The effect of Spinal Manipulative Therapy on Heart Rate Variability and pain in patients with chronic neck pain: A Randomized Controlled trial

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Abstract

Background

Recent experimental research has suggested that Spinal Manipulative Therapy (SMT) may reduce pain through modulation of the ascending pain signals and/or the central pain regulating mechanisms. People with persistent neck pain (NP) have also been found to have disturbances in Autonomic Nervous System (ANS) regulation. A common way to study ANS is to measure heart rate variability (HRV). It is not known if deviations in HRV are related to changes in pain perception or to the treatment response to SMT.

Commonly, an individual in pain will experience pain reduction when exposed to a second pain stimulus, a mechanism known as Conditioning Pain Modulation (CPM). Patients with persistent pain have been found to have a reduced CPM reaction. It is not known if this is predictive of treatment response to SMT.

The aim of the study is to examine the effects of SMT on HRV and pain and to test if a CPM test can be used to predict treatment response, in a population of patients with recurrent and persistent NP.

Method/Design

A multicentre randomized controlled clinical trial will be carried out in multidisciplinary primary care clinics. This setting is chosen to minimize bias resulting from patient preference to treatment modality and provider.

The subjects are either self-referred or referred from other health care practitioners locally. The treatment modalities are two well-known interventions for NP; SMT and stretching exercises compared to stretching exercises alone.

The subjective pain experience will be investigated by assessing pain intensity and the affective quality of pain. HRV will be measured using a portable heart monitor and CPM will be measured with a standardized cold-pressor-test. Measurements will be performed
at baseline, prior to the third treatment and after the fourth treatment.

Discussion

The study will utilize normal clinical procedures, which should aid transferability and external validity of the results. The study will provide knowledge regarding the underlying mechanisms of the effects of SMT. Furthermore, the study will examine if a CPM test is predictive of treatment outcome in a population of patients with recurrent and persistent NP.

Background

Musculoskeletal pain is a global burden due to a high prevalence and substantial costs worldwide (1). The most common conditions are low back pain (LBP) and neck pain (NP) (2). Despite years of research, diagnosing LBP and NP is still difficult, and up to 90 % of the cases are termed “non-specific”. This often results in treatments that are based on untested theories, e.g. theories of spinal dysfunction, instability or muscle weakness, but also on the preference of the healthcare provider and patient. Ideally, the diagnosis should rest upon an understanding of the pain mechanism (3), but due to the “non-specific” diagnosis of LBP and NP, a therapist will often not be able to select the most appropriate treatment for the individual patient. This may be the explanation for the moderate treatment effect sizes for most available treatments, potentially wasting resources and failing to improve patients’ health (4).

Chiropractic care including Spinal Manipulative Therapy (SMT) has been found to be a safe, effective, and cost-effective non-invasive treatment for some types of spinal pain (5-7). SMT has both local and regional pain-reducing effects (8), as well as central nervous system effects such as a general reduction of pain sensitivity (9).

SMT is thought to decrease pain by mechanically affecting muscular and joint function, i.e. normalising muscle tone and improving joint mobility. However, recent experimental
research has suggested that SMT may also be influencing the incoming/ascending pain signals (local nociceptive input affecting dorsal horn excitability or temporal summation) and/or the excitability of the central pain regulating mechanisms (9, 10). A systematic review concluded that short-term sympathetic up-regulation can be found with SMT, regardless of the spinal area being treated (11). This raises the question of whether the pain reducing effect of SMT is associated with a modulation of autonomic nervous system (ANS) activity.

Differences in ANS activity have been found between healthy controls and people with NP (12). In healthy individuals, acute pain results in an increased sympathetic response and often an increase in pain threshold induced by descending inhibition. However, in patients with chronic pain, it appears that persistent sympathetic activation could lead to hyperalgesia due to a decrease in descending inhibition (12). Further, in a recent study, chronic pain was reduced after treatment aimed at normalizing the ANS through biofeedback (12). This indicates a bidirectional relationship; ANS not only reacts to pain but pain is modulated by ANS activity. Furthermore, two studies (13, 14) (without control groups) have shown an association between positive treatment effects on pain and an increased Heart Rate Variability (HRV). HRV is mainly considered a proxy for ANS regulation, as it will depend on the balance in the autonomic system.

