Method Supplement 1. **English translation of the study's original protocol.**

COMPARISON OF THE EFFECTIVENESS OF 2 MANUAL THERAPIES ON FUNCTIONAL OUTCOME IN SUB-ACUTE AND CHRONIC LOW BACK PAIN LESS THAN 1 YEAR DURATION: A RANDOMISED CONTROLLED TRIAL.

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

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Biomedical research PROTOCOL SIGNATURE page

for the PRINCIPAL Investigator and the SPONSOR's representative

Biomedical research no. P110142 – IDRCB 2012-A 167-36

"COMPARISON OF THE EFFECTIVENESS OF 2 MANUAL THERAPIES ADMINISTERED BY OSTEOPATHS ON FUNCTIONAL OUTCOME IN SUB-ACUTE AND CHRONIC LOW BACK PAIN LESS THAN 1 YEAR DURATION: A RANDOMISED CONTROLLED TRIAL"

Version no. 1.1 dated 04/07/2013

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SPONSORSHIP DEPARTMENT
DRCD – APHP]

NB: This version corresponds to the protocol text and annexes sent to the Ethics Committee (CPP) and the competent authority for a request for opinion and authorisation, respectively, and to other parties involved in the research (hospital directors, etc.).

List of research sites

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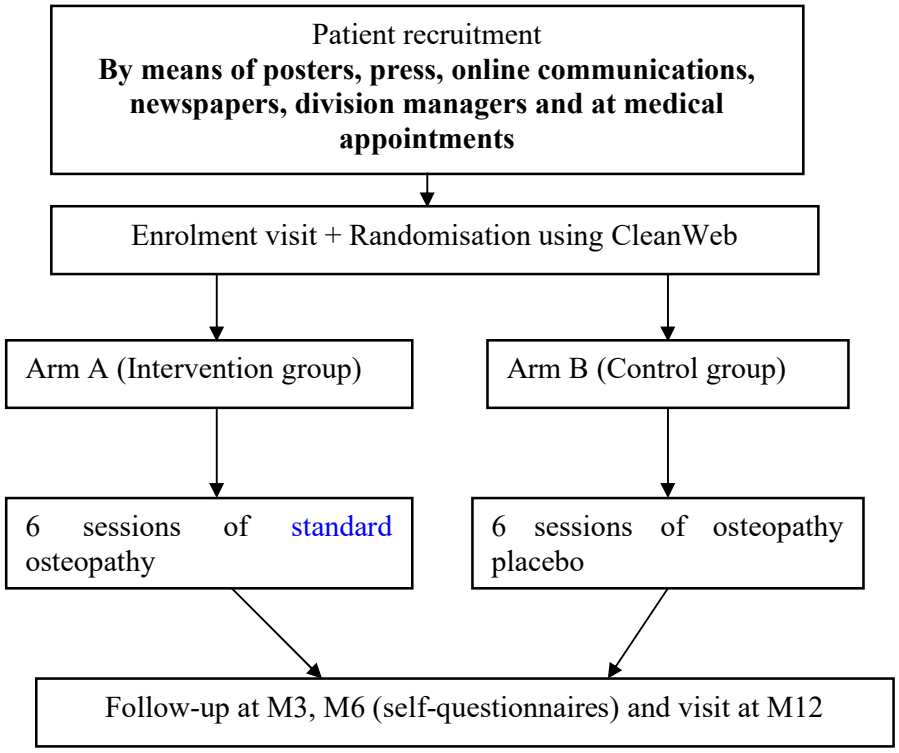
Protocol Summary

Study Title	Comparison of the Effectiveness of 2 Manual Therapies Administered by Osteopaths on Functional Outcome in Sub-acute and Chronic Low Back Pain Less Than 1 Year Duration: a Randomised Controlled Trial
Sponsor	AP-HP
Principal Investigator Scientific Leader	Prof. Serge Poiraudeau Dr Peggy Krief Mr Rafael Zegarra-Parodi
Introduction and hypothesis	Alternative 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 assess the effectiveness of two manual therapies on improving functional capacity at 3 months in patients who have had sub-acute or chronic common lower back pain for between 1 month and 1 year.
Secondary objectives	To assess the effectiveness of 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 non-steroidal anti-inflammatory drugs (NSAIDs) (at 3 and 12 months).
Study type	A randomised, controlled, multicentre trial comparing a manual therapy treatment with an osteopathic placebo treatment.
Inclusion criteria	- Patients with sub-acute or chronic common lower back pain as the main reason for consultation; - Common lower back pain for which the current episode has been progressing for between 1 month and 1 year; - Patient 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.
- Exclusion criteria	- Any chronic lower back pain secondary to an inflammatory (rheumatic disorders), tumour (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; - Chronic common lower back pain for which the current episode has been progressing for over 1 year; - 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 clinical trial therapeutic protocol.
Intervention	Six sessions of manual therapy at 15-day intervals.
Comparator	Six sessions of manual placebo therapy at 15-day intervals.

