Method Supplement 3. **English translation of the study's original statistical analysis plan.**

Statistical analysis plan

EVALUATION OF TWO MANUAL THERAPIES

ON THE FUNCTIONAL CAPACITIES OF PATIENTS WITH SUB-ACUTE OR CHRONIC LOW BACK PAIN.

A RANDOMISED CONTROLLED TRIAL.

Short title: LC *OSTEO* -- Ref.: P 110142 - IDRCB 2012-A00167-36

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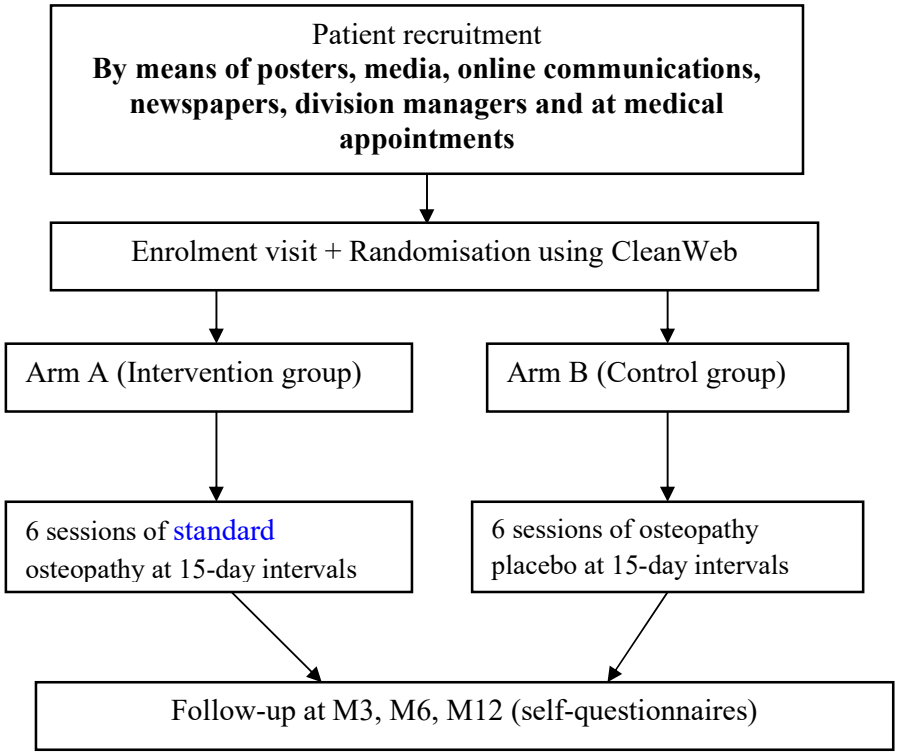
Protocol Summary

Study Title	Evaluation of two manual therapies on the functional capacities of patients with sub-acute or chronic low back pain. A randomised controlled trial.
Sponsor	AP-HP
Principal Investigator Scientific Leader	Prof. François Rannou Dr Peggy Krief Mr Rafael Zegarra-Parodi
Introduction and hypothesis	Complementary medicines such as manual therapy are being proposed increasingly more often, but there are few scientific studies on the efficacy of this therapy.
Primary objective	To evaluate the effectiveness of two manual therapies on improving functional capacity at 3 months in patients with sub-acute or chronic common low back pain.
Secondary objectives	To evaluate the effectiveness of a standard manual therapy on: - Pain (at 3 and 12 months); - Number and duration of sick-leave periods (at 12 months); - Number of relapses (at 12 months); - Quality of life (at 3 and 12 months); - Consumption of painkillers and NSAIDs (at 3 and 12 months).
Study type	A randomised, controlled, multicentre trial (2 sites) comparing a manual therapy treatment with an osteopathic placebo treatment.
Inclusion criteria	- Patients with sub-acute or chronic common low back pain as the first reason for consultation; - Patients between the ages of 18 and 66; - Patients able to speak and understand French; - Patients affiliated with a social security scheme or beneficiary of such a scheme; - Patients having given their written informed consent to take part before the start of the study.
Exclusion criteria	- Any chronic low back pain secondary to an inflammatory (rheumatic disorders), tumoural (myeloma, bone metastases) or infectious (osteomyelitis) cause and/or following spinal trauma in the past 3 months; - Recent history (< 6 months) of vertebral fracture or spinal surgery; - Patients with motor neurological signs (motor impairment) related to the reason for consultation; - Patients who are manual therapy practitioners or students (osteopaths, chiropractors, etc.); - Pregnant women; - Patients with an impairment which does not allow them to properly understand the basic trial process; - Patients taking part in another therapeutic protocol for a clinical study.
Intervention	Six sessions of manual therapy at 15-day intervals.
Comparator	Six sessions of manual placebo therapy at 15-day intervals.
Primary endpoint	Evaluation of functional capacity using the Quebec questionnaire (consisting of 20 items grouped into six activity categories: bed/rest, sitting/standing, ambulation, movement, bending/stooping and handling of large/heavy objects)

	at 3 months.
Secondary endpoints	- Pain evaluation using the numeric pain scale from 0 to 10, at 3 and 12 months; - Number an duration of sick-leave periods at 12 months; - Number of relapses at 12 months; - Functional capacity using the Quebec questionnaire at 12 months; - Quality of life evaluation using the SF-12 questionnaire at 3 and 12 months; - Consumption of painkillers and NSAIDs (at 3, 6 and 12 months)
Total number of patients expected	400 patients
Study duration	42 months
Duration of observation per patient	Maximum of 12 months of follow-up per patient from the time of their enrolment in the study
Expected results	This study will allow us to evaluate the effectiveness of manual therapy treatment in sub-acute or chronic common low back pain.

GENERAL OUTLINE OF THE STUDY



1 Protocol considerations

1.1 Research objectives

1.1.1 Primary objective

To evaluate the effectiveness of two manual therapies on improving functional capacity at 3 months in patients with sub-acute or chronic common low back pain.

1.1.2 Secondary objectives

To evaluate the effectiveness of standard osteopathic treatment on:

- pain (at 3 and 12 months);
- number and duration of sick-leave periods (at 12 months);
- number of recurrences (at 12 months);
- quality of life (at 3 and 12 months);
- consumption of painkillers and NSAIDs (at 3 and 12 months).

1.2 Experimental design

This is a randomised, controlled, multicentre trial comparing two manual therapies administered by osteopaths, a standard osteopathic treatment versus an osteopathic placebo treatment.

1.2.1 Randomisation

Randomisation will be centralised and stratified by site with variable block sizes.
The randomisation list will be generated by a computer program. The secret assignment will be ensured with the use of a Cleanweb-type eCRF.

1.2.2 Choice of comparator

For this trial, we chose to use an osteopathic placebo as the comparator. This choice was motivated by the importance of achieving blinding in the study. The primary endpoint in this study is functional impairment measured using the Quebec questionnaire. This is a patient-reported endpoint which will be highly subjective. A meta-analysis published by Wood[i] demonstrated that blinding is particularly important for subjective endpoints, with an overestimation of 25% in terms of the treatment effect.

The choice of osteopathic placebo will allow us to respond to a question related to the actual effectiveness of this intervention, as the effects linked to decorum and to contact with the therapist will be limited by the use of the placebo.
Comparator standardisation will be achieved thanks to the highly detailed description of the procedures to be carried out (Annex 3), and the making of a film to demonstrate the comparator.

1.2.3 Blinding

For this study, we decided to implement a patient blinding procedure by using a placebo intervention with patients blinded in terms of the hypotheses. Patients in the study will be blinded in terms of the treatment received. They will be informed that they are taking part in a study to compare 2 manual treatments for low back pain carried out by osteopaths. They will not be informed of the study hypotheses, i.e., that one manual treatment is a standard osteopathic treatment and that the other manual treatment will be an osteopathic placebo. They will be informed that we cannot explain all the study hypotheses to them due to scientific reasons, but that they will be informed of the results and the hypotheses at the end of the study.
The term “osteopathy” will not be used at any time during this study.
By definition, the therapists will not be blinded in terms of the treatment administered to the patients. The standard osteopathic treatment and the osteopathic placebo will be administered by specially trained osteopaths. The therapists must not use the term “osteopathy” in front of their patients. The therapists will have no other contact with the patients outside the sessions. They will not be involved in monitoring the patients, prescribing co-interventions or assessing patients.