Stretching is used both as a passive treatment intervention and as active home exercises for several conditions relating to the musculoskeletal system. The rationale behind stretching is to improve range of motion, reduce pain and perceived stiffness (15). The effect of stretching exercises in combination with other treatment modalities has been found to be a decrease in pain and disability in patients with NP (4, 16).

A pure placebo trial is not indicated when either evidence-based treatment options exists or when the patients taking part in the study are actively seeking care (17). Due to this,
all patients in this trial are given home stretching exercises to ensure that some care is provided. One previous study showed that SMT had a greater effect on pain in combination with home exercises (18). Using this design, the result will show if adding SMT to stretching will yield different HRV and pain responses.

As mentioned above, chiropractic treatment is considered non-invasive and safe (5-7). Common benign and short-lasting reactions to SMT are mild to moderate increases in pain in the area of treatment often coupled with fatigue (19), considered “normal reactions”. It has been shown that a normal reaction to treatment is a predictor for a good outcome (20), but the mechanism behind this is not known and appears not to have been previously studied or described in the literature. It may be hypothesized that the mechanisms behind normal reactions following SMT may also be explained by ANS reactions.

The research in the area so far suffers from some limitations: Small group-sizes, possible patient bias (positive expectations) towards the therapist and treatment method, short follow-up time and lack of a reasonable comparator treatment. A randomized design with a standardised control treatment would distinguish treatment effects from contextual effects. In order to study the neurological effect of SMT and stretching exercises compared to stretching alone in patients with persistent and recurrent NP in a clinical setting, a sufficiently large sample and a randomized design should be used. In order to study long term HRV responses, measurements over 2 weeks will be conducted.

Interestingly, when exposed to pain, a different noxious (painful) stimulus can be used as a conditioning (inhibitory/facilitatory) stimulus. The normal reaction is reduction in pain perception known as ‘pain inhibits pain’ or inhibitory conditioned pain modification (CPM). In patients with chronic pain, a reduced CPM response prevents the normal reaction to a painful stimulus to occur, and patients will not experience the normal “pain-inhibits-pain”
reaction (21).

In the study, a tool previously described in the literature (22) will be used to test the CPM response. The aim is to study if patients with reduced CPM prior to starting treatment will respond differently to a series of chiropractic treatments than patients with functioning CPM, i.e. to study if a test for CPM and its’ results can be used as a predictor of treatment outcome. Cold Pressor Test (CPT) is known to be a safe testing method with minimal adverse reactions (23).

Method/design

Study aim

The study aim is to determine the effects of a treatment series consisting of stretching and SMT vs stretching alone on HRV and pain in a clinical setting in a population of patients with recurrent or persistent NP. A secondary aim is to test CPM as a predictor of treatment outcome in terms of pain.

Setting

This multicentre randomized controlled clinical trial will be carried out in multidisciplinary primary care clinics where physiotherapists and chiropractors are consulted for musculoskeletal pain. These types of clinics are selected to minimize bias from patients having expectations towards a specific treatment modality.

A total of 6 clinics will take part in this study, and each clinic will include 20 subjects, resulting in 120 subjects in total, 60 in each treatment arm.

Two research trained clinicians will conduct all the measurements.

The treatments (both intervention and control) will be delivered by clinicians (licenced chiropractors) in the participating clinics.

Eligibility criteria

Inclusion criteria: minimum 18 years old, able to read and understand Swedish. The
presence of recurrent (at least one previous episode) and persistent (duration more than 6 months) NP, and no chiropractic treatment during the previous 3 months. This interval was chosen as research have shown that similar treatments seem to have little effect beyond three months (24).

Exclusion criteria: conditions or medications that will affect the HRV measurements such as cardiovascular disease, hypertension, diabetes, pregnancy, obesity (BMI >30), currently using pain-reducing medication on a daily basis, steroids, beta-blockers or antidepressants. All contraindications to SMT, i.e. anything that could seriously aggravate the pain (e.g. inflammatory conditions) or be indicative of cerebrovascular injuries (previous drop attacks or a recent episode of a new headache or dizziness) will exclude the patient from the study.

