomization procedure. As age and genders may play a role in migraine, block randomization was found necessary to balances arms by age and gender in order to reduce possibly age and gender biases.

Conducting x-rays prior to the active and placebo interventions was found applicable in order to visualize posture, joint and disc integrity.[56 57] As the total x-ray radiation dose varies from 0.2-0.8 mSv, the radiation exposure was considered low.[58 59] X-ray assessments were also found necessary in order to determine if full spine x-rays are useful for future studies or not.

As we are unaware of the mechanisms of possible efficacy, and both spinal cord and central descending inhibitory pathways has been postulated, we found no reasons to exclude a full spine treatment approach for the intervention group. It has furthermore been postulated that pain in different spinal regions should not be regarded as separate disorders but rather a single entity.[60] Similarly, including a full spine approach limits the differentiations between the two intervention groups. Thus, strengthen the likelihood of successful blinding in the placebo group being achieved. Similarly, all the placebo contacts will be performed outside the spinal column, thus, minimizing a possible spinal cord afferent input.

Innovative and scientific value

The RCT will highlight and validate the Gonstead CSMT for migraine which has not previously been studied. If CSMT proves to be effective, it will provide a non-pharmacological treatment option. This is especially important as some migraineurs do not have efficacy of prescript acute and/or prophylactic medications, while others have non-tolerable side-effects or co-morbidity of other diseases that contradict medication while others wish to avoid medication for various reasons. Thus, if CSMT works, it can really have an impact on migraine. The study also bridge cooperation between chiropractors and physicians, which is important in order to make the healthcare more efficient. Finally, our method might be applied in future chiropractic and other manual therapy RCTs on headache.

Ethics and dissemination

Ethics

The study has been approved by the Norwegian Regional Committee for Medical Research Ethics (REK) (2010/1639/REK) and the Norwegian Social Science Data Services (11-77). The declaration of Helsinki is otherwise followed. All data will be anonymised while participants must give oral and written informed consent. Insurance is provided through "The Norwegian System of Compensation to Patients" (NPE) which is an independent national body, set up to process compensation claims from patients who have suffered an injury as a result of treatment under the Norwegian health service. A stopping rule was defined for withdrawing participants from this study in accordance with recommendations in the CONSORT extension for Better Reporting of Harms.[61] If a participant reports to their chiropractor or research staff a severe adverse event, he or she will be withdrawn from the study and referred to their General Practitioner or hospital emergency department depending on the nature of the event. The final dataset will be available to the clinical investigator (AC), the independent and blinded statistician (JSB) and Study Director (MBR). Data will be stored in a locked cabinet at the Research Centre, Akershus University Hospital, Norway, for five years.

Dissemination

This project is due for completion three years after the start. Results will be published in peer-reviewed international scientific journals in accordance with the CONSORT 2010 Statement. Positive, negative, as well as inconclusive results will be published. In addition, a written lay summary of the results will be available to study participants on request. All authors should qualify for authorship according to the International Committee of Medical Journal Editors, 1997. Each author should have participated sufficiently in the work to take public responsibility for the content. The final decision on the order of authorship will be decided when the project has been finalised. The results from the study may, moreover, be presented as posters or oral presentations at national and/or international conferences.

Author Affiliations:

[1]Head and Neck Research Group, Research Centre, Akershus University Hospital, 1478 Lørenskog, Oslo, Norway (AC and MBR);

[2]Institute of Clinical Medicine, Akershus University Hospital, University of Oslo, 1474 Nordbyhagen, Oslo, Norway (AC, JSB, MBR);

[3]HØKH, Research Centre, Akershus University Hospital, 1478 Lørenskog, Oslo, Norway (JSB);

[4]Department of Chiropractic, Macquarie University, NSW 2109, Australia (PJT);

Authors' Contribution: AC and PJT had the original idea of the study. AC and MBR obtained funding. MBR planned the overall design. AC prepared the initial draft and PJT commented on the final version of the research protocol. JSB performed all the statistical analysis. AC, JSB, PJT and MBR was involved in the interpretation and assisted in revision and preparation of the manuscript. All authors have read and approved the final manuscript.

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Conflicts of Interests: All authors have completed the ICMJE uniform disclosure form and no conflicts of interest were reported for this study.

Ethical Approval: The Norwegian Regional Committee for Medical Research Ethics approved the project (ID of the approval: 2010/1639/REK).

Patient Consent: Obtained.

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Data Sharing Statement: No additional data available.

Figure 1 Study flow chart. CSMT, chiropractic spinal manipulative therapy; Placebo, sham manipulation; Control, continue usual pharmacological management without receiving manual intervention.

Figure 2 Expected participant's flow diagram. CSMT, chiropractic spinal manipulative therapy; Placebo, sham manipulation; Control, continue usual pharmacological management without receiving manual intervention.

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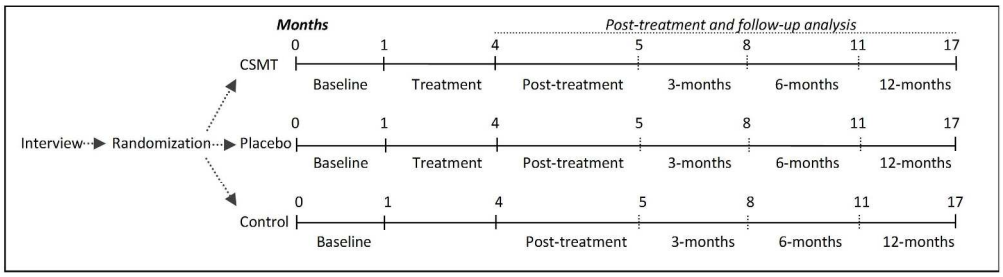
Table 1

Diagnostic criteria for migraine without aura by the International Classification of Headache Disorders-II	
A.	At least 5 attacks fulfilling criteria B-D
B.	Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)
C.	Headache has at least two of the following characteristics: 1. Unilateral location 2. Pulsating quality 3. Moderate or severe pain intensity 4. Aggravated by or causing avoidance of routine physical activity
D.	During headache at least one of the following: 1. Nausea and/or vomiting 2. Photophobia and phonophobia
E.	Not attributed to another disorder

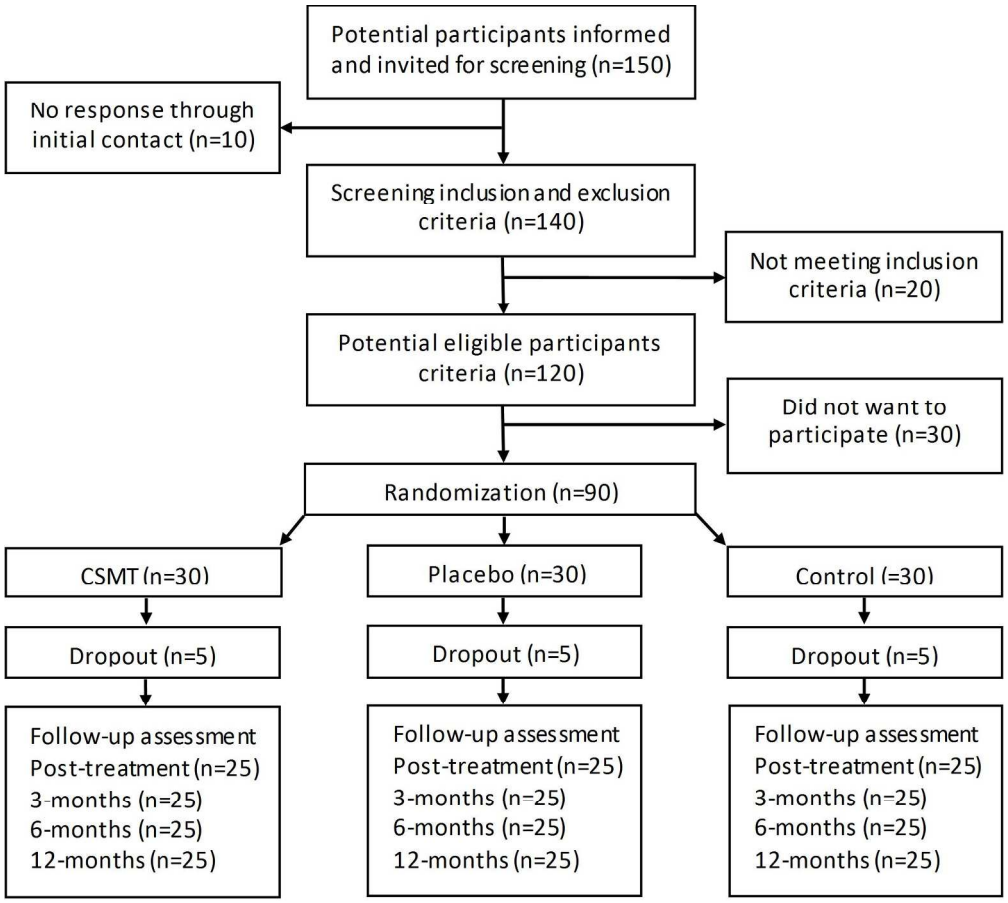
Diagnostic criteria for migraine with aura by the International Classification of Headache Disorders-II	
A.	At least 2 attacks fulfilling criteria B-D
B.	Aura consisting of at least one of the following, but no motor weakness: 1. fully reversible visual symptoms including positive features (i.e. flickering lights, spots or lines) and/or negative features (i.e. loss of vision)Moderate or severe pain intensity 2. fully reversible sensory symptoms including positive features (i.e. pins and needles) and/or negative features (i.e. numbness) 3. fully reversible dysphasic speech disturbance
C.	At least two of the following: 1. Homonymous visual symptoms and/or unilateral sensory symptoms 2. At least one aura symptom develops gradually over ≥5 minutes and/or different aura symptoms occur in succession over ≥5 minutes 3. Each symptom lasts ≥5 and ≤60 minute
D.	Headache fulfilling criteria B-D for 1.1 Migraine without aura begins during the aura or follows aura within 60 minutes
E.	Not attributed to another disorder