The assessment will be carried out by the patients themselves, who are therefore blinded in terms of the treatment received (self-assessment logs). The statistical analysis will also be carried out by a blinded statistician from the Clinical Epidemiology Centre. In particular, the data related to the intervention description will not be analysed until a later stage to prevent the statistician being unblinded.

1.2.4 Complexity of the intervention

Osteopathy is a complex intervention combining several components and is personalised according to the osteopathic diagnosis.

In order to comply with international recommendations[ii], this intervention will be standard, the therapists will be trained and the level of accuracy in terms of the protocol will be evaluated.

Intervention standardisation will be achieved thanks to the highly detailed description of the procedures to be carried out (Annex 2 + Chapter 6), and the making of a film to demonstrate the intervention according to the various situations.

1.2.5 Therapist influence

The attitude of the therapists can have a major influence on the intervention's success. The therapists taking part in this study must therefore have received and passed the equivalent training (Annex 3) to enable them to reproduce as accurately as possible all the clinical procedures as well as their interpretation for the intervention group.

Selection of 24 study practitioners

The study will be structured around three 6-month sessions (additional session if the enrolment period is extended). A total of 45 candidates will be selected as being eligible to take part in the study as practitioners. The 45 candidates will take part in 3 days of training and assessment, 2 of which will take place at the Cochin CHU Functional Rehabilitation Centre with the 3 osteopath trainers. Quality control is carried out continuously by the 3 osteopath trainers, in liaison with the clinical study technicians, in order to respond to questions from the practitioner osteopaths and to ensure standardisation of all of the procedures for the whole duration of the study. Following the assessments, 30 candidates will

be selected. These 30 candidates will be divided into 3 groups of 10, with each group corresponding to one 6-month session. The practitioners from one group will have the opportunity to take part in one of the next groups on the condition that they follow the osteopath trainer assessment process again.
Each group of 10 practitioners will consist of 8 practitioners taking part in the study plus 2 substitute practitioners, who can replace a practitioner at short notice in the event of unavailability. Each practitioner will be trained in the intervention and placebo, so that they are able to provide both approaches depending on patient assignment.

An audio recording will be made of the patients' sessions; 30 recordings will be chosen at random in each group. These recordings will be analysed by a sociologist in order to carry out a discourse analysis (duration, enthusiasm, empathy) on a numeric scale from 0 to 10. This is to confirm that the discourse by the therapists is the same in both arms.

The treatment and follow-up of patients will be centralised at the Cochin CHU Rehabilitation Department and Grenoble CHU Occupational Medicine Department, which allows the number of osteopaths to be reduced. Eight osteopaths, as well as two substitute osteopaths, will be involved in this study, every 6 months.

1.2.6 Comparator standardisation

The placebo must be standardised in the same way as the intervention will be standardised. Placebo standardisation will be achieved thanks to the highly detailed description of the procedures to be carried out (Annex 3).
The osteopaths will have 3 training/assessment days and will receive the detailed procedure of the sessions in the form of a DVD. This is also to confirm that the discourse by the therapists is the same in both arms.
The osteopathic interventions and osteopathic treatment placebo sessions will be recorded (audio), and a sociologist will analyse 30 random recordings to ensure that the duration of the sessions, the verbalisation, the quality of listening and dialogue, empathy and trust in the favourable outcome of the symptoms will be identical in both groups.

1.3 Population eligibility criteria

1.3.1 Inclusion criteria for patients

- Patients with sub-acute or chronic common low back pain as the main reason for consultation;
- Patients between the ages of 18 and 66;
- Working or in sick leave
- Patients able to speak and understand French;
- Patients affiliated with a social security scheme or beneficiary of such a scheme;
- Patients having provided written informed consent to take part before the start of the study.

1.3.2 Exclusion criteria

- Any chronic low back pain secondary to an inflammatory (rheumatic disorders), tumoural (myeloma, bone metastases) or infectious (osteomyelitis) cause and/or following spinal trauma in the past 3 months;
- Recent history (< 6 months) of vertebral fracture or spinal surgery;
- Patients with motor neurological signs (motor impairment) related to the reason for consultation;
- Patients who are manual therapy practitioners or students (osteopaths, chiropractors, etc.);
- Pregnant women;
- Patients with an impairment which does not allow them to properly understand the basic trial process;
- Patients taking part in another therapeutic protocol for a clinical study.

1.4 Intervention: osteopathic treatment

Patients in both groups (intervention and control) will receive 6 sessions of standard osteopathic treatment or osteopathic placebo treatment, at 15-day intervals. These sessions

will take place at the Cochin CHU Rehabilitation Department and Grenoble CHU Occupational Medicine Department.

1.4.1 Standardisation of the diagnostic part – 4 items

1.4.1.1 Osteopathic examination

The clinical procedures used in this study are commonly described, taught and practised in osteopathy: inspection, palpation of soft tissues and tests on all anatomical areas in each subject. The aim of the osteopathic examination is to assess the concomitant presence of the main clinical signs that have been associated with the presence of somatic dysfunction.

Table 1 – Clinical decision criteria on the presence or absence of somatic dysfunction based on 4 clinical signs: changes in soft-tissue texture, sensitivity/pain on palpation, restriction in movement/elasticity, and asymmetry of anatomical landmarks in movement

Osteopathic tests	Presence criteria	Absence criteria	References
Cranial (C test)	Restricted movement/elasticity and at least 2 other clinical signs found	0 to 1 clinical sign(s) found	McPartland
Neuromusculoskeletal (NMS test)	Restricted movement and at least 2 other clinical signs found	0 to 1 clinical sign(s) found	Hartmann
Visceral (V test)	Restricted movement and at least 2 other clinical signs found	0 to 1 clinical sign(s) found	Barral

The time assigned to the osteopathic examination is estimated to be 10 ± 2 minutes. The order in which the tests are performed is chosen in a way that optimises the subject's comfort for the duration of the clinical examination, as detailed in Annex 2[iii].

This general osteopathic examination will allow us to fill in the Outpatient Osteopathic SOAP Note Form (Annexe 5), which divides the body into 14 different anatomical regions to search for clinical signs associated with somatic dysfunction, according to the criteria set out in Table 1. Twelve areas (spine, pelvis and upper and lower limbs) are therefore assessed using neuromusculoskeletal tests, the cranium is assessed using cranial tests and the abdomen is

assessed using visceral tests. The full areas are therefore assessed, although seven have not been chosen as part of the anatomical areas included in the standard osteopathic treatment.

1.4.1.2 Clinical data collection

The osteopaths will fill in the Outpatient Osteopathic SOAP Note Form, a subjective and objective assessment form created by the American Academy of Osteopathy (AAO)**Error! Bookmark not defined.**[iv,v], which divides a subject's clinical assessment into 14 anatomical areas. It generally takes 4 minutes to fill in this document[53]. The osteopathic clinical data collected using this standardised form provide good intra- and inter-examiner accuracy when the recommendations of the authors are followed[vi].
Description of the Outpatient Osteopathic SOAP Note Form in Annex 5.

Clinical data interpretation
Each somatic dysfunction can be classified according to its importance on a scale from 0 to 3; a summary of the various degrees of severity is provided at the start of the table.

- 0 (none): no dysfunction present;
- 1 (mild): minimal dysfunction, the different endpoints are minor;
- 2 (moderate): the endpoints are clear, in particular hypomobility and/or changes in tissue texture;
- 3 (severe): major dysfunction, including somatic dysfunction endpoints, which are usually painful.

In the interest of simplification, both in methodological and practical terms, we decided to group and simplify these different scores into two categories: SD absent versus SD present. The clinical decision criteria regarding the presence or absence of somatic dysfunction used in our study are shown in Table 1.