**Procedure (Please see flow chart, fig. 1 and 2)**

Patients in this study are self-referred after hearing about the study from another health care provider, or reading about the study in an advertisement or newsletter. A research assistant calls the patient and assess eligibility using a standardized form. The patients are informed about the aim of the study and the study procedures. If eligible, the patient is scheduled for all study visits during this call. Logistical details of this recruitment stage will be adapted to individual clinics as some clinics have newsletters and some use social media to inform their patients about clinic news. Different local newspapers are also used to recruit patients, as the individual clinics are located in and around the Stockholm area. On their first visit, patients will sign an informed consent form and have their baseline measurements taken. Then, they will be randomized to one of the treatment arms and treated accordingly. On the day of the study visit, the participants will refrain from caffeine, nicotine, alcohol, and from performing strenuous exercise.

A standardized protocol is followed on the day of the first study visit: After consenting to
participate, the subjects will start by filling out a baseline questionnaire for demographic information. They will also answer questions concerning their NP (duration, episodes, intensity and frequency) as well as questions regarding pain levels and the affective quality of pain using the NRS-11 scale (25, 26), STarT Back (27, 28) and the short-form McGill Pain Questionnaire (29, 30). Pain will be measured as average pain over the last 24 hours. This information is collected on paper on the first visit, and transferred to a secure KI server by a research assistant. The follow up questionnaires are digital, administered through Karolinska Institutet, managed by Survey & Report by Artologic (https://www.artologik.com/en/SurveyAndReport.aspx).

The equipment used to measure HRV is called FirstBeat (https://www.firstbeat.com/en/). It is applied by the research clinician, and the participants will rest quietly for 5 minutes with the equipment attached before baseline resting values are ascertained over a period of 5 minutes. When patients leave, the HRV-equipment will still be attached to their chest, so that a measurement can be done the following night to record HRV at their deepest sleep (31). Data collected from the FirstBeat monitors are downloaded to a secure computer administered by Karolinska Institutet.

Finally, CPM will be tested with a structured CPM test (32). This test includes mechanical pressure point intensity and a cold pressor test (22). Reported pain measurements during the CPM test are noted in a paper form and transferred to a secure KI server by a research assistant.

After the measurements, study subjects are randomized into one of the two treatment arms. Their allocated clinician will conduct a standard anamnesis and examination procedure including neuro-orthopaedic tests to further assess exclusion criteria. The treatment protocol is then initiated according to allocation. All subjects will be scheduled to a treatment series consisting of 5 visits over 2 weeks.
Data on normal treatment reactions (tiredness/fatigue and pain/tenderness) are collected the day after the first treatment using SMS (https://www.sms-track.com/) to ascertain the type and level of reactions to the interventions (33, 34). These data are automatically stored in a secure server at Karolinska Institutet, accessible only by authorized researchers.

Before the subjects’ third treatment, a second measurement of HRV and CPM will be conducted, and measurements of pain will be ascertained, using the standardized protocol used at the initial visit.

Before the patients’ fifth treatment, or at least two days after the fourth visit, the final measurements will be conducted, this time the HRV-equipment will be taken off directly after the measurement. Again, the standard questionnaire measuring pain will be answered.

After the study period (4 visits), the clinicians are free to select any other treatment modality for the patients. However, patients will be monitored with questionnaires every other week (via email) regarding their affective quality of pain and pain levels for 2 months after their final measurement at the clinic. The clinicians will also report what treatment modalities were used after the initial two weeks of the study.

Patients who do not complete the full treatment plan will be asked to complete all measurements in order to study attrition and to complete a drop-out analysis.

Figure 1. Flow chart of the study procedure

Randomization procedure

Consecutively numbered opaque envelopes containing group allocation are created off-site at the research centre by a statistician. A 1:1 allocation ratio in randomly permuted blocks of different sizes according to a randomization schedule is used. SPSS v20 is used to generate the randomization code. The envelopes are opened consecutively by the
Blinding

The subjects will be unaware of what treatment the other group is receiving, as they will be told that the study is testing two different treatment modalities with similar clinical benefit to examine the effect over two weeks on physiological parameters and pain. Subjects in both treatment arms should feel that complying with their treatment plan during two weeks is a necessity for their improvement.

It will not be possible to blind the clinicians performing the treatments. The research clinicians who will collect the data in the experiment will be blinded to the treatment allocation. The statistical analysis will be performed with the treatment allocation blinded.