Table 2 Primary and secondary end-points
Primary end-points
1. Number of headache days in active treatment vs. placebo group.
2. Number of headache days in active treatment vs. control group.
Secondary end-points
3. Headache duration in hours in active treatment vs. placebo group.
4. Headache duration in hours in active treatment vs. control group.
5. Self-reported VAS in active treatment vs. placebo group.
6. Self-reported VAS in active treatment vs. control group.
7. Headache index (frequency x duration x intensity) in active treatment vs. placebo group.
8. Headache index in active treatment vs. control group.
9. Headache medication dosage in active treatment vs. placebo group.
10. Headache medication dosage in active treatment vs. control group.

* The data analysis is based on the run-in period vs. end of intervention. Point 11-40 is a duplicate of point 1-10 above at respectively 3, 6 and 12 months follow-up.



Study flow chart.
254x67mm (300 x 300 DPI)



Expected participant's flow diagram.
197x176mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Reported on page NO
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	14
	5b	Name and contact information for the trial sponsor	Supplied in ICMJE form by AC
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Supplied in ICMJE form by AC
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5,6

	6b	Explanation for choice of comparators	6
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7, Figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10, Figure 2
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6,7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7,8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7,8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7,8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	8
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9,10

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9,10,13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9,10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9,10
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9,10
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Supplied in ICMJE form by AC
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	13
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10,13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	All minor changes have been reported and approved by the Norwegian ethics committee prior to trial commenced.
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	14, Supplied in ICMJE form by AC
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	13
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13
	31b	Authorship eligibility guidelines and any intended use of professional writers	13

	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	13
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Chiropractic spinal manipulative therapy for migraine: A study protocol of a single-blinded placebo-controlled randomized clinical trial.

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Chiropractic spinal manipulative therapy for migraine: A study protocol of a single-blinded placebo-controlled randomized clinical trial.

Aleksander Chaibi[1,2], BPT, MChiro, PhD stud; Jūratė Šaltytė Benth[2,3], MMathStat, PhD; Peter J. Tuchin[4], Associate professor, BSc, GradDipChiro, DipOHS, PhD, FACC; Michael Bjørn Russell[1,2], professor, MD, PhD, DrMedSci

[1]Head and Neck Research Group, Research Centre, Akershus University Hospital, 1478 Lørenskog, Norway, [2]Institute of Clinical Medicine, Akershus University Hospital, University of Oslo, 1474 Nordbyhagen, Norway, [3]HØKH, Research Centre, Akershus University Hospital, Lørenskog, Norway, [4]Department of Chiropractic, Macquarie University, NSW 2109, Australia

Correspondence:

Aleksander Chaibi

BPT, MChiro, PhD student

Head and Neck Research Group

Research Centre

Akershus University Hospital

1478 Lørenskog

Norway

aleksander.chaibi@medisin.uio.no

Key words

Migraine, Headache, Randomized Controlled Trial, Chiropractic, Spinal Manipulation, Protocol

Abstract

Introduction: Migraine affects 15% of the population, and has substantial health and socioeconomic costs. Pharmacological management is first-line treatment. However, acute and/or prophylactic medicine might not be tolerated due to side effects or contraindications. Thus, we aim to assess the efficacy of chiropractic spinal manipulative therapy (CSMT) for migraineurs in a single-blinded placebo-controlled randomized clinical trial (RCT).

Method and analysis: According to the power calculations, 90 participants are needed in the RCT. Participants will be randomized into one of three groups; CSMT, placebo (sham manipulation) and control (usual non-manual management). The RCT consists of three stages: 1 month run-in, 3 months intervention and follow-up analyses at the end of intervention and 3, 6 and 12 months. Primary end-point is headache frequency, while headache duration, headache intensity, headache index (frequency x duration x intensity) and medicine consumption are secondary end-points. Primary analysis will assess a change in headache frequency from baseline to the end of intervention and follow-up, where the groups CSMT and placebo and CSMT and control will be compared. Due to two group-comparisons, p-values below 0.025 will be considered statistically significant. For all secondary end-points and analyses, p-value below 0.05 will be used. The results will be presented with the corresponding p-values and 95% confidence intervals (CI).

Ethics and dissemination: The RCT will follow the clinical trial guidelines from the International Headache Society. The Norwegian Regional Committee for Medical Research Ethics and the Norwegian Social Science Data Services has approved the project. Procedure will be conducted according to the declaration of Helsinki. The results will be published at scientific meetings and in peer-reviewed journals.

Trial registration: ClinicalTrials.gov identifier: NCT01741714, 2. December 2012.

Article summary

Strengths and limitations of the randomized controlled trial

- The study will be the first three-armed manual therapy RCT assessing the efficacy of chiropractic spinal manipulative therapy (CSMT) vs. placebo (sham manipulation) and control (continue usual pharmacological management without receiving manual intervention) for migraineurs.
- Strong internal validity, since a single chiropractor will conduct all interventions.
- The RCT has the potential to provide a non-pharmacological treatment option for migraineurs.
- Risk for drop-outs is increased due to strict exclusion criteria and 17 months duration of the RCT.
- A general accepted placebo has not been established for manual therapy, thus, there is a risk for unsuccessful blinding, while the investigator whom provides the interventions cannot be blinded for obvious reasons.

Background

Migraine is a common health problem with substantial health and socioeconomic costs. On the recent Global Burden of Disease study, migraine where ranked as the 3rd most common conditions.[1] About 15% of the general population have migraine.[2 3] Migraine is usually unilateral with pulsating and moderate/severe headache which is aggravated by routine physical activity, and is accompanied by photo- and phonophobia, nausea and sometimes vomiting.[4] Migraine exists in two major forms, migraine without aura (MO) and migraine with aura (MA) (Table 1). Aura is reversible neurological disturbances of the vision, sensory, and/or speech function, occurring prior to the headache. However, intra-individual variations from attack to attack are common.[5 6] The origin of migraine is debated. The painful impulses may origin from the trigeminal nerve, central and/or peripheral mechanisms.[7 8] Extracranial pain sensitive structures include skin, muscles, arteries, periosteum and joints. The skin is sensitive to all usual forms of pain stimuli, while especially temporal and neck muscles may be sources for pain and tenderness in migraine.[9-11] Similarly, the frontal supraorbital, superficial temporal, posterior and occipital arteries are sensitive to pain.[9 12]

Pharmacological management is the first treatment option for migraineurs. However, some patients do not tolerate acute and/or prophylactic medicine, due to side effects or contraindications due to co-morbidity of other diseases or wish to avoid medication for other reasons. The risk of medication overuse due to frequent migraine attacks represents a major health hazard with both direct and indirect cost concerns. The prevalence of medication overuse headache (MOH) is 1-2% in the general population,[13-15] i.e. about half the population suffering chronic headache (15 headache days or more per month) have MOH.[16] Migraine causes loss of 270 workdays per year per 1,000 persons from the general population.[17] This corresponds to about 3,700 work years lost per year in Norway due to migraine. The economic cost per migraineur was estimated to be $655 in USA and €579 in Europe per year.[18 19] Due to the high prevalence of migraine, the total cost per year was estimated to be $14.4 billion in the USA and €27 billion in the EU countries, Iceland, Norway and Switzerland at that time. Migraine costs more than neurological disorders such as dementia, multiple sclerosis, Parkinson's disease and stroke.[20] Thus, non-pharmacological treatment options are warranted. Diversified technique and Gonstead method are the two most commonly used chiropractic manipulative treatment modalities in the profession, used by 91% and 59% respectively,[21 22] along with other manual and non-manual interventions, i.e. soft tissue techniques, spinal and peripheral mobilization, rehabilitation, postural corrections and exercises as well as general nutrition and dietetic advises.

A few spinal manipulative therapy (SMT) randomized controlled trials (RCTs) using the Diversified technique have been conducted for migraine, suggesting an effect on headache frequency, headache duration, headache intensity and medicine consumption.[23-26] However, common for previous RCTs are the methodological shortcomings such as; inaccurate headache diagnosis, i.e. questionnaire diagnoses used are imprecise,[27] inadequate or no randomization procedure, lack of placebo group, inadequate and no validation of blinding concealment of participants, and primary and secondary end-points not pre-specified.[28-31] In addition, previous RCTs did not consequently adhere to the recommended clinical guidelines from the International Headache Society (IHS).[32 33] At present, no RCTs have applied the Gonstead CSMT method. Thus, considering the methodological shortcomings in previous RCTs, a clinical placebo-controlled RCT with improved methodological quality remains to be conducted for migraine.