1.4.2 Standardisation of the treatment part – 5 items

1.4.2.1 Selection of somatic dysfunctions to be treated during each session

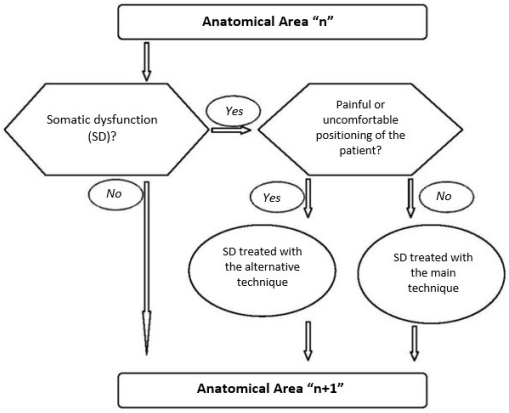
We decided that osteopathic treatment would be proposed on the basis of the data published and expert opinions in order to take into account the main somatic dysfunctions associated with low back pain (the most common ones). The patients would therefore receive treatment in an identical number of anatomical areas in neurological and biomechanical relation to the lumbar spine. This would therefore be a treatment based on the neurological model of somatic dysfunction in which the applied manual techniques would influence the perception of low back pain by changing the altered neurological reflexes: somatosomatic (posture), viscerosomatic and somatovisceral, in addition to their locoregional biomechanical action.[vii]

The locoregional effects of the osteopathic techniques which will be used are similar to the effects already described in the scientific literature[viii]:

- Reduction in muscle spasms;
- General relaxation;
- Improvement in movement;
- Drainage of cell exudates;
- Reduction in adherences;
- Improvement in microcirculation and drainage;
- Changes in the levels of serotonin and beta-endorphins in the blood
- Changes in the levels of endogenous cannabinoids in the blood[ix].

The osteopathic treatment will be standard and will include seven anatomical areas treated according to the results of the physical examination (personalised), as shown in the following diagram.

Diagram 1. Description of the sequence of anatomical areas for standard and personalised osteopathic treatment



Start of treatment

Area 1: Talocrural joint

Area 2: Root of mesentery

Area 3: Diaphragm

Area 4: Lumbar spine

Area 5: Sacroiliac joints

Area 6: Atlanto-occipital joints

Area 7: Temporomandibular joints

End of treatment

Each anatomical area must be treated with a main technique, but in the event of discomfort or pain in the patient's positioning, an alternative technique would be proposed (exactly the same principle as the main technique but performed in a different position) according to the following algorithm:

Algorithm 1. Decision-making algorithm for the techniques according to the presence of somatic dysfunction and patient pain/discomfort.

1.4.3 Selection of the technique to be used

The osteopathic technique is a non-forced manual response to the osteopathic diagnosis of somatic dysfunction. The choice of technique will be guided by (1) a previously suggested diagnosis, (2) compliance with contraindications in terms of manipulative treatment, and (3) patient comfort. Osteopathic manipulation is therefore not only a matter of spinal manipulation, although this is part of it.

1.4.3.1 Recommendations given to the patient

This advice will be similar in both groups as the advice given in osteopathy is not specific but an integral part of each consultation. A written document will be given to the patient with standardisation of the main advice given orally[x].

1.4.3.2 Consultation time

The osteopathic treatment and osteopathic placebo treatment sessions will last 30 minutes, with 15 minutes of preparation and setting up the patient on the treatment table (45 minutes in total).

1.4.4 Comparator: osteopathy placebo

The examination sequence will be exactly the same as the intervention group so that the examination time is equal in both groups (15 ± 2 minutes), like that of filling in the Outpatient Osteopathic SOAP Note Form (4 minutes).

- The same anatomical areas will be examined;
- The clinical signs of somatic dysfunction will not be studied;
- The results of this clinical examination should give the impression of being interpreted by the osteopath as far as the patient is concerned (the placebo treatment will be presented to the patient as being "test-dependant").

Unlike the standard osteopathic treatment, the placebo treatment will be light-touch (LT) http://www.jaoa.org/content/108/9/508.full, in order to prevent or at least reduce any therapeutic aspect of touching by the osteopath while maintaining the relationship of care developed during an osteopathic session. This now appears to be a good choice for simulating osteopathic treatment without simulating either a physiotherapy or massage approach[xi].

To reduce any beneficial effect to a minimum, which may be expected as with the osteopathic technique, the following protocol must be respected:

- use a fast and light touch by moving the hands every 5 seconds to prevent the body from responding mechanically to a prolonged force or contact;
- spread out and soften the surface of the hands which are carrying out the treatment to reduce the focalisation of the force.

The total treatment time is estimated to be 15 ± 2 minutes, the same as the intervention group. The total duration of the consultation will therefore be strictly identical to that of the interventional treatment, i.e. 45 minutes.

The location and severity of the SD is therefore not taken into account in the application of the placebo treatment, which will be standardised in a way that the patients receive exactly the same "treatment" as described in Annex 3. There is no alternative technique defined in the event of patient discomfort or pain; in this hypothesis, the light-touch protocol was defined in a way that allows it to be continued by changing the patient's position.

1.5 Diagram and conduct of the research

1.5.1 Sites

The recruiting sites are large University Hospitals (CHUs) in Île-de-France, within Assistance Publique des Hôpitaux de Paris, the head office of the AP-HP and a center in another French region at Grenoble CHU which is also a large structure, in order to optimise the eligible patient rate.

1.5.2 Recruitment method

A triple recruitment method will be organised:

1) Patient recruitment within Assistance Publique in the Île-de-France and Rhône-Alpes regions: Employees will be informed of the implementation of the study through the intranet portal, AP newspapers and by their division managers.
   Announcements will be prepared for the communication department, as well as letter templates for the division managers.
2) Local recruitment will be done in the two regions, informing the patients through local media and posters in pharmacies and waiting rooms of general practitioners and specialists, such as occupational physicians, rheumatologists and rehabilitation specialists. The information will refer to low back pain and manual therapy treatment. All patients who may be interested will be invited to contact a management centre **(green number)**, which will confirm the eligibility criteria,

provide the patient with information and refer the patient to an enrolment visit. The enrolment visit will be carried out by a specially trained physician.

3) A more traditional patient recruitment method will also be carried out at the time of consultation, through the same local networks of general practitioners and specialists agreeing to actively participate in this study.

   The recruitment of patients by occupational physicians from the 8 sites taking part in this study will be carried out as follows:

   - either directly in their “active files” for individuals already monitored for this condition, either working or on sick leave, and either with or without having adjusted their workstation;
   - or when identifying this condition at medical visits with the occupational physician (regular visits, pre-return to work, return to work after sick leave, etc.).

Patients recruited by these different methods will be referred to the Physical Medicine and Rehabilitation Department at Cochin Hospital or to Grenoble CHU Occupational Medicine Department for an inclusion visit, which will be centralised at two establishments: Cochin CHU and Grenoble CHU. This latter will include and follow-up potential participants. Enrolled patients will be evaluated at M3, M6 and M12. The evaluation will be carried out by post/over the phone by a clinical study technician, or if the patient prefers it can be done by logging on to an online platform to fill in the M3 and M6 self-questionnaires. A final visit with the physician will be carried out at 12 months.

1.5.3 Course of the study for each patient

D0: Enrolment/randomisation

- Verification of eligibility criteria;
- Patient information and collection of signed and dated informed consent form;
- Collection of all the information:
  - Quebec functional incapacity questionnaire;
  - numeric pain scale from 1 to 10;
  - number and duration of sick-leave periods since the start of the common low back pain;
  - number of relapses since the first episode of common low back pain;
  - SF-12 quality of life questionnaire;
  - consumption of painkillers and NSAIDs;
- Randomisation;
- Scheduling of appointment for the assigned intervention and the follow-up visits.

M3: Follow-up visit by phone/post by a clinical research technician or reporting of self-questionnaires by the patient via an online platform, according to the patient's preference

- Quebec functional capacity questionnaire;
- numeric pain scale from 1 to 10;
- number and duration of sick-leave periods since D0;
- number of relapses since D0;
- SF-12 quality of life questionnaire;
- consumption of painkillers and NSAIDs;
- adverse events;
- an additional criterion is collected: the end-of-treatment credibility in order to evaluate the patient's apprehension in terms of the osteopathic placebo treatment.