Sample size

Log root mean squared successive differences in RR intervals (RMSSD) is the primary measurement of HRV. We will also explore other aspects of HRV according to Task Force Standards (35) to get an overall impression of the subjects’ HRV. In a recent study that examined the reliability of HRV measures, the sample size was estimated to 20 subjects in each group to detect a mean change of 20% in RMSSD, and 20-50 subjects in each group to detect a change of 10% (36). A difference of 10-20% has been considered to be clinically important (36). This value has also been used by other researchers investigating changes in HRV from manual treatment (37). With a significance level of 5%, it was estimated that 60 subjects were needed in each treatment arm to reach a power of 80%. This is also in line with the general recommendations to detect a medium effect size (38).

A high number of dropouts is not expected in this study as it is conducted using an effective practise-based research network with established and tested routines developed to minimize the burden on participating patients.

Treatment arms
SMT in this study is defined both as a High-Velocity-Low-Amplitude (HVLA) thrust applied to the target joint, and also spinal mobilization (MOB) where the application of manual force to the spinal joints is within the passive range of joint motion and does not involve a thrust (39). The type of techniques applied will be decided upon and described by the participating clinicians (chiropractors), and both HVLA and MOB will be considered manual treatments as they have been found to have similar effects on several pain parameters in a recent multicentre study (40). This also provides the possibility for the chiropractor to adapt the force applied to the individual patient, which is normally done in the clinical encounter.

As the participating chiropractors have similar educational backgrounds and have received the same instructions concerning their limited choice of treatment techniques, we expect that they will have a similar approach to SMT. Data on the specific interventions will be collected.

The common modality used in both treatment arms is a program of home stretching exercises. Both groups will receive both verbal and written instructions describing the home stretching exercises that have been recommended as a low-cost first instance intervention for NP (additional file no.1) (16). Patients will be instructed to keep an exercise diary to monitor their exercise frequency (additional file no.1) (16).

The testing of HRV and CPM will be conducted by the two research clinicians, to ensure consistent high quality throughout the study. The two research clinicians will meet several times in advance of the study to test and calibrate the examination procedures and their communication with the study subjects.

**Outcome measures**

**Experimental measures**

The primary outcome is HRV, the variation in beat-to-beat heart rate, an indicator of
parasympathetic and sympathetic modulation of the heart rhythm. Deviations in HRV have been found in patients with both acute and chronic pain. Patients with various chronic pain conditions show reduced parasympathetic activity at rest, the proposed mechanism behind central sensitisation (41). Thus, vagus activity, assessed through HRV, is suggested to correlate with pain severity and could possibly be used as a proxy for treatment efficacy in patients with chronic pain (41). There are some studies showing that SMT influence HRV, but the quality is questioned (42).

In this study, CPM consists of the evaluation of a painful test stimulus followed by a second evaluation after the painful conditioning stimulus has been withdrawn (sequential stimuli) (21). CPM is a well-known concept in modern medicine, particularly when it comes to prediction of post-operative pain (43). It has been suggested that a dysfunctional CPM response can be a pathogenic factor in the development of chronic pain, but also that a dysfunctional CPM response can be the result of chronic pain, hence a possible bi-directional relationship (44).

There is a growing body of evidence suggesting that CPM may be an important biomarker of chronic pain and a predictor of treatment response (21). One may suggest that in patients with chronic pain and a dysfunctional CPM response, treatments with approaches that address the central nervous system mechanisms (e.g., pharmacological and cognitive) could be the first choice of treatment. Patients with chronic pain that demonstrate a dysfunctional CPM might also be particularly sensitive to interventions that help to reduce specific local nociceptive input (e.g., physical medicine and manual treatment). However, standardization of CPM testing is lacking (32).

Our study will use a structured CPM testing protocol with a standardized clamp pressing on the thumb nail for 10 seconds as the test stimulus, and cold water (0-2°C) as the conditioning stimulus (22). A NRS 11 point scale will record pain associated with both
stimuli. This allow us to examine if the CPM responses are predictive of treatment outcomes after SMT and stretching exercises.

**Patient- reported outcome measures:**

Secondary measurements such as disability and health related quality of life will be collected. The subjective pain experience will also be evaluated, as this is important when considering chronic pain (45). These will be collected using the standard instruments described below:

The neck disability index is an instrument designed to measure disability, and has been shown to be reliable and valid in Swedish (46).

Pain intensity is measured with a validated NRS-11 scale where the subjects grades their perceived pain level using the anchors “no pain” and “worst possible pain” (25, 26).

Measures of self-rated health is assessed by EQ-5D, a translated (Swedish) and validated questionnaire with five domains and three answer options in each (47, 48).