The SMT mechanism of action on migraine is unknown. It is argued that migraine might originate from a complexity of nociceptive afferent responses involving the upper cervical spine (C1, C2 and C3), leading to a hypersensitivity state of the trigeminal pathway conveying sensory information for the face and much of the head.[34 35] Research has thus, suggested that SMT may stimulate neural inhibitory systems at different spinal cord levels, as well as it might activate various central descending inhibitory pathways.[36-40] However, although the proposed physiological mechanisms are not fully understood, there are likely additional unexplored mechanisms which could explain the effect SMT has on mechanical pain sensitisation.

The objective of this study is to assess the efficacy of CSMT vs. placebo (sham manipulation) and controls (continue usual pharmacological management without receiving manual intervention) for migraineurs in a RCT.

Method and design

This is a single-blinded placebo-controlled RCT with three parallel groups (CSMT, placebo and control). Our primary hypothesis is that CSMT gives at least 25% reduction in average number of headache days per month (30 days/month) as compared to placebo and control from baseline to the end of intervention, and we expect the same reduction to maintain at 3, 6 and 12 months follow-up. If the CSMT treatment is effective, it will be offered to participants whom received placebo or control after study completion, i.e. after 12 months follow-up. The study will adhere to the recommended clinical trial guidelines from the IHS,[32 33] and the methodological CONSORT and SPIRIT guidelines.[41 42]

Patient population

Participants will be recruited in the period January to September 2013 through Akershus University Hospital, through general practitioners and media advertisement, i.e. poster with general information will be put up at general practitioners offices along with oral information, in Akershus and Oslo counties, Norway. Participants will receive posted information about the project followed by a short telephone interview. Participants recruited from the general practitioners offices will have to contact the clinical investigator whose contact details have been provided on the poster in order to obtain extensive information about the study.

Eligible participants are between 18 and 70 years of age and have at least one migraine attack per month. Participants are diagnosed according to the diagnostic criteria of the International Classification of Headache Disorders (ICHD-II) by a neurologist at Akershus University Hospital.[43] Participants are only allowed to have co-occurrence of tension-type headache and not other primary headaches.

Exclusion criteria are contraindication to SMT, spinal radiculopathy, pregnancy, depression and CSMT within the previous 12 months. Participants whom during the RCT receive any manual interventions by physiotherapists, chiropractors, osteopaths or other health professionals to treat musculoskeletal pain and disability, and includes massage therapy, joint mobilization and manipulation,[44] changed their prophylactic headache medicine or pregnancy will be withdrawn from the study at that time and be regarded as drop-outs. Participants are allowed to continue and change their usual acute migraine medication throughout the trial.

In response to initial contact, participants fulfilling the inclusion criteria will be invited to further assessment by the chiropractic investigator. The assessment includes an interview and a physical examination with special emphasis on the whole spinal column. Oral and written information about the project will be provided in advance and oral and written consent will be obtained from all accepted participants during the interview and by the clinical investigator. In accordance with good clinical practice, all patients will be informed about the harms and benefits as well as possible adverse reactions of the intervention primarily including local tenderness and tiredness on the treatment day. No serious adverse events have been reported for the chiropractic Gonstead method.[45 46] Participants randomized into active or placebo interventions, will undergo a full spine radiographic examination and be scheduled for 12 intervention sessions. The control group will not be exposed to this assessment.

Clinical randomized controlled trial

The clinical RCT consist of 1 month run-in and 3 months intervention. Time profile will be assessed from baseline to end of follow-up for all end-points (Figure 1).

Run-in

The participants will fill in a validated diagnostic paper headache diary one month prior to intervention which will be used as baseline data for all participants.[47 48] The validated diary includes questions directly related to the primary and secondary end-points. X-rays will be taken in standing position in the anterior-posterior and lateral planes of the entire spine. The x-rays will be assessed by the chiropractic investigator.

Randomization

Prepared sealed lots with the three interventions i.e. active treatment, placebo and the control group, will be subdivided into four subgroups by age and gender i.e. 18-39 and 40-70 years of age and men and women, respectively. Participants will be equally allocated to the three groups by allowing the participant to draw one lot only. The block randomization will be administrated by an external trained party with no involvement from the clinical investigator.

Intervention

Active treatment consists of CSMT using the Gonstead method,[21] 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.

The placebo intervention consists 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 will be performed outside the spinal column with adequate joint slack and without soft tissue pre-tension so no joint cavitations occur. In some sessions, the participant lay either 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 will stand at the participant's left side and place 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 lay 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 will be delivered as a non-intentional push in the gluteal region. The sham manipulation alternatives will be equally interchanged among the placebo participant's according to protocol during the 12-week treatment period to strengthen the study validity. Both the active and the placebo group will receive the same structural and motion assessment prior to and after each

intervention. No additional co-interventions or advises will be given to participants during the trial period. The treatment period will include 12 consultations, i.e. twice per week the first three weeks followed by once a week the next two and once every second week until 12 weeks are reached. Fifteen minutes will be allocated per consultation for each participant. All interventions will be conducted at Akershus University Hospital and administered by an experienced chiropractor (AC). The control group will continue usual care, i.e. pharmacological management without receiving manual intervention by the clinical investigator. The same exclusion criteria apply for the control group during the whole study period.

Blinding

After each treatment session, the participants whom receive active or placebo will complete a de-blinding questionnaire administrated by an external 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), where 0 represents absolutely uncertain and 10 represents absolutely certainty. The control group and the clinical investigator can for obvious reasons not be blinded.[49 50]

Follow-up

Follow-up analysis will be conducted on the end-points measured after the end of intervention and 3, 6 and 12 months follow-up. During this period all participants will continue to fill in a diagnostic paper headache diary and return it on a monthly basis. In the case of unreturned diary or missing values in the diary, the participants will be contacted immediately upon detection to minimize recall bias. Participants will be contacted by phone to secure compliance.

Primary and secondary end-points

The primary and secondary end-points are listed in Table 2. The end-points adhere to the recommended IHS clinical trial guidelines.[32 33] We define number of headache days to be primary end-point and expect at least 25% reduction in average number of days from baseline to the end of intervention, with the same level of reduction maintaining at follow-up. Based on previous reviews on migraine, a 25% reduction is considered to be a conservative estimate.[30] A 25% reduction is also expected in secondary end-points from baseline to the end of intervention, retaining at follow-up for headache duration, headache intensity, and headache index, where the index is calculated as number of headache days (30 days) x average headache duration (hours per day) x average intensity

(0-10 NRS). A 50% reduction in medication consumption from baseline to the end of intervention and to follow-up is expected.

Data Processing

A flowchart of the participants is shown in Figure 2. Baseline demographic and clinical characteristics will be tabulated as means and standard deviations (SD) for continuous variables and proportions and percentages for categorical variables. Each of three groups will be described separately. Primary and secondary end-points will be presented by suitable descriptive statistics in each group and for each time point. Normality of end-points will be assessed graphically and transformation will be considered if necessary.

Change in primary and secondary end-points from baseline to the end of intervention and to follow-up will be compared between active and placebo and active and control group. Null-hypothesis states that there is no significant difference between the groups in average change, while the alternative hypothesis states that a difference of at least 25% exists. Because of two group-comparisons in the primary end-point, p-values below 0.025 will be considered statistically significant. For all secondary end-points and analyses, a significance level of 0.05 will be used.

Due to follow-up period, repeated recordings of primary and secondary end-points will be available, and analyses of trend in primary and secondary end-points will be of main interest. Intra-individual correlations (cluster effect) are likely to be present in data with repeated measurements. Cluster effect will thus be assessed by calculating intra-class correlation coefficient (ICC) quantifying the proportion of total variation attributable to the intra-individual variations. The trend in end-points will be assessed by a linear regression model for longitudinal data (linear mixed model) to correctly account for possible cluster effect. Linear mixed model handles unbalanced data, enabling all available information from randomized patients to be included, also from drop-outs. Regression models with fixed effects for time component and group allocation as well as the interaction between the two will be estimated. The interaction will quantify possible differences between groups regarding time trend in the end-points. Random effects for patients will be included to adjust the estimates for intra-individual correlations. Random slopes will be considered. The linear mixed models will be estimated by SAS PROC MIXED procedure. The results will be presented as averages estimated by the model at each time point within each group with the corresponding p-values and 95% CI.

Both per-protocol and intention-to-treat analyses will be conducted as drop-outs will likely be present. All analyses will be performed by a statistician, blinded for group allocation and participants. All adverse effects will also be registered and presented. Participants who experience any sort of

adverse effects during the trial period will be entitled to call the clinical investigator on the project cell phone. The data will be analyzed with SPSS v22 and SAS v9.3.

Power calculation

Sample size calculations are based on the results in a recently published group comparison study on topiramate.[51] We hypothesize that the average difference in reduction of number of days with headache per month between active and the placebo group is 2.5 days. The same difference is assumed between active and control group. Standard deviation for reduction in each group is assumed to be equal 2.5. Under the assumption of on average 10 headache 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, we set a significance level at 0.025. A sample size of 20 patients is required in each group to detect a statistically significant average difference in reduction of 25% with 80% power. To allow for drop-outs, the investigators plan to recruit 120 participants.