M6: Follow-up visit by phone/post by a clinical research technician or reporting of self-questionnaires by the patient via an online platform, according to the patient's preference. This assessment is carried out after 6 months of follow-up, i.e. 3 months after the end of treatment by manual therapy A or B, in order to collect all of the endpoints, i.e.:

- Quebec functional capacity questionnaire;
- numeric pain scale from 1 to 10;
- number and duration of sick-leave periods since the Month 3 visit;
- number of relapses since the Month 3 visit;
- SF-12 quality of life questionnaire;
- consumption of painkillers and NSAIDs;
- adverse events.

M12: End-of-study follow-up

The end-of-study follow-up will be carried out by the study doctor at a visit. The patients may, if they wish, choose to send their self-assessment card by post in a prepaid envelope, or choose to be contacted by phone by a clinical study technician, with the following information being collected over the phone:

- Quebec functional capacity questionnaire;
- numeric pain scale from 1 to 10;
- number and duration of sick-leave periods since phone call 3;
- number of relapses since phone call 3;
- SF-12 quality of life questionnaire;
- consumption of painkillers and NSAIDs;
- adverse events.

1.5.4 Visit dates

The dates of each of the visits are established by the protocol, with a margin of ± 15 days between the visits, in the event that it cannot be carried out or for independent practical reasons.

1.5.5 Place where the manual therapy sessions are carried out

The manual therapy sessions will be carried out at Grenoble CHU for participants included in this center, and at Cochin CHU for others. At Cochin Hospital, we have 8 consultation rooms per week: 7 from Monday to Saturday morning and 1 on Friday afternoon. As such, we have 8

half-days per week and 5 patients to be treated every 45 minutes for each half-day in the morning and 6 in the afternoon.

1.5.6 Expected duration of participation for each patient

The duration of the patient's participation in the study is 12 months.

1.5.7 Expected number of subjects to be enrolled and justification

The primary objective of the study is to evaluate the functional capacity in patients with sub-acute or chronic common low back pain using the Quebec score at 3 months. The p-value is 0.05. The desired power is equal to 0.90. In order to have an effect size of 0.35 for the difference between the average variations of the Quebec scale between the two groups (i.e. a difference between the averages of 7 points with a standard deviation of 20), 173 patients would have to be enrolled into each study arm, i.e. around 400 in total, taking into account losses-to-follow-up.

2 Statistical analysis

2.1 Endpoints

2.1.1 Primary endpoint

The primary endpoint is functional capacity at 3 months according to the Quebec questionnaire. This is a validated questionnaire consisting of 20 items grouped into 6 activity categories: bed/rest, sitting/standing, ambulation, movement, bending/stooping and handling of large/heavy objects. Scoring is done using a 6-point ordinal scale, from 0 (no difficulty) to 5 (incapable). An overall score is given (maximum 100); the highest scores correspond to the most severe physical impairment. If 3 values or fewer are missing, the missing values will be replaced by the mean.

2.1.2 Secondary endpoints

The secondary endpoints are as follows:

- back pain evaluated using a numeric scale from 0 to 10 at 3 and 12 months;
- number of sick-leave periods at 12 months;
- duration of sick-leave periods at 12 months;
- functional capacity (Quebec) at 12 months;
- number of low back pain relapses at 12 months;
- quality of life physical component assessment using the SF-12 questionnaire at 3 and 12 months. The SF-12 questionnaire is a short version of the Medical Outcomes Study Short-Form General Health Survey (SF-36) with only 12 of the 36 questions. It makes it possible to measure 2 main aspects: the physical component and the mental component (modification compared to the protocol which proposed 8 criteria) represented by 2 scores.
- The percentage of patients taking grades I, II or III painkillers at 3 and 12 months.
- The percentage of patients taking NSAIDs at 3 and 12 months.

2.2 Statistical analyses

The profile of selected patients and their effective follow-up through the course of the trial will be carried out in accordance with the CONSORT statement, according to a patient flow diagram.

Subjects withdrawing from the study early and the reason for this will also undergo a descriptive analysis by group and for the total population.

The patient follow-up parameters will be analysed for each treatment group and for the total population:

- Total follow-up duration;
- Treatment duration;
- Number of visits;
- Treatment compliance.

For each group, and at each of the evaluation dates, the qualitative endpoints will be described by their sample size, percentage and data missing by response method, and the quantitative endpoints will be described by their sample size, mean, standard deviation, median and interquartile range (25^{th} percentile - 75^{th} percentile), as well as the minimum and maximum.

The time period between randomisation and the osteopathic sessions will also be described.

The analysis population will involve all patients randomised into their randomisation group except:

1) Patients enrolled by mistake;
2) Patients withdrawing their informed consent and permission to use their data;
3) Patients not having given their consent.

A randomised patient who has not undergone the intervention or has partially undergone it will still be analysed. A description by group of these protocol deviations will be provided.

The primary endpoint is the change in the Quebec score between the baseline and 3 months. The variable to be studied will therefore be the difference in Quebec score between randomisation (D0) and the Month 3 visit: Δ = value at M3 – value at D0. The other differences will also be calculated (between the Month 12 visit and the enrolment visit). Comparison of the differences in Δ between the groups will be studied with a CLDA

(Constrained Longitudinal Data Analysis) linear model, taking into account the correlation of repeated measurements in the same subject (random patient effect with an unstructured variance-covariance matrix) under the hypothesis of randomly missing data. In this model, the baseline values are included in the response vector with the only condition that the average of this baseline must be the same for each group, which is the case in our studies as the subjects are randomly distributed. There is therefore no reason, in theory, to believe that one group would have a higher baseline than another. The CLDA technique is consistent with the intention-to-treat principle provided that all patients have at least one initial value for the endpoint or a post-baseline value, which allows all eligible randomised patients to be included. A center effect will also be added and possibly an interaction between the center and the treatment (in case of significance) in order to take into account on the one hand the differences between the centers and on the other hand the heterogeneity of the treatment effect between the centers. In addition, a therapeutic effect (osteopathic intervention or osteopathic placebo) fitted in the center will be added to take into account the correlation between patients subjected to the same therapist. The results will be expressed in the form of the difference between the average changes from baseline in each of the groups at 3 and 12 months with a 95% confidence interval and p-value of the associated test.

The following criteria will be analysed in the same way as the quantitative primary endpoint: back pain, as well as the 2 SF-12 summary scores).

For the binary qualitative criteria, a logistic regression model using marginal standardization estimation allows to estimate the percentage differences (with a 95% confidence interval and p-value for the associated test) at 3 and 12 months. A center effect and a therapist effect will be included in the model.

For the number of sick-leave periods, the duration of sick-leave periods, and the number of relapses in low back pain, the analysis will be carried out using a negative binomial regression model including an offset term which allows to take into account the time spent by the patient in the trial. The results will be presented in the form of mean ratio (with a 95% confidence interval and p-value of the associated test). If difficulties are encountered in terms of estimations (non-convergent model), the endpoints may be presented and analysed in binary form (number of patients with at least one sick-leave period, number of patients with at least one episode of low back pain) or quantitative form (duration of sick-leave periods).

The frequency of adverse events (serious, non-serious or both) will be described in each of the 2 groups (no statistical tests are planned).

All the tests will be bilateral and at the 5% threshold. The confidence intervals will be calculated at 95%. The CLDA model (MIXED procedure) will be carried out using SAS 9.4 software (SAS Institute). The other analyses will be carried out using R 3.2.2 software (R Foundation for Statistical Computing). The glm function and the stdReg package will be used for for marginal standardised logistic regressions. The glm.nb and coef.test functions will be used for negative binomial regression (with robust estimation of variance). Other softwares may be used if necessary.

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Method Supplement 4. **English translation of the study's final statistical analysis plan and summary of changes.**

Statistical analysis plan

EVALUATION OF TWO MANUAL THERAPIES

ON THE FUNCTIONAL CAPACITIES OF PATIENTS WITH SUB-ACUTE OR CHRONIC LOW BACK PAIN.