To assess the affective quality of pain, the Swedish version of the short-form McGill pain questionnaire-2 will be used. This is a validated questionnaire (29, 30) used in clinical trials designed to measure the subjective pain experience.

These questionnaires will be given at baseline, and again at the 2nd and 3rd measurements. In addition, they will be administered every other week the following 2 months after the study period has ended. Pain intensity (NRS-11) (25, 26) will be collected daily during the two week study period using text-messages (SMS) and every other week the following 2 months using emailed questionnaires.

The most common side-effects following SMT are local tenderness and tiredness of a short duration (19). In this study, the reactions to both treatment arms will be monitored using SMS sent to the participants one day after the first treatment.

**Time line**
The data collection is expected to commence in January 2019 and to be finished within 12 months.

**Analysis**

Intention to treat analysis will be applied.

Univariate multiple regression analysis (one outcome) and/or multivariate multiple regression analysis (more than one outcome) will be used to analyse the primary and secondary outcomes of the trial.

GROUP (treatments, intervention or control) is binary and in the primary analysis, we estimate HRV = b0 + b1GROUP (One-way analysis of variance). The secondary outcome, Pain, will be analysed with the same modelling strategy.

Next, the model HRV = b0 + b1GROUP + b2PAIN + b3GROUP * PAIN + b4Z will be used. If b3 is statistically significant, stratification and adding b3 to b1 will yield different results if the distribution of Z differs in GROUP = 0 (control) and GROUP = 1 (intervention). In this case we will not stratify on GROUP and we will not use b3GROUP * PAIN if b3 is non-statistically significant.

If appropriate age and sex will be included as covariates and controlled for in the model.

To investigate the relationship between CPM and Pain we plan to use the same modelling strategy: PAIN = b0 + b1CPM.

**Ethical aspects**

SMT is applied clinically in musculoskeletal health care and has been examined in a variety of research studies. Serious complications are very rare (49, 50). The present study examines two commonly used treatment protocols in a clinical environment, which means that the subjects will not be subjected to a treatment that they would not normally receive when consulting for care. All test methods are well-established procedures commonly used in research practice. If a subject experience an unexpected reaction to
treatment or testing procedure, the subject will be taken out from the study by the research assistant, and undertake an individual treatment plan.

The clinicians (chiropractors) who performs the treatments all have an academic degree, are licensed by the Swedish National Board of Health and Welfare (the national Patient Safety Act applies) and has a personal liability insurance through their professional federation (https://www.lkr.se/) (Nordic Insurances). Thus, the subjects are insured in case of adverse events from treatment.

When screening for eligibility, both written and verbal information about the purpose of the study, treatments, measurements and SMS procedures will be provided. At the study visit the patient will have an opportunity to ask the research clinician relevant questions, but will also be provided with a telephone number where a part of the research group not involved in the data collection can answer all the questions they may have. All study subjects will sign informed consent forms before entering the trial.

Upon registration in the study, each subject will receive a subject identification number (ID), replacing personal identity number and name, which all measurement data and patient reported data will be linked to. The key that match the subject ID with personal identity number and name will be securely stored in a locked fireproof cabinet at Karolinska Institutet in accordance with the National Board of Health and Welfare's requirements for storage of journal documents.

During the data collection, data are recorded and processed by the research clinicians, and all entries in the databases are recorded using the subject ID only. During the analyses, data will be completely anonymised and only the involved researchers will have access to the data, which will be stored electronically at Karolinska Institutet in accordance with local rules and European GDPR regulations.

All reporting will be done at the group level without the possibility of identifying any
individual study subjects. The results of the study will be published in open access journals, and will be communicated through several professional channels nationally and internationally.

Central ethical approval has been confirmed from the Regional Ethical Review Board in Stockholm (ref approval no. 2018/2137-31) and has approved participation of all individual centres in the trial.

Discussion

The pain-reducing effects of SMT on certain spinal pain conditions are well established, as are the normal reactions to such treatment (5-7). However, the mechanisms behind these effects are not well understood, although it is hypothesized that the pain-reducing effects could be mediated through the ANS (12). Therefore, the study of HRV responses to SMT as part of a short treatment plan and its relation to pain sensitivity and normal reactions to treatment will advance the knowledge regarding the mechanisms involved in the specific effects of SMT.