Discussion

Methodological considerations

Current SMT RCTs on migraine suggest treatment efficacy regarding headache frequency, duration and intensity. However, a firm conclusion requires clinical single-blinded placebo-controlled RCTs with few methodological shortcomings.[30] Such studies should adhere to the recommended IHS clinical trial guidelines with headache frequency as primary end-point and headache duration, headache intensity, headache index and medication consumption as secondary end-points.[32 33] Headache index, combination of 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.[33 52 53] The primary and secondary end-points will be collected prospectively in a validated diagnostic headache diary for all participants in order to minimize recall bias.[47 48] To our knowledge, this is the first prospective manual therapy three-armed single-blinded placebo-controlled RCT to be conducted for migraine. The study design adheres to the recommendations for pharmacological RCTs as far as possible. RCTs that include a placebo and control group are advantageous to pragmatic RCTs that compare two active treatment arms. RCTs also provide the best approach for producing safety as well as efficacy data.

An unsuccessful blinding is a possible risk to the RCT. Blinding is often difficult as there is no single validated standardized chiropractic sham intervention which can be used as a control group to this

date. It is however, necessary to include a placebo group in order to produce a true net effect of the active intervention. Consensus about an appropriate placebo for a clinical trial of SMT among experts representing both clinicians and academics has, however, not be reached.[54] No previous studies have to our knowledge, validated a successful blinding of a CSMT clinical trial with multiple treatment sessions. We intend to minimize this risk by following the proposed protocol for the placebo group. The placebo response is furthermore high in pharmacological and assumed similarly high for non-pharmacological clinical studies and might also be higher in manual therapy RCTs were attention and physical contact is involved.[55] Similarly, a natural concern with regards to attention bias will be involved for the control group as they are not being seen by anyone or not seen as much by the clinical investigator as the other two groups.

There are always risks for drop-outs due to various reasons. As the trial duration is 17 months with a 12 months follow-up period, the risk for loss to follow-up is thus enhanced. Co-occurrence of other manual intervention during the trial period is another possible risk, as those whom receive manipulation or other manual physical treatments elsewhere during the trial period will be withdrawn from the study and regarded as drop-outs at the time of violation.

The external validity of the RCT might be a weakness as there is only one investigator. However, we found that advantageous to multiple investigators, in order to provide similar information to participants in all three groups and manual intervention in the CSMT and the placebo group. Thus, we intend to eliminate inter-investigator variability which might be present if there are two or more investigators. Although the Gonstead method is the second most commonly used technique among chiropractors, we do not see an issue of concern when it comes to generalizability and external validity. As the majority of included participants are expected to be enrolled in the study from the Akershus University Hospital, generalizability should not be an issue of concern. Furthermore, the block randomization procedure will provide a homogenous sample across the three groups.

The internal validity is however strong by having one treating clinician. It reduces the risk of potential selection, information and experimental biases. Furthermore, the diagnosis of all participants is performed by experienced neurologists and not by questionnaires. A direct interview has higher sensitivity and specificity as compared to questionnaire.[27] Individual motivational factors which can influence participant's perception as well as personal preferences when treating are both reduced by having one investigator. In addition, the internal validity is further strengthened by a concealed validated randomization procedure. As age and genders may play a role in migraine, block randomization was found necessary to balance arms by age and gender in order to reduce possible age- and/or gender-related bias.

Conducting x-rays prior to the active and placebo interventions was found applicable in order to visualize posture, joint and disc integrity.[56 57] As the total x-ray radiation dose varies from 0.2-0.8 mSv, the radiation exposure was considered low.[58 59] X-ray assessments were also found necessary in order to determine if full spine x-rays are useful in future studies or not.

As we are unaware of the mechanisms of possible efficacy, and both spinal cord and central descending inhibitory pathways has been postulated, we see no reasons to exclude a full spine treatment approach for the intervention group. It has furthermore been postulated that pain in different spinal regions should not be regarded as separate disorders but rather a single entity.[60] Similarly, including a full spine approach limits the differentiations between the CSMT and the placebo group. Thus, strengthen the likelihood of successful blinding in the placebo group being achieved. In addition, all the placebo contacts will be performed outside the spinal column, thus, minimizing a possible spinal cord afferent input.

Innovative and scientific value

This RCT will highlight and validate the Gonstead CSMT for migraineurs which has not previously been studied. If CSMT proves to be effective, it will provide a non-pharmacological treatment option. This is especially important as some migraineurs do not have efficacy of prescript acute and/or prophylactic medications, while others have non-tolerable side-effects or co-morbidity of other diseases that contradict medication while others wish to avoid medication for various reasons. Thus, if CSMT works, it can really have an impact on migraine treatment. The study also bridges cooperation between chiropractors and physicians, which is important in order to make the healthcare more efficient. Finally, our method might be applied in future chiropractic and other manual therapy RCTs on headache.

Ethics and dissemination

Ethics

The study has been approved by the Norwegian Regional Committee for Medical Research Ethics (REK) (2010/1639/REK) and the Norwegian Social Science Data Services (11-77). The declaration of Helsinki is otherwise followed. All data will be anonymised while participants must give oral and written informed consent. Insurance is provided through "The Norwegian System of Compensation to Patients" (NPE) which is an independent national body, set up to process compensation claims from patients who have suffered an injury as a result of treatment under the Norwegian health service. A stopping rule was defined for withdrawing participants from this study in accordance with recommendations in the CONSORT extension for Better Reporting of Harms.[61] If a participant reports to their chiropractor or research staff a severe adverse event, he or she will be withdrawn from the study and referred to their General Practitioner or hospital emergency department depending on the nature of the event. The final dataset will be available to the clinical investigator (AC), the independent and blinded statistician (JSB) and Study Director (MBR). Data will be stored in a locked cabinet at the Research Centre, Akershus University Hospital, Norway, for five years.

Dissemination

This project is due for completion three years after the start. Results will be published in peer-reviewed international scientific journals in accordance with the CONSORT 2010 Statement. Positive, negative, as well as inconclusive results will be published. In addition, a written lay summary of the results will be available to study participants on request. All authors should qualify for authorship according to the International Committee of Medical Journal Editors, 1997. Each author should have participated sufficiently in the work to take public responsibility for the content. The final decision on the order of authorship will be decided when the project has been finalised. The results from the study may, moreover, be presented as posters or oral presentations at national and/or international conferences.

Author Affiliations:

[1]Head and Neck Research Group, Research Centre, Akershus University Hospital, 1478 Lørenskog, Oslo, Norway (AC and MBR);

[2]Institute of Clinical Medicine, Akershus University Hospital, University of Oslo, 1474 Nordbyhagen, Oslo, Norway (AC, JSB, MBR);

[3]HØKH, Research Centre, Akershus University Hospital, 1478 Lørenskog, Oslo, Norway (JSB);

[4]Department of Chiropractic, Macquarie University, NSW 2109, Australia (PJT);

Authors' Contribution: AC and PJT had the original idea of the study. AC and MBR obtained funding. MBR planned the overall design. AC prepared the initial draft and PJT commented on the final version of the research protocol. JSB performed all the statistical analysis. AC, JSB, PJT and MBR was involved in the interpretation and assisted in revision and preparation of the manuscript. All authors have read and approved the final manuscript.

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Conflicts of Interests: All authors have completed the ICMJE uniform disclosure form and no conflicts of interest were reported for this study.

Ethical Approval: The Norwegian Regional Committee for Medical Research Ethics approved the project (ID of the approval: 2010/1639/REK).

Patient Consent: Obtained.

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Data Sharing Statement: No additional data available.

Figure 1 Study flow chart. CSMT, chiropractic spinal manipulative therapy; Placebo, sham manipulation; Control, continue usual pharmacological management without receiving manual intervention.

Figure 2 Expected participant's flow diagram. CSMT, chiropractic spinal manipulative therapy; Placebo, sham manipulation; Control, continue usual pharmacological management without receiving manual intervention.