A RANDOMISED CONTROLLED TRIAL.

Short title: LC *OSTEO* -- Ref.: P 110142 - IDRCB 2012-A00167-36

Ct.gov registration number: NCT02034864

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Date	Version	Author	Signature	Comments
22/12/2017	V1	Gabriel Baron- Isabelle Boutron		Document created
16/02/2018	V2	Gabriel Baron Christelle Nguyen Isabelle Boutron		Second version of the SAP before the database is frozen

List of research sites

No.	Principal Investigator at the site (name, title, role)	Department	Site address	Telephone Fax
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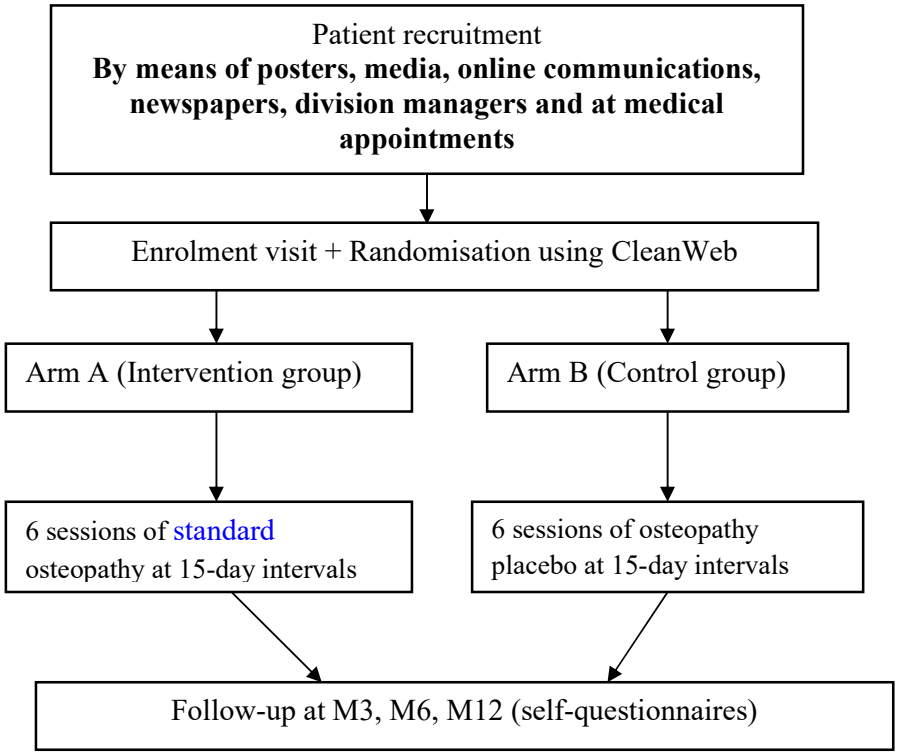
Table of contents

Protocol Summary

Study Title	Evaluation of two manual therapies on the functional capacities of patients with sub-acute or chronic low back pain. A randomised controlled trial.
Sponsor	AP-HP
Principal Investigator Scientific Leader	Prof. François Rannou Dr Peggy Krief Mr Rafael Zegarra-Parodi
Introduction and hypothesis	Complementary medicines such as manual therapy are being proposed increasingly more often, but there are few scientific studies on the efficacy of this therapy.
Primary objective	To evaluate the effectiveness of two manual therapies on improving functional capacity at 3 months in patients with sub-acute or chronic common low back pain.
Secondary objectives	To evaluate the effectiveness of a standard manual therapy on: - Pain (at 3 and 12 months); - Number and duration of sick-leave periods (at 12 months); - Number of relapses (at 12 months); - Quality of life (at 3 and 12 months); - Consumption of painkillers and NSAIDs (at 3 and 12 months).
Study type	A superiority randomised, controlled, multicentre trial (2 sites) comparing a manual therapy treatment with an osteopathic placebo treatment.
Inclusion criteria	- Patients with sub-acute or chronic common low back pain as the first reason for consultation; - Patients between the ages of 18 and 66; - Patients able to speak and understand French; - Patients affiliated with a social security scheme or beneficiary of such a scheme; - Patients having given their written informed consent to take part before the start of the study.
Exclusion criteria	- Any chronic low back pain secondary to an inflammatory (rheumatic disorders), tumoural (myeloma, bone metastases) or infectious (osteomyelitis) cause and/or following spinal trauma in the past 3 months; - Recent history (< 6 months) of vertebral fracture or spinal surgery; - Patients with motor neurological signs (motor impairment) related to the reason for consultation; - Patients who are manual therapy practitioners or students (osteopaths, chiropractors, etc.); - Pregnant women; - Patients with an impairment which does not allow them to properly understand the basic trial process; - Patients taking part in another therapeutic protocol for a clinical study.
Intervention	Six sessions of manual therapy at 15-day intervals.
Comparator	Six sessions of manual placebo therapy at 15-day intervals.
Primary endpoint	Evaluation of functional capacity using the Quebec questionnaire (consisting of 20 items grouped into six activity categories: bed/rest, sitting/standing, ambulation, movement, bending/stooping and handling of large/heavy objects)

	at 3 months.
Secondary endpoints	- Low back pain evaluation using the numeric pain scale from 0 to 100, at 3 and 12 months; - Number of sick-leave periods at 12 months; - Duration of sick-leave periods at 12 months; - Number of relapses at 12 months; - Functional capacity using the Quebec questionnaire at 12 months; - Quality of life physical component evaluation using the SF-12 questionnaire at 3 and 12 months; - Quality of life mental component evaluation using the SF-12 questionnaire at 3 and 12 months; - Consumption of painkillers and NSAIDs (yes/no) (at 3 and 12 months); - Consumption of NSAIDs (yes/no) (at 3 and 12 months).
Total number of patients expected	400 patients
Study duration	42 months
Duration of observation per patient	Maximum of 12 months of follow-up per patient from the time of their enrolment in the study
Expected results	This study will allow us to evaluate the effectiveness of manual therapy treatment in sub-acute or chronic common low back pain.

GENERAL OUTLINE OF THE STUDY



1 Protocol considerations

1.1 Research objectives

1.1.1 Primary objective

To evaluate the effectiveness of two manual therapies on improving functional capacity at 3 months in patients with sub-acute or chronic common low back pain.

1.1.2 Secondary objectives

To evaluate the effectiveness of standard osteopathic treatment on:

- pain (at 3 and 12 months);
- number and duration of sick-leave periods (at 12 months);
- number of recurrences (at 12 months);
- quality of life (at 3 and 12 months);
- consumption of painkillers and NSAIDs (at 3 and 12 months).

1.2 Experimental design

This is a superiority, randomised, controlled, multicentre trial comparing two manual therapies administered by osteopaths, a standard osteopathic treatment versus an osteopathic placebo treatment.

1.2.1 Randomisation

Randomisation will be centralised and stratified by site with variable block sizes.
The randomisation list will be generated by a computer program. The secret assignment will be ensured with the use of a Cleanweb-type eCRF.

1.2.2 Choice of comparator

For this trial, we chose to use an osteopathic placebo as the comparator. This choice was motivated by the importance of achieving blinding in the study. The primary endpoint in this study is functional impairment measured using the Quebec questionnaire. This is a patient-reported endpoint which will be highly subjective. A meta-analysis published by Wood[i] demonstrated that blinding is particularly important for subjective endpoints, with an overestimation of 25% in terms of the treatment effect.

The choice of osteopathic placebo will allow us to respond to a question related to the actual effectiveness of this intervention, as the effects linked to decorum and to contact with the therapist will be limited by the use of the placebo.
Comparator standardisation will be achieved thanks to the highly detailed description of the procedures to be carried out (Annex 3), and the making of a film to demonstrate the comparator.