Primary endpoint	Assessment of functional capacity using the Quebec Back Pain Disability Scale 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 assessment using the numeric pain scale from 1 to 10, at 3 and 12 months; - Number and duration of sick leave periods at 12 months; - Number of recurrences at 12 months; - Functional capacity using the Quebec questionnaire at 12 months; - Quality of life assessment using the SF-12 questionnaire at 3 and 12 months; - Consumption of painkillers and NSAIDs (at 3 and 12 months).
Total number of patients expected	400 patients
Study duration	2.5 years
Patient observation duration	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 assess the effectiveness of manual therapy treatment in sub-acute or chronic common lower back pain.

GENERAL OUTLINE OF THE STUDY



Visits	D0	D15	M1	M1.5	M2	M2.5	M3	M6	M12
Inclusion/exclusion criteria, Information	X								
Information – Consent	X								
Enrolment Randomisation	X								
Examination and osteopathic treatment (intervention group) or placebo (control group)		X	X	X	X	X	X		
Assessment									
Quebec	X						X	X	X
Numeric pain scale	X						X	X	X
Number and duration of sick leave periods	X						X	X	X
Relapses	X						X	X	X
SF-12	X						X	X	X
Treatment credibility assessment							X		
Consumption of painkillers and NSAIDs	X						X	X	X
Adverse events / Serious adverse events		X	X	X	X	X	X	X	X

1 What is known about the issue

Chronic common lower back pain represents a public health problem, particularly at the socio-professional and economic level. Beyond the human suffering, they lead to functional disorders which disrupt professional activity. They account for a heavy financial burden on society as they lead to significant employee absenteeism and therefore a loss in efficiency for the company[3,4]. Numerous treatments have been proposed for this condition, but they have not been effective enough to reduce its incidence. Osteopathy, one example of manual therapy, belongs to the category of emerging alternative medicines which patients may resort to, although few scientific studies have been implemented to demonstrate their effectiveness[1,19,26,28]. We aim to assess the effectiveness of two manual therapies administered by osteopaths in patients who have had sub-acute or chronic common lower back pain for less than a year; this is particularly relevant as the assessment of alternative medicines is part of the AP-HP's 2010-2014 Strategic Plan.

1.1 Definition and epidemiology of sub-acute and chronic common lower back pain

1.1.1 Definition

Sub-acute and chronic common lower back pain is defined as a regular pain in the lower back area which can radiate as far as the knee without surpassing it, with sub-acute pain lasting between 4 and 12 weeks and chronic pain lasting more than 3 months, and for which secondary causes (infectious, inflammatory, tumour or traumatic causes) are ruled out from being at the origin of lower back pain, known as symptomatic causes[2].

1.1.2 Epidemiology

According to Llorca[3], lower back pain is the leading cause of disability in the under-45 population working in the industrial sector, the leading cause of restricted activity in individuals between the ages of 45 and 65, and the third leading cause of chronic disability. Its incidence is between 60% and 90% and its prevalence varies depending on the age and definition adopted. In France, it accounts for almost one-quarter of the reasons for rheumatology consultations and between 2% and 4% of general medical consultations. It has a considerable annual cost, amounting to around 1.5 billion euros in France.

Lumbar radicular pain (Table 98) and osteoarticular diseases (Table 57) account for the vast majority of the occupational diseases reported and recognised at the AP-HP. Osteoarticular diseases account for around 75% of sick leave causes at the AP-HP. Musculoskeletal disorders (MSDs) accounted for around 49% of all workplace accidents at the AP-HP in 2008 and 77% of workplace accidents involving sick leave. MSDs accounted for 85.5% of all sick leave days (workplace accidents or illness), which was around 44,000 days in total in 2008. (Source: Statutory Medicine and Control Department of the AP-HP 2008).