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Table 1

Diagnostic criteria for migraine without aura by the International Classification of Headache Disorders-II

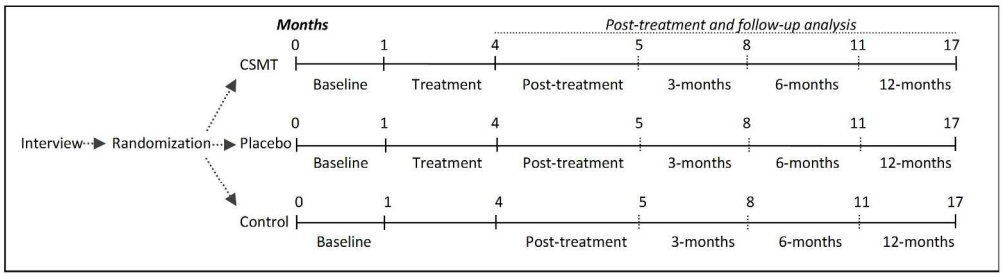
A. At least 5 attacks fulfilling criteria B-D
B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)
C. Headache has at least two of the following characteristics:
    1. Unilateral location
    2. Pulsating quality
    3. Moderate or severe pain intensity
    4. Aggravated by or causing avoidance of routine physical activity
D. During headache at least one of the following:
    1. Nausea and/or vomiting
    2. Photophobia and phonophobia
E. Not attributed to another disorder

Diagnostic criteria for migraine with aura by the International Classification of Headache Disorders-II

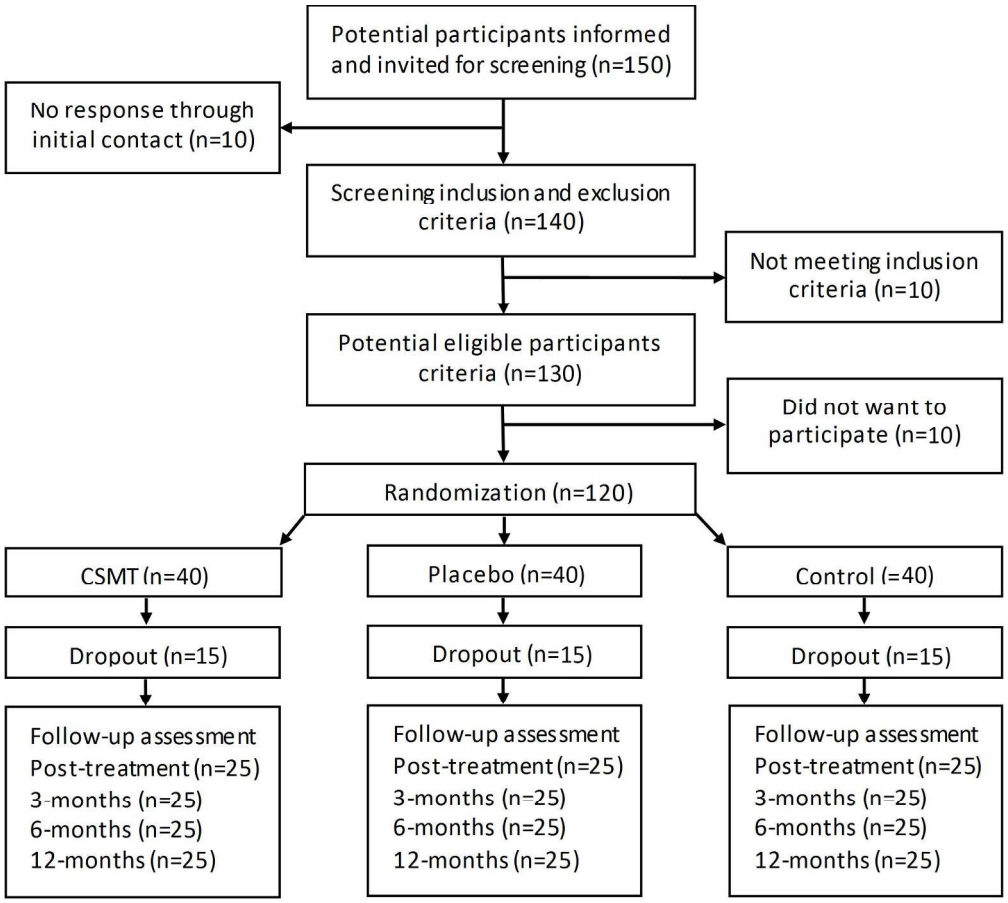
A. At least 2 attacks fulfilling criteria B-D
B. Aura consisting of at least one of the following, but no motor weakness:
    1. fully reversible visual symptoms including positive features (i.e. flickering lights, spots or lines) and/or negative features (i.e. loss of vision)Moderate or severe pain intensity
    2. fully reversible sensory symptoms including positive features (i.e. pins and needles) and/or negative features (i.e. numbness)
    3. fully reversible dysphasic speech disturbance
C. At least two of the following:
    1. Homonymous visual symptoms and/or unilateral sensory symptoms
    2. At least one aura symptom develops gradually over ≥5 minutes and/or different aura symptoms occur in succession over ≥5 minutes
    3. Each symptom lasts ≥5 and ≤60 minute
D. Headache fulfilling criteria B-D for 1.1 Migraine without aura begins during the aura or follows aura within 60 minutes
E. Not attributed to another disorder

Table 2 Primary and secondary end-points
Primary end-points
1. Number of headache days in active treatment vs. placebo group.
2. Number of headache days in active treatment vs. control group.
Secondary end-points
3. Headache duration in hours in active treatment vs. placebo group.
4. Headache duration in hours in active treatment vs. control group.
5. Self-reported VAS in active treatment vs. placebo group.
6. Self-reported VAS in active treatment vs. control group.
7. Headache index (frequency x duration x intensity) in active treatment vs. placebo group.
8. Headache index in active treatment vs. control group.
9. Headache medication dosage in active treatment vs. placebo group.
10. Headache medication dosage in active treatment vs. control group.

* The data analysis is based on the run-in period vs. end of intervention. Point 11-40 is a duplicate of point 1-10 above at respectively 3, 6 and 12 months follow-up.



Study flow chart.
254x67mm (300 x 300 DPI)



Expected participant's flow diagram.
197x176mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Reported on page NO
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	14
	5b	Name and contact information for the trial sponsor	Supplied in ICMJE form by AC
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Supplied in ICMJE form by AC
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5,6

	6b	Explanation for choice of comparators	6
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7, Figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10, Figure 2
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6,7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7,8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7,8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7,8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	8
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9,10

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9,10,13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9,10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9,10
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9,10
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Supplied in ICMJE form by AC
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	13
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10,13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	All minor changes have been reported and approved by the Norwegian ethics committee prior to trial commenced.
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	14, Supplied in ICMJE form by AC
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	13
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13
	31b	Authorship eligibility guidelines and any intended use of professional writers	13

	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	13
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Chiropractic spinal manipulative therapy for migraine: A study protocol of a single-blinded placebo-controlled randomized clinical trial.

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Chiropractic spinal manipulative therapy for migraine: A study protocol of a single-blinded placebo-controlled randomized clinical trial.

Aleksander Chaibi[1,2], BPT, MChiro, PhD stud; Jūratė Šaltytė Benth[2,3], MMathStat, PhD; Peter J. Tuchin[4], Associate professor, BSc, GradDipChiro, DipOHS, PhD, FACC; Michael Bjørn Russell[1,2], professor, MD, PhD, DrMedSci

[1]Head and Neck Research Group, Research Centre, Akershus University Hospital, 1478 Lørenskog, Norway, [2]Institute of Clinical Medicine, Akershus University Hospital, University of Oslo, 1474 Nordbyhagen, Norway, [3]HØKH, Research Centre, Akershus University Hospital, Lørenskog, Norway, [4]Department of Chiropractic, Macquarie University, NSW 2109, Australia

Correspondence:

Aleksander Chaibi

BPT, MChiro, PhD student

Head and Neck Research Group

Research Centre

Akershus University Hospital

1478 Lørenskog

Norway

aleksander.chaibi@medisin.uio.no

Key words

Migraine, Headache, Randomized Controlled Trial, Chiropractic, Spinal Manipulation, Protocol

Abstract

Introduction: Migraine affects 15% of the population, and has substantial health and socioeconomic costs. Pharmacological management is first-line treatment. However, acute and/or prophylactic medicine might not be tolerated due to side effects or contraindications. Thus, we aim to assess the efficacy of chiropractic spinal manipulative therapy (CSMT) for migraineurs in a single-blinded placebo-controlled randomized clinical trial (RCT).

Method and analysis: According to the power calculations, 90 participants are needed in the RCT. Participants will be randomized into one of three groups; CSMT, placebo (sham manipulation) and control (usual non-manual management). The RCT consists of three stages: 1 month run-in, 3 months intervention and follow-up analyses at the end of intervention and 3, 6 and 12 months. Primary end-point is headache frequency, while headache duration, headache intensity, headache index (frequency x duration x intensity) and medicine consumption are secondary end-points. Primary analysis will assess a change in headache frequency from baseline to the end of intervention and follow-up, where the groups CSMT and placebo and CSMT and control will be compared. Due to two group-comparisons, p-values below 0.025 will be considered statistically significant. For all secondary end-points and analyses, p-value below 0.05 will be used. The results will be presented with the corresponding p-values and 95% confidence intervals (CI).

Ethics and dissemination: The RCT will follow the clinical trial guidelines from the International Headache Society. The Norwegian Regional Committee for Medical Research Ethics and the Norwegian Social Science Data Services has approved the project. Procedure will be conducted according to the declaration of Helsinki. The results will be published at scientific meetings and in peer-reviewed journals.

Trial registration: ClinicalTrials.gov identifier: NCT01741714, 2. December 2012.

Article summary

Strengths and limitations of the randomized controlled trial

- The study will be the first three-armed manual therapy RCT assessing the efficacy of chiropractic spinal manipulative therapy (CSMT) vs. placebo (sham manipulation) and control (continue usual pharmacological management without receiving manual intervention) for migraineurs.
- Strong internal validity, since a single chiropractor will conduct all interventions.
- The RCT has the potential to provide a non-pharmacological treatment option for migraineurs.
- Risk for drop-outs is increased due to strict exclusion criteria and 17 months duration of the RCT.
- A general accepted placebo has not been established for manual therapy, thus, there is a risk for unsuccessful blinding, while the investigator whom provides the interventions cannot be blinded for obvious reasons.