1.2.3 Blinding

For this study, we decided to implement a patient blinding procedure by using a placebo intervention with patients blinded in terms of the hypotheses. Patients in the study will be blinded in terms of the treatment received. They will be informed that they are taking part in a study to compare 2 manual treatments for low back pain carried out by osteopaths. They will not be informed of the study hypotheses, i.e., that one manual treatment is a standard osteopathic treatment and that the other manual treatment will be an osteopathic placebo. They will be informed that we cannot explain all the study hypotheses to them due to scientific reasons, but that they will be informed of the results and the hypotheses at the end of the study.
The term “osteopathy” will not be used at any time during this study.
By definition, the therapists will not be blinded in terms of the treatment administered to the patients. The standard osteopathic treatment and the osteopathic placebo will be administered by specially trained osteopaths. The therapists must not use the term “osteopathy” in front of their patients. The therapists will have no other contact with the patients outside the sessions. They will not be involved in monitoring the patients, prescribing co-interventions or assessing patients.

The assessment will be carried out by the patients themselves, who are therefore blinded in terms of the treatment received (self-assessment logs). The statistical analysis will also be carried out by a blinded statistician from the Clinical Epidemiology Centre. In particular, the data related to the intervention description will not be analysed until a later stage to prevent the statistician being unblinded.

1.2.4 Complexity of the intervention

Osteopathy is a complex intervention combining several components and is personalised according to the osteopathic diagnosis.

In order to comply with international recommendations[ii], this intervention will be standard, the therapists will be trained and the level of accuracy in terms of the protocol will be evaluated.

Intervention standardisation will be achieved thanks to the highly detailed description of the procedures to be carried out (Annex 2 + Chapter 6), and the making of a film to demonstrate the intervention according to the various situations.

1.2.5 Therapist influence

The attitude of the therapists can have a major influence on the intervention's success. The therapists taking part in this study must therefore have received and passed the equivalent training (Annex 3) to enable them to reproduce as accurately as possible all the clinical procedures as well as their interpretation for the intervention group.

Selection of 24 study practitioners

The study will be structured around three 6-month sessions (additional session if the enrolment period is extended). A total of 45 candidates will be selected as being eligible to take part in the study as practitioners. The 45 candidates will take part in 3 days of training and assessment, 2 of which will take place at the Cochin CHU Functional Rehabilitation Centre with the 3 osteopath trainers. Quality control is carried out continuously by the 3 osteopath trainers, in liaison with the clinical study technicians, in order to respond to questions from the practitioner osteopaths and to ensure standardisation of all of the procedures for the whole duration of the study. Following the assessments, 30 candidates will

be selected. These 30 candidates will be divided into 3 groups of 10, with each group corresponding to one 6-month session. The practitioners from one group will have the opportunity to take part in one of the next groups on the condition that they follow the osteopath trainer assessment process again.
Each group of 10 practitioners will consist of 8 practitioners taking part in the study plus 2 substitute practitioners, who can replace a practitioner at short notice in the event of unavailability. Each practitioner will be trained in the intervention and placebo, so that they are able to provide both approaches depending on patient assignment.

An audio recording will be made of the patients' sessions; 30 recordings will be chosen at random in each group. These recordings will be analysed by a sociologist in order to carry out a discourse analysis (duration, enthusiasm, empathy) on a numeric scale from 0 to 10. This is to confirm that the discourse by the therapists is the same in both arms.

The treatment and follow-up of patients will be centralised at the Cochin CHU Rehabilitation Department, which allows the number of osteopaths to be reduced. Eight osteopaths, as well as two substitute osteopaths, will be involved in this study, every 6 months.

1.2.6 Comparator standardisation

The placebo must be standardised in the same way as the intervention will be standardised. Placebo standardisation will be achieved thanks to the highly detailed description of the procedures to be carried out (Annex 3).
The osteopaths will have 3 training/assessment days and will receive the detailed procedure of the sessions in the form of a DVD. This is also to confirm that the discourse by the therapists is the same in both arms.
The osteopathic interventions and osteopathic treatment placebo sessions will be recorded (audio), and a sociologist will analyse 30 random recordings to ensure that the duration of the sessions, the verbalisation, the quality of listening and dialogue, empathy and trust in the favourable outcome of the symptoms will be identical in both groups.

1.3 Population eligibility criteria

1.3.1 Inclusion criteria for patients

- Patients with sub-acute or chronic common low back pain as the main reason for consultation;
- Patients between the ages of 18 and 66;
- Patients able to speak and understand French;
- Patients affiliated with a social security scheme or beneficiary of such a scheme;
- Patients having provided written informed consent to take part before the start of the study.

1.3.2 Exclusion criteria

- Any chronic low back pain secondary to an inflammatory (rheumatic disorders), tumoural (myeloma, bone metastases) or infectious (osteomyelitis) cause and/or following spinal trauma in the past 3 months;
- Recent history (< 6 months) of vertebral fracture or spinal surgery;
- Patients with motor neurological signs (motor impairment) related to the reason for consultation;
- Patients who are manual therapy practitioners or students (osteopaths, chiropractors, etc.);
- Pregnant women;
- Patients with an impairment which does not allow them to properly understand the basic trial process;
- Patients taking part in another therapeutic protocol for a clinical study.

1.4 Intervention: osteopathic treatment

Patients in both groups (intervention and control) will receive 6 sessions of standard osteopathic treatment or osteopathic placebo treatment, at 15-day intervals. These sessions will take place at the Cochin CHU Rehabilitation Department.

1.4.1 Standardisation of the diagnostic part – 4 items

1.4.1.1 Osteopathic examination

The clinical procedures used in this study are commonly described, taught and practised in osteopathy: inspection, palpation of soft tissues and tests on all anatomical areas in each subject. The aim of the osteopathic examination is to assess the concomitant presence of the main clinical signs that have been associated with the presence of somatic dysfunction.

Table 1 – Clinical decision criteria on the presence or absence of somatic dysfunction based on 4 clinical signs: changes in soft-tissue texture, sensitivity/pain on palpation, restriction in movement/elasticity, and asymmetry of anatomical landmarks in movement

Osteopathic tests	Presence criteria	Absence criteria	References
Cranial (C test)	Restricted movement/elasticity and at least 2 other clinical signs found	0 to 1 clinical sign(s) found	McPartland
Neuromusculoskeletal (NMS test)	Restricted movement and at least 2 other clinical signs found	0 to 1 clinical sign(s) found	Hartmann
Visceral (V test)	Restricted movement and at least 2 other clinical signs found	0 to 1 clinical sign(s) found	Barral

The time assigned to the osteopathic examination is estimated to be 10 ± 2 minutes. The order in which the tests are performed is chosen in a way that optimises the subject's comfort for the duration of the clinical examination, as detailed in Annex 2[iii].

This general osteopathic examination will allow us to fill in the Outpatient Osteopathic SOAP Note Form (Annexe 5), which divides the body into 14 different anatomical regions to search for clinical signs associated with somatic dysfunction, according to the criteria set out in Table 1. Twelve areas (spine, pelvis and upper and lower limbs) are therefore assessed using neuromusculoskeletal tests, the cranium is assessed using cranial tests and the abdomen is assessed using visceral tests. The full areas are therefore assessed, although seven have not been chosen as part of the anatomical areas included in the standard osteopathic treatment.

1.4.1.2 Clinical data collection

The osteopaths will fill in the Outpatient Osteopathic SOAP Note Form, a subjective and objective assessment form created by the American Academy of Osteopathy (AAO)[Error! Bookmark not defined.,iv,v], which divides a subject's clinical assessment into 14 anatomical areas. It generally takes 4 minutes to fill in this document[53]. The osteopathic clinical data collected using this standardised form provide good intra- and inter-examiner accuracy when the recommendations of the authors are followed[vi].

Description of the Outpatient Osteopathic SOAP Note Form in Annex 5.

Clinical data interpretation

Each somatic dysfunction can be classified according to its importance on a scale from 0 to 3; a summary of the various degrees of severity is provided at the start of the table.

- 0 (none): no dysfunction present;
- 1 (mild): minimal dysfunction, the different endpoints are minor;
- 2 (moderate): the endpoints are clear, in particular hypomobility and/or changes in tissue texture;
- 3 (severe): major dysfunction, including somatic dysfunction endpoints, which are usually painful.

In the interest of simplification, both in methodological and practical terms, we decided to group and simplify these different scores into two categories: SD absent versus SD present. The clinical decision criteria regarding the presence or absence of somatic dysfunction used in our study are shown in Table 1.