The development of CPM as a clinical prediction tool could potentially inform clinicians on what to expect in terms of treatment response concerning stretching and manual treatment. The knowledge gathered will inform future clinical studies regarding useful outcome measures, minimally clinically relevant change values, and necessary sample sizes in this type of research.

There are some challenges to consider with the current design: The data collection demands effective recruitment to ensure sufficient number of subjects to adequately power the trial. As mentioned, the study will utilize an existing practise-based research network, where chiropractors have participated and successfully recruited patients in previous studies, thus we believe that it is feasible to include the required number of subjects.
Based on previous experience with multi-centre clinical trials, procedures are in place to minimize the burden on the subjects in the study. However, attrition is to be expected to some degree. Reminder-functions in the email and text-message measurement protocols have been included, some of which are automatic, but some will require monitoring and individual follow up. As subjects deal with only one research clinician and one treating clinician, we believe that the personal contact will be optimal, thus reducing attrition. The testing methods require a highly structured testing protocol as the testing equipment is highly sensitive. However, we believe that this is achievable considering the experience of the research group members.

A pilot study was conducted prior to commencing the full-scale study. It resulted in changes to the recruitment strategy with regards to the use of newspapers and advertising. The responsibility of booking eligible patients was transferred to a research assistant from the local receptionist.

**Trial status**

Patient recruitment will begin in January 2019, and is expected to be completed by December 2019.

**Abbreviations**

NP: Neck Pain

NRS-11: Numerical rating scale (11 steps, 0-10)

ANS: Autonomic Nervous System

SMT: Spinal Manipulative Therapy

CMP: Conditioned Pain Modulation

HRV: Heart Rate Variability

HVLA: High Velocity, Low Amplitude

MOB: Spinal Mobilization
Declarations

Ethics approval and consent to participate

All study subjects will sign informed consent forms before entering the trial.

Availability of data and material

All collected data will be stored for at least 10 years and can only be identified by code number. Only researchers who are directly involved in the project will have access to the material. Anonymized information may be shared with other researchers upon request, pending ethical approval.

Competing interests

None of the authors have any competing interests to disclose. None of the funding bodies are involved in or have influence over the design of the study, the interpretation of the results, or the decision to publish the results.

Trial modifications

Will be recorded in clinicaltrials.gov

Authors’ contributions

AB, IA and AE instigated this study, drafted the first version of the manuscript and are part of the project management group. IA and AE were involved in the management and supervision of the trial. SO’N is involved in the project design and testing protocol. All authors have been involved in the planning and design of the study as well as critical revision and intellectual improvement of the manuscript. All authors have read and approved the final manuscript.

Authors’ information

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SO’N is employed as an associate clinical professor at IRS, University of Southern Denmark and also works as a Chiropractor at the Spine Centre of Southern Denmark, Lillebaelt Hospital. He is funded partly by a tenure position (Uni. Southern Denmark), partly by external post-doc grants.

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Consent for publication

Not applicable

Data monitoring

Participants are not exposed to any excess risk because of participating in this trial. We did therefore not deem it necessary to have a data monitoring committee or an external audit.

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Figures

Figure 1

Flow chart of the study procedure
| ENROLMENT                  | -t₁  | 0   | t₁  | t₂  | t₃  | t₄  | t₅  | tₓ  |
|----------------------------|------|-----|-----|-----|-----|-----|-----|-----|
| Eligibility screen         | X    |     |     |     |     |     |     |     |
| over the phone             |      |     |     |     |     |     |     |     |
| Informed consent           | X    |     |     |     |     |     |     |     |
| Baseline measurements      | X    |     |     |     |     |     |     |     |
| Allocation                 |      | X   |     |     |     |     |     |     |

| INTERVENTIONS:             |      |     |     |     |     |     |     |     |
| SMT and home exercises     |      |     |     |     |     |     |     |     |
| Home exercises only        |      |     |     |     |     |     |     |     |

| ASSESSMENTS:               |      |     |     |     |     |     |     |     |
| SMS on adverse reactions   | X    |     |     |     |     |     |     |     |
| SMS on pain levels (NRS-11)|      |     |     |     |     |     |     |     |
| Pain questionnaires        | X    | X   |     | X   | X   | X   | X   | X   |
| CPM                        | X    | X   | X   | X   |     |     |     |     |
| HRV                        | X    | X   | X   | X   |     |     |     |     |

**Figure 2**

Spirit figure

**Supplementary Files**

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