Background

Migraine is a common health problem with substantial health and socioeconomic costs. On the recent Global Burden of Disease study, migraine where ranked as the 3rd most common conditions.[1] About 15% of the general population have migraine.[2 3] Migraine is usually unilateral with pulsating and moderate/severe headache which is aggravated by routine physical activity, and is accompanied by photo- and phonophobia, nausea and sometimes vomiting.[4] Migraine exists in two major forms, migraine without aura (MO) and migraine with aura (MA) (Table 1). Aura is reversible neurological disturbances of the vision, sensory, and/or speech function, occurring prior to the headache. However, intra-individual variations from attack to attack are common.[5 6] The origin of migraine is debated. The painful impulses may origin from the trigeminal nerve, central and/or peripheral mechanisms.[7 8] Extracranial pain sensitive structures include skin, muscles, arteries, periosteum and joints. The skin is sensitive to all usual forms of pain stimuli, while especially temporal and neck muscles may be sources for pain and tenderness in migraine.[9-11] Similarly, the frontal supraorbital, superficial temporal, posterior and occipital arteries are sensitive to pain.[9 12]

Pharmacological management is the first treatment option for migraineurs. However, some patients do not tolerate acute and/or prophylactic medicine, due to side effects or contraindications due to co-morbidity of other diseases or wish to avoid medication for other reasons. The risk of medication overuse due to frequent migraine attacks represents a major health hazard with both direct and indirect cost concerns. The prevalence of medication overuse headache (MOH) is 1-2% in the general population,[13-15] i.e. about half the population suffering chronic headache (15 headache days or more per month) have MOH.[16] Migraine causes loss of 270 workdays per year per 1,000 persons from the general population.[17] This corresponds to about 3,700 work years lost per year in Norway due to migraine. The economic cost per migraineur was estimated to be $655 in USA and €579 in Europe per year.[18 19] Due to the high prevalence of migraine, the total cost per year was estimated to be $14.4 billion in the USA and €27 billion in the EU countries, Iceland, Norway and Switzerland at that time. Migraine costs more than neurological disorders such as dementia, multiple sclerosis, Parkinson's disease and stroke.[20] Thus, non-pharmacological treatment options are warranted. Diversified technique and Gonstead method are the two most commonly used chiropractic manipulative treatment modalities in the profession, used by 91% and 59% respectively,[21 22] along with other manual and non-manual interventions, i.e. soft tissue techniques, spinal and peripheral mobilization, rehabilitation, postural corrections and exercises as well as general nutrition and dietetic advises.

A few spinal manipulative therapy (SMT) randomized controlled trials (RCTs) using the Diversified technique have been conducted for migraine, suggesting an effect on headache frequency, headache duration, headache intensity and medicine consumption.[23-26] However, common for previous RCTs are the methodological shortcomings such as; inaccurate headache diagnosis, i.e. questionnaire diagnoses used are imprecise,[27] inadequate or no randomization procedure, lack of placebo group, inadequate and no validation of blinding concealment of participants, and primary and secondary end-points not pre-specified.[28-31] In addition, previous RCTs did not consequently adhere to the recommended clinical guidelines from the International Headache Society (IHS).[32 33] At present, no RCTs have applied the Gonstead CSMT method. Thus, considering the methodological shortcomings in previous RCTs, a clinical placebo-controlled RCT with improved methodological quality remains to be conducted for migraine.

The SMT mechanism of action on migraine is unknown. It is argued that migraine might originate from a complexity of nociceptive afferent responses involving the upper cervical spine (C1, C2 and C3), leading to a hypersensitivity state of the trigeminal pathway conveying sensory information for the face and much of the head.[34 35] Research has thus, suggested that SMT may stimulate neural inhibitory systems at different spinal cord levels, as well as it might activate various central descending inhibitory pathways.[36-40] However, although the proposed physiological mechanisms are not fully understood, there are likely additional unexplored mechanisms which could explain the effect SMT has on mechanical pain sensitisation.

The objective of this study is to assess the efficacy of CSMT vs. placebo (sham manipulation) and controls (continue usual pharmacological management without receiving manual intervention) for migraineurs in a RCT.

Method and design

This is a single-blinded placebo-controlled RCT with three parallel groups (CSMT, placebo and control). Our primary hypothesis is that CSMT gives at least 25% reduction in average number of headache days per month (30 days/month) as compared to placebo and control from baseline to the end of intervention, and we expect the same reduction to maintain at 3, 6 and 12 months follow-up. If the CSMT treatment is effective, it will be offered to participants whom received placebo or control after study completion, i.e. after 12 months follow-up. The study will adhere to the recommended clinical trial guidelines from the IHS,[32 33] and the methodological CONSORT and SPIRIT guidelines.[41 42]

Patient population

Participants will be recruited in the period January to September 2013 through Akershus University Hospital, through general practitioners and media advertisement, i.e. poster with general information will be put up at general practitioners offices along with oral information, in Akershus and Oslo counties, Norway. Participants will receive posted information about the project followed by a short telephone interview. Participants recruited from the general practitioners offices will have to contact the clinical investigator whose contact details have been provided on the poster in order to obtain extensive information about the study.

Eligible participants are between 18 and 70 years of age and have at least one migraine attack per month. Participants are diagnosed according to the diagnostic criteria of the International Classification of Headache Disorders (ICHD-II) by a neurologist at Akershus University Hospital.[43] Participants are only allowed to have co-occurrence of tension-type headache and not other primary headaches.

Exclusion criteria are contraindication to SMT, spinal radiculopathy, pregnancy, depression and CSMT within the previous 12 months. Participants whom during the RCT receive any manual interventions by physiotherapists, chiropractors, osteopaths or other health professionals to treat musculoskeletal pain and disability, and includes massage therapy, joint mobilization and manipulation,[44] changed their prophylactic headache medicine or pregnancy will be withdrawn from the study at that time and be regarded as drop-outs. Participants are allowed to continue and change their usual acute migraine medication throughout the trial.

In response to initial contact, participants fulfilling the inclusion criteria will be invited to further assessment by the chiropractic investigator. The assessment includes an interview and a physical examination with special emphasis on the whole spinal column. Oral and written information about the project will be provided in advance and oral and written consent will be obtained from all accepted participants during the interview and by the clinical investigator. In accordance with good clinical practice, all patients will be informed about the harms and benefits as well as possible adverse reactions of the intervention primarily including local tenderness and tiredness on the treatment day. No serious adverse events have been reported for the chiropractic Gonstead method.[45 46] Participants randomized into active or placebo interventions, will undergo a full spine radiographic examination and be scheduled for 12 intervention sessions. The control group will not be exposed to this assessment.

Clinical randomized controlled trial

The clinical RCT consist of 1 month run-in and 3 months intervention. Time profile will be assessed from baseline to end of follow-up for all end-points (Figure 1).

Run-in

The participants will fill in a validated diagnostic paper headache diary one month prior to intervention which will be used as baseline data for all participants.[47 48] The validated diary includes questions directly related to the primary and secondary end-points. X-rays will be taken in standing position in the anterior-posterior and lateral planes of the entire spine. The x-rays will be assessed by the chiropractic investigator.

Randomization

Prepared sealed lots with the three interventions i.e. active treatment, placebo and the control group, will be subdivided into four subgroups by age and gender i.e. 18-39 and 40-70 years of age and men and women, respectively. Participants will be equally allocated to the three groups by allowing the participant to draw one lot only. The block randomization will be administrated by an external trained party with no involvement from the clinical investigator.

Intervention

Active treatment consists of CSMT using the Gonstead method,[21] 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.

The placebo intervention consists 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 will be performed outside the spinal column with adequate joint slack and without soft tissue pre-tension so no joint cavitations occur. In some sessions, the participant lay either 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 will stand at the participant's left side and place 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 lay 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 will be delivered as a non-intentional push in the gluteal region. The sham manipulation alternatives will be equally interchanged among the placebo participant's according to protocol during the 12-week treatment period to strengthen the study validity. Both the active and the placebo group will receive the same structural and motion assessment prior to and after each

intervention. No additional co-interventions or advises will be given to participants during the trial period. The treatment period will include 12 consultations, i.e. twice per week the first three weeks followed by once a week the next two and once every second week until 12 weeks are reached. Fifteen minutes will be allocated per consultation for each participant. All interventions will be conducted at Akershus University Hospital and administered by an experienced chiropractor (AC). The control group will continue usual care, i.e. pharmacological management without receiving manual intervention by the clinical investigator. The same exclusion criteria apply for the control group during the whole study period.

Blinding

After each treatment session, the participants whom receive active or placebo will complete a de-blinding questionnaire administrated by an external 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), where 0 represents absolutely uncertain and 10 represents absolutely certainty. The control group and the clinical investigator can for obvious reasons not be blinded.[49 50]

Follow-up

Follow-up analysis will be conducted on the end-points measured after the end of intervention and 3, 6 and 12 months follow-up. During this period all participants will continue to fill in a diagnostic paper headache diary and return it on a monthly basis. In the case of unreturned diary or missing values in the diary, the participants will be contacted immediately upon detection to minimize recall bias. Participants will be contacted by phone to secure compliance.