Sub-acute and chronic common lower back pain is extremely common. It will only become chronic in 8% of patients, but they account for over 85% of the costs incurred. The factors leading to chronicity and non-return to work are essentially a history of lower back pain, the presence of sciatica, the severity of the functional impairment, age and dissatisfaction at work[4].

1.2 Therapeutic methods and the limitations of their effectiveness

1.2.1 Medicinal treatments

Level 1, 2 and 3 analgesics act on lower back pain but these alone cannot solve the problem of chronic pain and the resulting disability[3]. Their use must comply with the contraindications and be limited to acute or short-lasting episodes, to prevent dependency.

NSAIDs at inflammatory doses may be prescribed for analgesic purposes in the short-term, in accordance with the contraindications. NSAIDs have proven to be effective particularly in acute episodes[5].

Muscle relaxants have not proven to be effective in chronic lower back pain compared to placebo[5]. They are essentially prescribed to patients with resurgence of pain over a period which must not exceed 2 weeks.

Antidepressants seem to develop an actual analgesic effect in chronic lower back pain[5], independent of their antidepressant effect.

Epidural corticosteroid injections appear to have a short-term analgesic effect in patients with lower back pain or sciatica [6].

1.2.2 Non-medicinal treatments

Physical therapy combined with physical exercises appears to be effective in terms of pain reduction and functional improvement in chronic lower back pain[7,8].

Multidisciplinary management, combining education and advice sessions, intense physical exercises either supervised or not by a physical therapist, and psychological management (at proportions yet to be determined), essentially allow for an improvement in functional capacity, leading to an earlier and longer-lasting return to work[9]. The improvement in terms of pain has not been demonstrated[10].

Spinal traction has not proven to be effective[11].

Spinal manipulations are slightly effective in terms of pain but studies are controversial: their effectiveness in terms of pain does not appear to be better than other existing treatments (physical therapy, painkillers, etc.)[12,13].

Acupuncture appears to have a short-term and long-term effect in terms of pain and functional capacity in chronic lower back pain[14,15]. This is likely to be a placebo effect (decorum)[16].

Percutaneous electrical stimulation treatment has not yet demonstrated its effectiveness. The 2005 literature review by Khadilkar was not able to reach any conclusions regarding the effectiveness of transcutaneous electrical nerve stimulation (TENS) due to the low number of randomised controlled studies and the contradictory results[17,18].

The choice of literature on the management of sub-acute and chronic common lower back pain was limited to randomised controlled trials. Most of the studies identified involve multiple and partial endpoints (pain, return to work, functional score, subjective improvement assessed by the patient, etc.). This means that the studies cannot be compared to each other and the results are very mixed. As a result of these methodological limitations, a gold-standard treatment cannot be recommended; all that can be recommended are proposals aimed at helping healthcare professionals manage these patients.

The following table provides a summary of the treatments and therapeutic effectiveness according to the levels of scientific evidence on sub-acute or chronic common lower back pain.

Treatment	Endpoint	Level of evidence	Therapeutic effectiveness
Physical therapy	Pain, function	1	Slightly effective in terms of pain Slightly effective in terms of function
Multidisciplinary programmes	Pain, function, return to work	1	Effective in terms of function and return to work Not proven to be effective in terms of pain
Acupuncture	Pain, function	1	Slightly effective in terms of pain and function
Spinal manipulation	Pain, function	1	Slightly effective in terms of pain Not proven to be effective in terms of function
Corticosteroid injection	Pain	2	Effective in the short-term
Antidepressant	Pain	2	Slightly effective
NSAID	Pain	2	Effective in the short-term
Analgesic	Pain	2	Moderately effective
Paracetamol	Pain	2	Slightly effective
Muscle relaxant	Pain	2	Not proven to be effective
TENS	Pain	2	Not proven to be effective
Spinal traction	Pain	2	Not proven to be effective

Table 1: Summary table of the treatments and their effectiveness in chronic lower back pain. Slightly effective = $5 \leq \Delta$ VAS < 15; moderately effective = $15 \leq \Delta$ VAS < 25; highly effective = Δ VAS ≥ 25.

These treatment methods are adapted to each patient according to the objectives set with them: the aim is to prevent excessive use of medication while ensuring therapeutic accompaniment which comforts the patient.

Allopathic medicine has its limitations: while it has proven to be effective in acute common lower back pain (continued activity + paracetamol), the situation is quite different for sub-acute (4 to 12 weeks) and chronic (> 3 months) lower back pain.

1.3 Data published on the effects of an osteopathic treatment on patients with lower back pain

(See Annexe 1 page 60 for further information on osteopathy.)