1.4.2 Standardisation of the treatment part – 5 items

1.4.2.1 Selection of somatic dysfunctions to be treated during each session

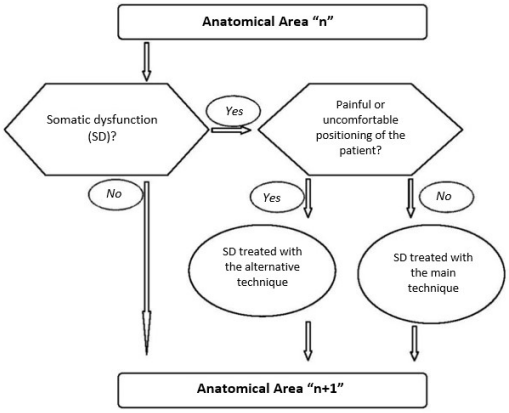
We decided that osteopathic treatment would be proposed on the basis of the data published and expert opinions in order to take into account the main somatic dysfunctions associated with low back pain (the most common ones). The patients would therefore receive treatment in an identical number of anatomical areas in neurological and biomechanical relation to the lumbar spine. This would therefore be a treatment based on the neurological model of somatic dysfunction in which the applied manual techniques would influence the perception of low back pain by changing the altered neurological reflexes: somatosomatic (posture), viscerosomatic and somatovisceral, in addition to their locoregional biomechanical action.[vii]

The locoregional effects of the osteopathic techniques which will be used are similar to the effects already described in the scientific literature[viii]:

- Reduction in muscle spasms;
- General relaxation;
- Improvement in movement;
- Drainage of cell exudates;
- Reduction in adherences;
- Improvement in microcirculation and drainage;
- Changes in the levels of serotonin and beta-endorphins in the blood
- Changes in the levels of endogenous cannabinoids in the blood[ix].

The osteopathic treatment will be standard and will include seven anatomical areas treated according to the results of the physical examination (personalised), as shown in the following diagram.

Diagram 1. Description of the sequence of anatomical areas for standard and personalised osteopathic treatment



Start of treatment

Area 1: Talocrural joint

Area 2: Root of mesentery

Area 3: Diaphragm

Area 4: Lumbar spine

Area 5: Sacroiliac joints

Area 6: Atlanto-occipital joints

Area 7: Temporomandibular joints

End of treatment

Each anatomical area must be treated with a main technique, but in the event of discomfort or pain in the patient's positioning, an alternative technique would be proposed (exactly the same principle as the main technique but performed in a different position) according to the following algorithm:

Algorithm 1. Decision-making algorithm for the techniques according to the presence of somatic dysfunction and patient pain/discomfort.

1.4.3 Selection of the technique to be used

The osteopathic technique is a non-forced manual response to the osteopathic diagnosis of somatic dysfunction. The choice of technique will be guided by (1) a previously suggested diagnosis, (2) compliance with contraindications in terms of manipulative treatment, and (3) patient comfort. Osteopathic manipulation is therefore not only a matter of spinal manipulation, although this is part of it.

1.4.3.1 Recommendations given to the patient

This advice will be similar in both groups as the advice given in osteopathy is not specific but an integral part of each consultation. A written document will be given to the patient with standardisation of the main advice given orally[x].

1.4.3.2 Consultation time

The osteopathic treatment and osteopathic placebo treatment sessions will last 30 minutes, with 15 minutes of preparation and setting up the patient on the treatment table (45 minutes in total).

1.4.4 Comparator: osteopathy placebo

The examination sequence will be exactly the same as the intervention group so that the examination time is equal in both groups (15 ± 2 minutes), like that of filling in the Outpatient Osteopathic SOAP Note Form (4 minutes).

- The same anatomical areas will be examined;
- The clinical signs of somatic dysfunction will not be studied;
- The results of this clinical examination should give the impression of being interpreted by the osteopath as far as the patient is concerned (the placebo treatment will be presented to the patient as being "test-dependant").

Unlike the standard osteopathic treatment, the placebo treatment will be light-touch (LT) http://www.jaoa.org/content/108/9/508.full, in order to prevent or at least reduce any therapeutic aspect of touching by the osteopath while maintaining the relationship of care developed during an osteopathic session. This now appears to be a good choice for simulating osteopathic treatment without simulating either a physiotherapy or massage approach[xi].

To reduce any beneficial effect to a minimum, which may be expected as with the osteopathic technique, the following protocol must be respected:

- use a fast and light touch by moving the hands every 5 seconds to prevent the body from responding mechanically to a prolonged force or contact;
- spread out and soften the surface of the hands which are carrying out the treatment to reduce the focalisation of the force.

The total treatment time is estimated to be 15 ± 2 minutes, the same as the intervention group. The total duration of the consultation will therefore be strictly identical to that of the interventional treatment, i.e. 45 minutes.

The location and severity of the SD is therefore not taken into account in the application of the placebo treatment, which will be standardised in a way that the patients receive exactly the same "treatment" as described in Annex 3. There is no alternative technique defined in the event of patient discomfort or pain; in this hypothesis, the light-touch protocol was defined in a way that allows it to be continued by changing the patient's position.

1.5 Diagram and conduct of the research

1.5.1 Sites

The recruiting sites are large University Hospitals (CHUs) in Île-de-France, within Assistance Publique des Hôpitaux de Paris, the head office of the AP-HP, in order to optimise the eligible patient rate.

1.5.2 Recruitment method

A triple recruitment method will be organised:

1) Patient recruitment within Assistance Publique in the Île-de-France and Rhône-Alpes regions: Employees will be informed of the implementation of the study through the intranet portal, AP newspapers and by their division managers.
   Announcements will be prepared for the communication department, as well as letter templates for the division managers.
2) Local recruitment will be done in the two regions, informing the patients through local media and posters in pharmacies and waiting rooms of general practitioners and specialists, such as occupational physicians, rheumatologists and rehabilitation specialists. The information will refer to low back pain and manual therapy treatment. All patients who may be interested will be invited to contact a management centre **(green number)**, which will confirm the eligibility criteria,

provide the patient with information and refer the patient to an enrolment visit. The enrolment visit will be carried out by a specially trained physician.

3) A more traditional patient recruitment method will also be carried out at the time of consultation, through the same local networks of general practitioners and specialists agreeing to actively participate in this study.

   The recruitment of patients by occupational physicians from the 8 sites taking part in this study will be carried out as follows:

   - either directly in their “active files” for individuals already monitored for this condition, either working or on sick leave, and either with or without having adjusted their workstation;
   - or when identifying this condition at medical visits with the occupational physician (regular visits, pre-return to work, return to work after sick leave, etc.).

Patients recruited by these different methods will be referred to the Physical Medicine and Rehabilitation Department at Cochin Hospital, which will be centralised at one establishment: Cochin CHU. Enrolled patients will be evaluated at M3, M6 and M12. The evaluation will be carried out by post/over the phone by a clinical study technician, or if the patient prefers it can be done by logging on to an online platform to fill in the M3 and M6 self-questionnaires. A final visit with the physician will be carried out at 12 months.

1.5.3 Course of the study for each patient

D0: Enrolment/randomisation

- Verification of eligibility criteria;
- Patient information and collection of signed and dated informed consent form;
- Collection of all the information:
  - Quebec functional incapacity questionnaire;
  - numeric pain scale from 1 to 10;
  - number and duration of sick-leave periods since the start of the common low back pain;
  - number of relapses since the first episode of common low back pain;
  - SF-12 quality of life questionnaire;
  - consumption of painkillers and NSAIDs;
- Randomisation;
- Scheduling of appointment for the assigned intervention and the follow-up visits.

M3: Follow-up visit by phone/post by a clinical research technician or reporting of self-questionnaires by the patient via an online platform, according to the patient's preference

- Quebec functional capacity questionnaire;
- numeric pain scale from 1 to 10;
- number and duration of sick-leave periods since D0;
- number of relapses since D0;
- SF-12 quality of life questionnaire;
- consumption of painkillers and NSAIDs;
- adverse events;
- an additional criterion is collected: the end-of-treatment credibility in order to evaluate the patient's apprehension in terms of the osteopathic placebo treatment.