Primary and secondary end-points

The primary and secondary end-points are listed in Table 2. The end-points adhere to the recommended IHS clinical trial guidelines.[32 33] We define number of headache days to be primary end-point and expect at least 25% reduction in average number of days from baseline to the end of intervention, with the same level of reduction maintaining at follow-up. Based on previous reviews on migraine, a 25% reduction is considered to be a conservative estimate.[30] A 25% reduction is also expected in secondary end-points from baseline to the end of intervention, retaining at follow-up for headache duration, headache intensity, and headache index, where the index is calculated as number of headache days (30 days) x average headache duration (hours per day) x average intensity

(0-10 NRS). A 50% reduction in medication consumption from baseline to the end of intervention and to follow-up is expected.

Data Processing

A flowchart of the participants is shown in Figure 2. Baseline demographic and clinical characteristics will be tabulated as means and standard deviations (SD) for continuous variables and proportions and percentages for categorical variables. Each of three groups will be described separately. Primary and secondary end-points will be presented by suitable descriptive statistics in each group and for each time point. Normality of end-points will be assessed graphically and transformation will be considered if necessary.

Change in primary and secondary end-points from baseline to the end of intervention and to follow-up will be compared between active and placebo and active and control group. Null-hypothesis states that there is no significant difference between the groups in average change, while the alternative hypothesis states that a difference of at least 25% exists.

Due to follow-up period, repeated recordings of primary and secondary end-points will be available, and analyses of trend in primary and secondary end-points will be of main interest. Intra-individual correlations (cluster effect) are likely to be present in data with repeated measurements. Cluster effect will thus be assessed by calculating intra-class correlation coefficient (ICC) quantifying the proportion of total variation attributable to the intra-individual variations. The trend in end-points will be assessed by a linear regression model for longitudinal data (linear mixed model) to correctly account for possible cluster effect. Linear mixed model handles unbalanced data, enabling all available information from randomized patients to be included, also from drop-outs. Regression models with fixed effects for time component and group allocation as well as the interaction between the two will be estimated. The interaction will quantify possible differences between groups regarding time trend in the end-points and serve as an omnibus test. Random effects for patients will be included to adjust the estimates for intra-individual correlations. Random slopes will be considered. The linear mixed models will be estimated by SAS PROC MIXED procedure. The two pairwise comparisons will be performed by deriving individual time point contrasts within each group with the corresponding p-values and 95% confidence intervals (CI).

Both per-protocol and intention-to-treat analyses will be conducted if relevant.. All analyses will be performed by a statistician, blinded for group allocation and participants. All adverse effects will also be registered and presented. Participants who experience any sort of adverse effects during the trial period will be entitled to call the clinical investigator on the project cell phone. The data will be analyzed with SPSS v22 and SAS v9.3. Because of two group-comparisons in the primary end-point, p-

values below 0.025 will be considered statistically significant. For all secondary end-points and analyses, a significance level of 0.05 will be used. Missing values might appear in incomplete interview questionnaires, incomplete headache diaries, missed intervention sessions and/or due to drop-outs. The pattern of missingness will be assessed and missing values handled adequately.

Power calculation

Sample size calculations are based on the results in a recently published group comparison study on topiramate.[51] We hypothesize that the average difference in reduction of number of days with headache per month between active and the placebo group is 2.5 days. The same difference is assumed between active and control group. Standard deviation for reduction in each group is assumed to be equal 2.5. Under the assumption of on average 10 headache 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, we set a significance level at 0.025. A sample size of 20 patients is required in each group to detect a statistically significant average difference in reduction of 25% with 80% power. To allow for drop-outs, the investigators plan to recruit 120 participants.

Discussion

Methodological considerations

Current SMT RCTs on migraine suggest treatment efficacy regarding headache frequency, duration and intensity. However, a firm conclusion requires clinical single-blinded placebo-controlled RCTs with few methodological shortcomings.[30] Such studies should adhere to the recommended IHS clinical trial guidelines with headache frequency as primary end-point and headache duration, headache intensity, headache index and medication consumption as secondary end-points.[32 33] Headache index, combination of 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.[33 52 53] The primary and secondary end-points will be collected prospectively in a validated diagnostic headache diary for all participants in order to minimize recall bias.[47 48] To our knowledge, this is the first prospective manual therapy three-armed single-blinded placebo-controlled RCT to be conducted for migraine. The study design adheres to the recommendations for pharmacological RCTs as far as possible. RCTs that include a placebo and control group are advantageous to pragmatic RCTs that compare two active treatment arms. RCTs also provide the best approach for producing safety as well as efficacy data.

An unsuccessful blinding is a possible risk to the RCT. Blinding is often difficult as there is no single validated standardized chiropractic sham intervention which can be used as a control group to this date. It is however, necessary to include a placebo group in order to produce a true net effect of the active intervention. Consensus about an appropriate placebo for a clinical trial of SMT among experts representing both clinicians and academics has, however, not be reached.[54] No previous studies have to our knowledge, validated a successful blinding of a CSMT clinical trial with multiple treatment sessions. We intend to minimize this risk by following the proposed protocol for the placebo group. The placebo response is furthermore high in pharmacological and assumed similarly high for non-pharmacological clinical studies and might also be higher in manual therapy RCTs were attention and physical contact is involved.[55] Similarly, a natural concern with regards to attention bias will be involved for the control group as they are not being seen by anyone or not seen as much by the clinical investigator as the other two groups.

There are always risks for drop-outs due to various reasons. As the trial duration is 17 months with a 12 months follow-up period, the risk for loss to follow-up is thus enhanced. Co-occurrence of other manual intervention during the trial period is another possible risk, as those whom receive manipulation or other manual physical treatments elsewhere during the trial period will be withdrawn from the study and regarded as drop-outs at the time of violation.

The external validity of the RCT might be a weakness as there is only one investigator. However, we found that advantageous to multiple investigators, in order to provide similar information to participants in all three groups and manual intervention in the CSMT and the placebo group. Thus, we intend to eliminate inter-investigator variability which might be present if there are two or more investigators. Although the Gonstead method is the second most commonly used technique among chiropractors, we do not see an issue of concern when it comes to generalizability and external validity. As the majority of included participants are expected to be enrolled in the study from the Akershus University Hospital, generalizability should not be an issue of concern. Furthermore, the block randomization procedure will provide a homogenous sample across the three groups.

The internal validity is however strong by having one treating clinician. It reduces the risk of potential selection, information and experimental biases. Furthermore, the diagnosis of all participants is performed by experienced neurologists and not by questionnaires. A direct interview has higher sensitivity and specificity as compared to questionnaire.[27] Individual motivational factors which can influence participant's perception as well as personal preferences when treating are both reduced by having one investigator. In addition, the internal validity is further strengthened by a concealed validated randomization procedure. As age and genders may play a role in migraine, block

randomization was found necessary to balance arms by age and gender in order to reduce possible age- and/or gender-related bias.

Conducting x-rays prior to the active and placebo interventions was found applicable in order to visualize posture, joint and disc integrity.[56 57] As the total x-ray radiation dose varies from 0.2-0.8 mSv, the radiation exposure was considered low.[58 59] X-ray assessments were also found necessary in order to determine if full spine x-rays are useful in future studies or not.

As we are unaware of the mechanisms of possible efficacy, and both spinal cord and central descending inhibitory pathways has been postulated, we see no reasons to exclude a full spine treatment approach for the intervention group. It has furthermore been postulated that pain in different spinal regions should not be regarded as separate disorders but rather a single entity.[60] Similarly, including a full spine approach limits the differentiations between the CSMT and the placebo group. Thus, strengthen the likelihood of successful blinding in the placebo group being achieved. In addition, all the placebo contacts will be performed outside the spinal column, thus, minimizing a possible spinal cord afferent input.

Innovative and scientific value

This RCT will highlight and validate the Gonstead CSMT for migraineurs which has not previously been studied. If CSMT proves to be effective, it will provide a non-pharmacological treatment option. This is especially important as some migraineurs do not have efficacy of prescript acute and/or prophylactic medications, while others have non-tolerable side-effects or co-morbidity of other diseases that contradict medication while others wish to avoid medication for various reasons. Thus, if CSMT works, it can really have an impact on migraine treatment. The study also bridges cooperation between chiropractors and physicians, which is important in order to make the healthcare more efficient. Finally, our method might be applied in future chiropractic and other manual therapy RCTs on headache.

Ethics and dissemination

Ethics

The study has been approved by the Norwegian Regional Committee for Medical Research Ethics (REK) (2010/1639/REK) and the Norwegian Social Science Data Services (11-77). The declaration of Helsinki is otherwise followed. All data will be anonymised while participants must give oral and written informed consent. Insurance is provided through "The Norwegian System of Compensation to Patients" (NPE) which is an independent national body, set up to process compensation claims from patients who have suffered an injury as a result of treatment under the Norwegian health service. A stopping rule was defined for withdrawing participants from this study in accordance with recommendations in the CONSORT extension for Better Reporting of Harms.[61] If a participant reports to their chiropractor or research staff a severe adverse event, he or she will be withdrawn from the study and referred to their General Practitioner or hospital emergency department depending on the nature of the event. The final dataset will be available to the clinical investigator (AC), the independent and blinded statistician (JSB) and Study Director (MBR). Data will be stored in a locked cabinet at the Research Centre, Akershus University Hospital, Norway, for five years.