Considering that sub-acute and chronic common lower back pain represent a significant public health problem and that allopathic medicine has its limitations, patients are resorting to osteopathy, which belongs to the category of emerging alternative medicines, although few scientific studies have been conducted. Furthermore, the assessment of alternative medicines is part of the AP-HP's 2010-2014 Strategic Plan.

1.3.1 Effects on pain

A meta-analysis of randomised clinical studies assessing the effects of osteopathic manipulative treatment (OMT) in patients with chronic lower back pain showed that this treatment significantly reduced the pain, with better effects compared to the placebo and which last at least 3 months[19]. This meta-analysis published by Licciardone *et al*. in 2005 studied the results of 6 randomised clinical studies conducted in the USA and in the UK[20,21,22,23,24,25]. A total of 525 subjects with lower back pain were enrolled in the various randomised clinical studies. There was a significant reduction ($p = 0.001$) in the chronic lower back pain treated with OMT, and the effect size was modest at -0.30 (95% CI=[-0.47;-0.13]), which corresponds to a reduction of 6.5 mm on the VAS. There is also a significant reduction ($p = 0.02$) in pain in these randomised clinical studies in patients treated with OMT versus active treatment or versus placebo, with an effect size of -0.26 (95% CI=[-0.48;-0.05]).

1.3.2 Effects on functional capacity

In 2004, the "United Kingdom back pain exercise and manipulation (UK BEAM) Trial" team [26] published a study on 1,334 patients with chronic common lower back pain on the effects of spinal manipulations compared to the "best care", either with or without a therapeutic exercise programme. The comparator treatment ("best care") consisted of higher quality care than that of routine practice, as the general practitioners had received specific training in patients with lower back pain before the study. The main measurement instrument was the Roland-Morris Disability Questionnaire, which was used at the start of the study, at 3 months then at 12 months. There was a significant difference between the spinal manipulation and "best care" scores compared to "best care" alone at 3 months ($p = 0.001$) and at 12 months ($p = 0.01$).

The authors also used the SF-36 questionnaire to compare these same therapeutic approaches and observed a very significant difference at 3 months (p = 0.001) and a significant difference at 12 months (p = 0.01).
Throughout the whole study, the management method providing the best results was spinal manipulation (8 sessions of 20 minutes carried out by osteopaths, chiropractors and physiotherapists) combined with muscle reinforcement sessions (8 group sessions each lasting 60 minutes in the 6 weeks after the manipulations).

While the treatments assessed are not used in routine practice by osteopaths, as these professionals include other technical approaches, the authors concluded that the spinal manipulative treatment together with the treatment by the attending physician improves the patient's back function and quality of life more effectively than the treatment by the attending physician alone[27].
There are few osteopathic studies and they have significant methodological bias, as osteopathy belongs to the category of "complex interventions"[28] and it is difficult to implement blinding.

2 Research objectives

2.1 Primary objective

To assess the effectiveness of two manual therapies on improving the functional capacity at 3 months in patients with sub-acute or chronic common lower back pain for which the current episode has been progressing for between 1 month and 1 year.

2.2 Secondary objectives

To assess 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).

3 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.

This study will be planned, implemented, analysed and reported in accordance with the recommendations of the 2010 CONSORT Statement[29] and the CONSORT Statement extension for the assessment of non-pharmacological treatments[30,31].

The randomised, controlled trial is considered the gold standard for therapeutic assessment. However, the assessment of non-pharmacological treatments raises specific methodological issues related to the choice of comparator, difficulties in achieving blinding, the complexity of the intervention and the therapist's influence on the intervention's success[32].

The planning of this study took these difficulties into account.

3.1 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.

3.2 Choice of comparator

For this trial, we chose to use an osteopathic placebo as the comparator. This choice was motivated by the important 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[33] demonstrated that blinding is particularly important for subjective endpoints, with an overestimation of 25% in terms of the treatment effect.

The other comparators which were not chosen were as follows:

1) Standard medical treatment. However, in this situation, the blinding of patients and therefore the assessors was not possible, with a risk of disappointment in the patients randomised into the standard treatment group.
2) Physical therapy treatment. However, this choice would not allow us to respond to the question put forward.

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.