M6: Follow-up visit by phone/post by a clinical research technician or reporting of self-questionnaires by the patient via an online platform, according to the patient's preference. This assessment is carried out after 6 months of follow-up, i.e. 3 months after the end of treatment by manual therapy A or B, in order to collect all of the endpoints, i.e.:

- Quebec functional capacity questionnaire;
- numeric pain scale from 1 to 10;
- number and duration of sick-leave periods since the Month 3 visit;
- number of relapses since the Month 3 visit;
- SF-12 quality of life questionnaire;
- consumption of painkillers and NSAIDs;
- adverse events.

M12: End-of-study follow-up

The end-of-study follow-up will be carried out by the study doctor at a visit. The patients may, if they wish, choose to send their self-assessment card by post in a prepaid envelope, or choose to be contacted by phone by a clinical study technician, with the following information being collected over the phone:

- Quebec functional capacity questionnaire;
- numeric pain scale from 1 to 10;
- number and duration of sick-leave periods since phone call 3;
- number of relapses since phone call 3;
- SF-12 quality of life questionnaire;
- consumption of painkillers and NSAIDs;
- adverse events.

1.5.4 Visit dates

The dates of each of the visits are established by the protocol, with a margin of ± 15 days between the visits, in the event that it cannot be carried out or for independent practical reasons.

1.5.5 Place where the manual therapy sessions are carried out

The manual therapy sessions will be carried out at Cochin CHU. At Cochin Hospital, we have 8 consultation rooms per week: 7 from Monday to Saturday morning and 1 on Friday afternoon. As such, we have 8 half-days per week and 5 patients to be treated every 45 minutes for each half-day in the morning and 6 in the afternoon.

1.5.6 Expected duration of participation for each patient

The duration of the patient's participation in the study is 12 months.

1.5.7 Expected number of subjects to be enrolled and justification

The primary objective of the study is to evaluate the average change in functional capacity in patients with sub-acute or chronic common low back pain using the Quebec score at 3 months. The p-value is 0.05. The desired power is equal to 0.90. In order to have an effect size of 0.35 for the difference between the average variations of the Quebec scale between the two groups (i.e. a difference between the averages of 7 points with a standard deviation of 20), 173 patients would have to be enrolled into each study arm, i.e. around 400 in total, taking into account losses-to-follow-up.

2 Statistical analysis

2.1 Endpoints

2.1.1 Primary endpoint

The primary endpoint is the average change in functional capacity at 3 months according to the Quebec questionnaire. This is a validated questionnaire consisting of 20 items grouped into 6 activity categories: bed/rest, sitting/standing, ambulation, movement, bending/stooping and handling of large/heavy objects. Scoring is done using a 6-point ordinal scale, from 0 (no difficulty) to 5 (incapable). An overall score is given (maximum 100); the highest scores correspond to the most severe physical impairment. If 3 values or fewer are missing, the missing values will be replaced by the mean.

2.1.2 Secondary endpoints

The secondary endpoints are as follows:

- average change in back pain evaluated using a numeric scale from 0 to 100 at 3 and 12 months;
- number of sick-leave periods at 12 months;
- duration of sick-leave periods at 12 months;
- average change in functional capacity (Quebec) at 12 months;
- number of low back pain relapses at 12 months;
- average change in the quality of life physical component assessment using the SF-12 questionnaire at 3 and 12 months. The SF-12 questionnaire is a short version of the Medical Outcomes Study Short-Form General Health Survey (SF-36) with only 12 of the 36 questions;
- average change in the quality of life mental component assessment using the SF-12 questionnaire at 3 and 12 months;
- percentage of patients taking grade I, II or III painkillers at 3 and 12 months;
- percentage of patients taking NSAIDs at 3 and 12 months.

2.2 Statistical analyses

The profile of selected patients and their effective follow-up through the course of the trial will be carried out in accordance with the CONSORT statement, according to a patient flow diagram.

Subjects withdrawing from the study early and the reason for this will also undergo a descriptive analysis by group and for the total population.

The patient follow-up parameters will be analysed for each treatment group and for the total population:

- Total follow-up duration;
- Treatment duration;
- Number of visits;
- Treatment compliance.

For each group, and at each of the evaluation dates, the qualitative endpoints will be described by their sample size, percentage and data missing by response method, and the quantitative endpoints will be described by their sample size, mean, standard deviation, median and interquartile range (25^{th} percentile - 75^{th} percentile), as well as the minimum and maximum.

The time period between randomisation and the osteopathic sessions will also be described. The same will be done for the time period between the diagnosis of low back pain and randomisation as well as for the time period between the last episode and randomisation.

The analysis population will involve all patients randomised into their randomisation group except:

1) Patients enrolled by mistake;
2) Patients withdrawing their informed consent and permission to use their data;
3) Patients not having given their consent.

A randomised patient who has not undergone the intervention or has partially undergone it will still be analysed. A description by group of these protocol deviations will be provided.

The primary endpoint is the change in the Quebec score between the baseline and 3 months. The variable to be studied will therefore be the difference in Quebec score between randomisation (D0) and the Month 3 visit: Δ = value at M3 – value at D0. The other

differences will also be calculated (between the Month 12 visit and the enrolment visit). Comparison of the differences in Δ between the groups will be studied with a CLDA (Constrained Longitudinal Data Analysis) linear model, taking into account the correlation of repeated measurements in the same subject (random patient effect with an unstructured variance-covariance matrix) under the hypothesis of randomly missing data. In this model, the baseline values are included in the response vector with the only condition that the average of this baseline must be the same for each group, which is the case in our studies as the subjects are randomly distributed. There is therefore no reason, in theory, to believe that one group would have a higher baseline than another. The CLDA technique is consistent with the intention-to-treat principle provided that all patients have at least one initial value for the endpoint or a post-baseline value, which allows all eligible randomised patients to be included. The results will be expressed in the form of the difference between the average changes from baseline in each of the groups at 3 and 12 months with a 95% confidence interval and p-value of the associated test.

The following criteria will be analysed in the same way as the quantitative primary endpoint: back pain, as well as the 2 SF-12 summary scores).

For the binary qualitative criteria, a Poisson model with log link allows to estimate the percentage differences (with a 95% confidence interval and p-value for the associated test) at 3 and 12 months (as well as the relative risk).

For the number of sick-leave periods, the duration of sick-leave periods, and the number of relapses in low back pain, the analysis will be carried out using a negative binomial regression model including an offset term which allows to take into account the time spent by the patient in the trial. The results will be presented in the form of mean ratio (with a 95% confidence interval and p-value of the associated test). If difficulties are encountered in terms of estimations (non-convergent model), the endpoints may be presented and analysed in binary form (percentage of patients with at least one sick-leave period, percentage of patients with at least one episode of low back pain) or quantitative form (duration of sick-leave periods).

The frequency of adverse events (serious, non-serious or both) will be described in each of the 2 groups (no statistical tests are planned).

All the tests will be bilateral and at the 5% threshold. The confidence intervals will be calculated at 95%. The CLDA model (MIXED procedure) will be carried out using SAS 9.4 software (SAS Institute). The other analyses will be carried out using R 3.2.2 software (R Foundation for Statistical Computing). The glm function will be used for the Poisson model and to estimate the confidence interval of the difference between the proportions. The glm.nb

and coef.test functions will be used for negative binomial regression (with robust estimation of variance). Other software or other functions may be used if necessary.

Summary of changes between study's original and final statistical analysis plans.

Administrative changes • Location of the clinical research unit and title of Prof Isabelle Boutron were amended. • Participation of CHU Grenoble as an investigating center was removed.
Study design • A precision about the superiority design was added.
Endpoints • Endpoints were described with more details. • A mistake about data collection for NSAIDs at 6 months was corrected.
Inclusion criteria • "Working or in sick leave" was removed.
Analyses • Descriptive analyses of the time period between the diagnosis of low back pain and randomisation as well as for the time period between the last episode and randomisation were added. • Model and functions used for analyses were described with more details.

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