Dissemination

This project is due for completion three years after the start. Results will be published in peer-reviewed international scientific journals in accordance with the CONSORT 2010 Statement. Positive, negative, as well as inconclusive results will be published. In addition, a written lay summary of the results will be available to study participants on request. All authors should qualify for authorship according to the International Committee of Medical Journal Editors, 1997. Each author should have participated sufficiently in the work to take public responsibility for the content. The final decision on the order of authorship will be decided when the project has been finalised. The results from the study may, moreover, be presented as posters or oral presentations at national and/or international conferences.

Author Affiliations:

[1]Head and Neck Research Group, Research Centre, Akershus University Hospital, 1478 Lørenskog, Oslo, Norway (AC and MBR);

[2]Institute of Clinical Medicine, Akershus University Hospital, University of Oslo, 1474 Nordbyhagen, Oslo, Norway (AC, JSB, MBR);

[3]HØKH, Research Centre, Akershus University Hospital, 1478 Lørenskog, Oslo, Norway (JSB);

[4]Department of Chiropractic, Macquarie University, NSW 2109, Australia (PJT);

Authors' Contribution: AC and PJT had the original idea of the study. AC and MBR obtained funding. MBR planned the overall design. AC prepared the initial draft and PJT commented on the final version of the research protocol. JSB performed all the statistical analysis. AC, JSB, PJT and MBR was involved in the interpretation and assisted in revision and preparation of the manuscript. All authors have read and approved the final manuscript.

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Conflicts of Interests: All authors have completed the ICMJE uniform disclosure form and no conflicts of interest were reported for this study.

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Patient Consent: Obtained.

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Data Sharing Statement: No additional data available.

Figure 1 Study flow chart. CSMT, chiropractic spinal manipulative therapy; Placebo, sham manipulation; Control, continue usual pharmacological management without receiving manual intervention.

Figure 2 Expected participant's flow diagram. CSMT, chiropractic spinal manipulative therapy; Placebo, sham manipulation; Control, continue usual pharmacological management without receiving manual intervention.

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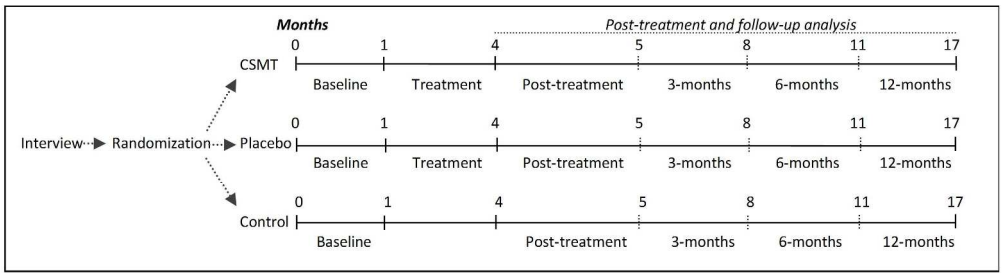
Table 1

Diagnostic criteria for migraine without aura by the International Classification of Headache Disorders-II	
A.	At least 5 attacks fulfilling criteria B-D
B.	Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)
C.	Headache has at least two of the following characteristics: 1. Unilateral location 2. Pulsating quality 3. Moderate or severe pain intensity 4. Aggravated by or causing avoidance of routine physical activity
D.	During headache at least one of the following: 1. Nausea and/or vomiting 2. Photophobia and phonophobia
E.	Not attributed to another disorder

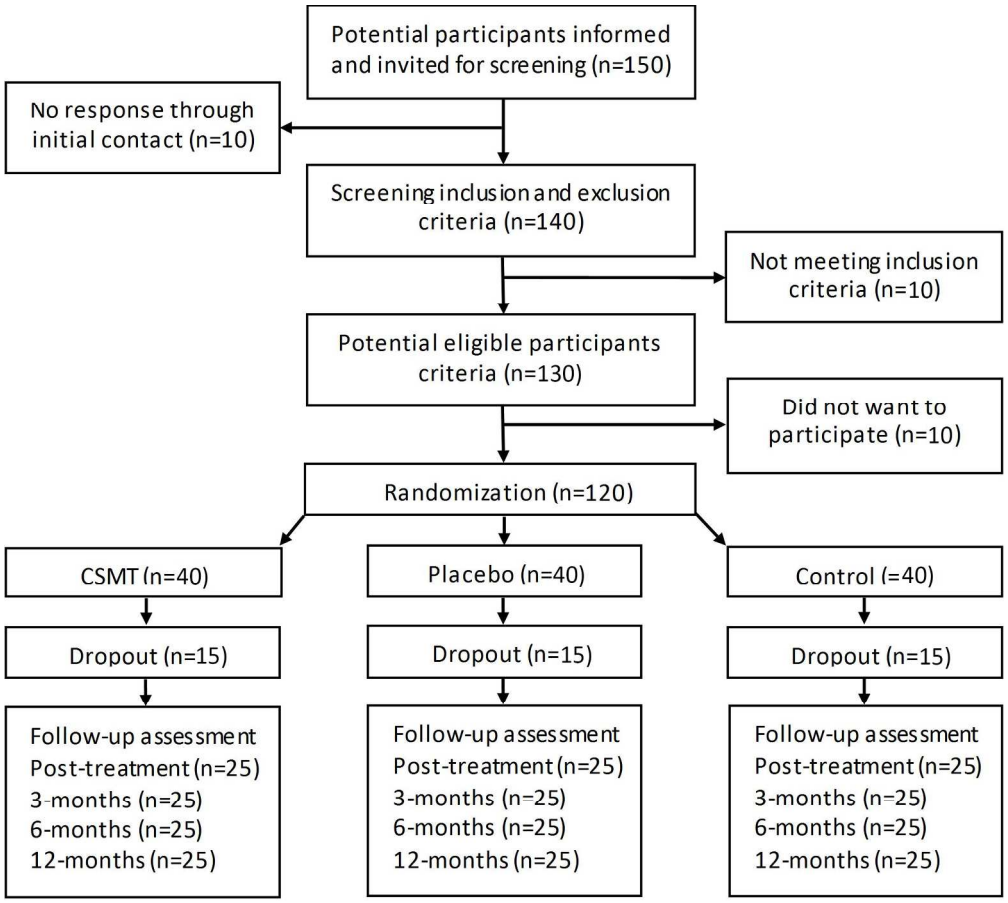
Diagnostic criteria for migraine with aura by the International Classification of Headache Disorders-II	
A.	At least 2 attacks fulfilling criteria B-D
B.	Aura consisting of at least one of the following, but no motor weakness: 1. fully reversible visual symptoms including positive features (i.e. flickering lights, spots or lines) and/or negative features (i.e. loss of vision)Moderate or severe pain intensity 2. fully reversible sensory symptoms including positive features (i.e. pins and needles) and/or negative features (i.e. numbness) 3. fully reversible dysphasic speech disturbance
C.	At least two of the following: 1. Homonymous visual symptoms and/or unilateral sensory symptoms 2. At least one aura symptom develops gradually over ≥5 minutes and/or different aura symptoms occur in succession over ≥5 minutes 3. Each symptom lasts ≥5 and ≤60 minute
D.	Headache fulfilling criteria B-D for 1.1 Migraine without aura begins during the aura or follows aura within 60 minutes
E.	Not attributed to another disorder

Table 2 Primary and secondary end-points
Primary end-points
1. Number of headache days in active treatment vs. placebo group.
2. Number of headache days in active treatment vs. control group.
Secondary end-points
3. Headache duration in hours in active treatment vs. placebo group.
4. Headache duration in hours in active treatment vs. control group.
5. Self-reported VAS in active treatment vs. placebo group.
6. Self-reported VAS in active treatment vs. control group.
7. Headache index (frequency x duration x intensity) in active treatment vs. placebo group.
8. Headache index in active treatment vs. control group.
9. Headache medication dosage in active treatment vs. placebo group.
10. Headache medication dosage in active treatment vs. control group.

* The data analysis is based on the run-in period vs. end of intervention. Point 11-40 is a duplicate of point 1-10 above at respectively 3, 6 and 12 months follow-up.



Study flow chart.
254x67mm (300 x 300 DPI)



Expected participant's flow diagram.
197x176mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Reported on page NO
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	14
	5b	Name and contact information for the trial sponsor	Supplied in ICMJE form by AC
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Supplied in ICMJE form by AC
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5,6

	6b	Explanation for choice of comparators	6
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7, Figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10, Figure 2
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6,7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7,8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7,8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7,8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	8
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9,10

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9,10,13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9,10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9,10
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9,10
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Supplied in ICMJE form by AC
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	13
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10,13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	All minor changes have been reported and approved by the Norwegian ethics committee prior to trial commenced.
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	14, Supplied in ICMJE form by AC
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	13
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13
	31b	Authorship eligibility guidelines and any intended use of professional writers	13

	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	13
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.