3.3 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. A modified Zelen design was not chosen as some of the patients will be recruited by occupational and rehabilitation physicians, and patients would have the opportunity to discuss this with each other, leading to a significant risk of this design failing.
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 lower 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 the other manual treatment is 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 the study.
The success of the blinding will not be assessed during the study as several methodology studies have shown this not to be useful and that such procedures involve a risk in terms of the methodological plan[34,35]. On the other hand, the credibility of the treatment received will be systematically assessed[36].
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. Clinical study technicians who are blinded in terms of the treatment received will be in charge of administering the assessments to patients.

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.

3.4 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[37], this intervention will be standard, the therapists will be trained and the level of accuracy in terms of the protocol will be assessed.

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.

The osteopaths dedicated to managing the intervention group and the control group will be trained before starting the study, in order to standardise the treatment (see 4.5.2 to 4.5.5). They will therefore have 3 training/assessment days and will receive the detailed procedure in the form of a DVD. Accuracy in terms of the protocol will be assessed through audio recordings of the sessions; 30 recordings will be chosen at random from 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.

In order to ensure maximum transparency at all stages, the making of the DVD as well as the recruitment, training and assessment of practitioners will go through a non-profit association.

3.5 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.

Special attention will also be paid to the style of communication of all the study practitioners, due to their placebo effect on patients with chronic musculoskeletal pain and treated with a complex intervention[16].

All practitioners must therefore follow the same style of communication during their treatments. Phrases or key words, expressing a more positive message on the issue of

treatment, will also be emphasised[16]. The treatment sessions will be recorded (audio) in both groups (see 3.6 Comparator standardisation, page 24-25/92).

Osteopath expertise

Performance of the practitioner recruitment procedure in accordance with the inclusion criteria

Context of osteopathic teaching in France compared to international standards

In 2007, French regulations opted for a study plan in which the number of hours was 40% lower than those elsewhere in Europe, Australia and New Zealand, and those recommended by the WHO regarding specific osteopath training[38]. In the field, osteopath training in France is highly varied. This situation justifies the fact that the study only included practitioners with training in accordance with European standards, in order to assess the osteopathic treatment in its most commonly practised form at the international level. This training allows practitioners to master clinical examination, diagnostic reasoning to assess the presence or absence of somatic dysfunctions as well as mastering all of the techniques described, adapted to the various anatomical areas, and which are not always approached in short or partial training courses.

Justification for choosing a high level of professional qualification for the practitioners

The European Qualifications Framework for Lifelong Learning (EQF) is the benchmark system created to standardise professional training and professional practice in Europe[39], [40], [41]. As of 2012, all the professional qualifications issued by higher education establishments in Europe should theoretically refer to a qualification level as described in the EQF[42]. Despite the current context in France in terms of the lack of qualifications for manual therapies, in January 2011, 10 private osteopathy teaching establishments obtained the highest level of professional qualification: level 1 of the French National Professional Qualifications Framework (RNCP)[43]. Eight of these 10 osteopathy teaching centres made a joint request mainly referring to the EQF procedures to define a professional qualification for the practice of osteopathy in France.

These 8 establishments issue the osteopath diploma after a 5-year full-time course in accordance with the recommendations made by the WHO on the subject[38]. For osteopathic practitioners who are already practising, they have the possibility of obtaining level 1 of the RNCP by undertaking a personal validation of prior experience (VAE) at any of these 10 establishments.

Inclusion criteria for study practitioners

The study practitioners must therefore be able to demonstrate the following points:

1/ Holders of an Osteopath Diploma issued: in France by one of the 10 establishments registered with level 1 of the RNCP, or abroad in a country where osteopathy is recognised and regulated;

2/ Holders of authorisation to practice osteopathy in France, issued by the competent authorities (Regional Health Agency, ARS);

3/ Holders of appendices to their training diplomas ("competency log"), in accordance with the European regulations on professional qualifications, who are able to demonstrate osteopathic training of at least 4,200 hours in accordance with the WHO Benchmarks and the existing professional competency regulations: General Osteopathic Council – GOsC (UK)[44], Forum for Osteopathic Regulation in Europe – FORE (Europe)[45], and Switzerland[46]);

4/ Up-to-date Individual Professional Liability and Legal Protection.

Selection of 24 study practitioners

The study will be structured around 3 6-month sessions. 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. Following the assessments, 30 candidates will be selected. These 30 candidates will be divided into 3 groups of 10, with each group corresponding to 1 6-month session.

Each group of 10 practitioners will be made up 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 the placebo, so that they are able to provide both approaches depending on patient allocation.

Overview of the training and assessment

The practitioner preparation and assessment phase will be carried out on 3 days over the course of a month. The assessment must be carried out each time, one month before the start of the first patient enrolments (the first training day will therefore be two months before the first enrolment):

Training and assessment

Dates: 2 days at a 15-day interval in the presence of 15 practitioners for the 6-month session.

Trainers: 2 osteopath supervisors and 1 clinical psychologist

Qualification of the trainers: Professional osteopaths and practising teachers, who hold a university diploma or a Master's in Education.

Role of the trainers: to provide criteria for verbalisation in accordance with the study requirements.

Assessment: 1 day, 15 days after the second training session carried out by 2 certifying osteopaths who will be different from the trainers.

The training and assessment will take place at the CEESO facilities (175 bd Anatole France, 93200 Saint-Denis).

Summary of the practitioner training procedure

Day 1

Presentation of the study as well as the basic methodological principles for assessment of a complex intervention, presentation and detailed description of the clinical procedures for the treatment group and the osteopathic placebo group, presentation of the assessment table and distribution of the DVD showing the techniques.

Aim: to acquire knowledge of the techniques and procedures in a sequenced manner. Group self-assessment with the help of a video tool.

Day 2

Recap on knowledge and sequencing, work on the specific parameters described in the literature regarding manual therapies for improving the intra- and inter-practitioner accuracy of the study's diagnostic procedures, description and validation by the osteopath supervisors of the different stages to reproduce the tests, their interpretation as well as the manipulation techniques, and then the implementation of all the clinical procedures in a timed manner.

Aim: understanding of the criteria to be worked on to improve the accuracy of the tests, their interpretation and the performance of the techniques so that the treatment will be standard and

personalised, acquisition of the implementation of intervention and placebo sessions from start to finish in 30 mins facing the patient, then proper explanation of the follow-up form in 10 mins. Group self-assessment including the video tool.

Teaching sheets for the training

1/ Understanding of the study

Detailed presentation of the study and its implications; complex interventions; specific features of the study compared to a doctor's surgery situation.

Role of the practitioners, rights and duties, relationships with the investigators.

Data from the literature on the reproducibility of the osteopathic tests and the methods for improvement.

The point on the osteopathic semiology, the somatic dysfunction study criteria and treatment.

2/ Test section

Presentation and demonstration of the tests by the osteopath supervisors.

Patient set-up and practitioner positioning.

Direction and amount of force used for the tests.

Interpretation of the tissue response to pressure applied.

Patient handling.

Verbalisation (main key words) for describing to the patient what the practitioner is doing.

3/ Standard osteopathic treatment

Presentation and demonstration of the 14 techniques by the osteopath supervisors one by one at first (Day 1) then in sequence (Day 2).

Patient set-up and practitioner positioning.

Direction and amount of force used for the techniques.

Interpretation of the tissue response to pressure applied.

Patient handling.

Verbalisation (main key words) for describing to the patient what the practitioner is doing.

4/ Osteopathic placebo treatment

Presentation and demonstration of the standardised procedure by the osteopath supervisors.

Patient set-up and practitioner positioning.

Direction and amount of force used for the techniques.
Patient handling.
Verbalisation (main key words) for describing to the patient what the practitioner is doing.

5/ Management of general verbalisation and end of the session

Presentation and detailed description of the verbalisation to be used according to the various phases of the consultation: questioning, physical examination, presentation of diagnosis, presentation of techniques, presentation of the issue of manual treatment.
Standardisation of key words to be used according to each phase of the consultation.
Advice and supervision by a clinical psychologist.
Presentation and detailed description of the standard healthy lifestyle advice to be given to patients for the next session: job, nutrition and hydration, "stay active", etc.

6/ Filling in of clinical forms

Presentation and explanation of the documents to be entered in the Outpatient Osteopathic SOAP Note Form: location and severity of the somatic dysfunction, techniques used, standardised abbreviations and specific points.

Performance of the practitioner assessment procedure

Day 3

Assessment in front of the certifying osteopaths who must fill in the assessment table (Annex 3) and in the presence of the other candidates. Two jurors, each having taken part in the training. Debriefing of the assessment in front of the other candidates, for training purposes.

For the record, each candidate is assessed over an hour, structured as follows:

- Presentation of the study and its key points (5 mins)
- Information collection practice (tests and symptom history) (10 mins)
- Standard osteopathic treatment practice (15 mins) for the osteopaths dedicated to the intervention group
- Osteopathic placebo treatment practice (15 mins) for the osteopaths dedicated to the control group
- End of consultation and advice (5 mins)

- Information regarding the form and time for any questions (10 mins)

In other words, 15 hours of assessment split between the two jurors (one full day).
The 8 chosen practitioners as well as the 2 substitute practitioners will be appointed.

The administrative data information will be sent to Dr Sanchez (plan, phone numbers and email addresses, traceability of reported assessment tables, etc.) for the planning of standard osteopathic treatment or osteopathic placebo treatment sessions at the sites dedicated to managing study patients.
A total of 3 training sessions will be carried out at 6-month intervals.

An audio recording will be made of the patients' sessions; 30 recordings will be chosen at random from 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 the Grenoble CHU Occupational Medicine Department, which allows the number of osteopaths to be reduced. Eight osteopaths (4 for the intervention group and 4 for the control group) as well as 2 substitute osteopaths will be involved in this study.

3.6 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 carrying out the placebo intervention will therefore 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 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.

4 Eligibility criteria of the population

4.1 Inclusion criteria for patients

- Patients with sub-acute or chronic common lower back pain as the main reason for consultation;
- Common lower back pain for which the current episode has been progressing for between 1 month and 1 year;
- Patients between the ages of 18 and 66;
- Working or on 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.

4.2 Exclusion criteria

- Any chronic lower back pain secondary to an inflammatory (rheumatic disorders), tumour (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;
- Chronic common lower back pain for which the current episode has been progressing for over 1 year;
- 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 clinical trial therapeutic protocol.

5 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 at the Grenoble CHU Occupational Medicine Department.

5.1 Standardisation of the diagnostic part – 4 items

5.1.1 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.

Somatic dysfunction is a pathological entity referenced in the International Classification of Diseases, which is defined as "impaired or altered function of related components of the somatic (bodywork) system including: the skeletal, arthrodial, and myofascial structures, and their related vascular, lymphatic, and neural elements"[47]. The clinical signs which have been associated with joint somatic dysfunction have traditionally been described with the acronym "SART" (Sensitivity/pain on palpation; Asymmetry of the bony landmarks; Restriction in passive joint movement; changes in the Texture of the surrounding soft tissues)[48]. The osteopath determines the severity of the somatic dysfunction according to the significance and concomitant presence of the palpated clinical signs which can be improved and reduced following suitable manual treatment.

There are three main categories of osteopathic tests according to the anatomical areas being assessed: cranial[49], neuromusculoskeletal[50] and visceral[51]. The clinical signs associated with somatic dysfunction will be studied and interpreted according to the criteria set out in Table 1 in terms of presence (which will require a manipulation technique) and absence (no manipulation technique performed).

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 mobility/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 signs symptoms found	0 to 1 sign(s) symptom found	McPartland
Neuromusculoskeletal (NMS test)	Restricted movement and at least 2 other signs symptoms found	0 to 1 sign(s) symptom found	Hartmann
Visceral (V test)	Restricted movement and at least 2 other signs symptoms found	0 to 1 sign(s) symptom 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[52].

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 in the 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 7 have not been chosen as part of the anatomical areas included in the standard osteopathic treatment.

5.1.2 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)[48,53,54], 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 file provide good intra- and inter-examiner accuracy when the recommendations of the authors are followed[55].

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.

5.2 Standardisation of the treatment part – 5 items

5.2.1 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 lower back pain (the most common ones). The patients would therefore receive treatment in an identical number of anatomical areas in neurological and biomechanical terms with 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 lower back pain by changing the altered neurological reflexes: somatosomatic (posture), viscerosomatic and somatovisceral, in addition to their locoregional biomechanical action.[56]

The locoregional effects of the osteopathic techniques which will be used are similar to the effects already described in the scientific literature[57]:

- Reduction in muscle spasms;
- General relaxation;
- Improvement in movement;
- Drainage of cell exudates;
- Reduction in adherences;

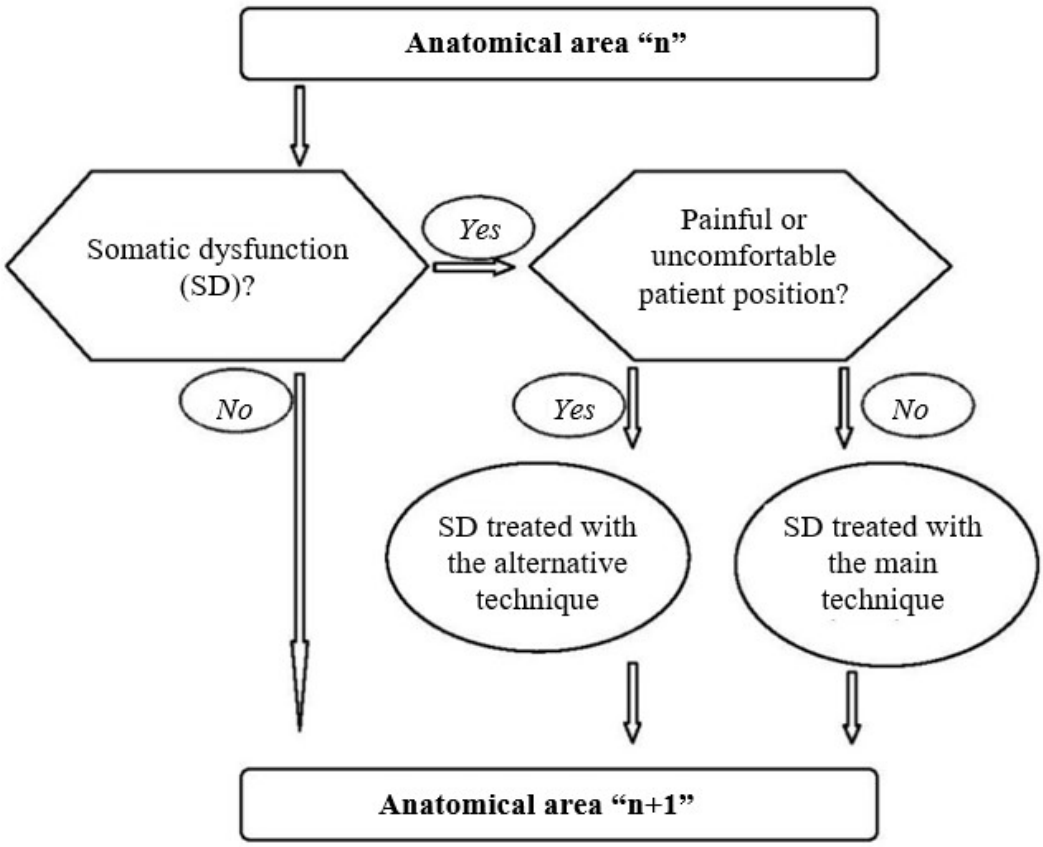
- Improvement in microcirculation and drainage;
- Changes in the levels of serotonin and beta-endorphins in the blood[27];
- Changes in the levels of endogenous cannabinoids in the blood[58].

The osteopathic treatment will be standard and will include 7 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 algorithm for the techniques according to the presence of somatic dysfunction and patient pain/discomfort.



Description of the 7 anatomical areas for standard and personalised osteopathic treatment

Anatomical area 1: Talocrural joint

It is advisable to assess the overall biomechanical function of the lower limbs in the understanding of chronic lower back pain mechanisms[59], as these pains can be associated with adaptation impairment in terms of trunk rotation when walking. Functional instability of the ankle has also been recognised as a predisposing factor for lower back pain due to impaired trunk-stability muscle reflexes which have been associated with this, although no cause-effect link has ever been proven[60].

Anatomical area 2: Root of mesentery

The mesentery is rich in mechanoreceptors and graviceptors[61,62], the reflex neurological paths of which electively borrow those of the orthosympathetic system through the splanchnic nerves and transit through the middle vertebral levels (T9-T10-T11)[63,64]. The release of

visceral connective tissue tension would allow the intra-abdominal pressure to be better distributed and to restore better flexibility to the serous mesenteric joint. These two factors are involved in the construction of the composite beam of the lumbar spine[65]. In order to relieve the pressure on the intervertebral discs, this stabilises on the intra-abdominal cavity, which varies in geometry and pressure[66]. As such, the mechanical information originating from the mesentery could influence the spinal posture by directly modulating the sensitivity thresholds of the musculature of the lumbar spine and the lower limbs.

Anatomical area 3: Diaphragm

Chronic discogenic pain is conveyed by the sinuvertebral nerve[67], which also conveys the nociceptive influx of the anterior longitudinal ligament. In the lower back area, the anterior longitudinal ligament would be the extension of the pillars of the diaphragm[68]. The manual techniques on the diaphragm could therefore theoretically act on the nociceptive reflex arcs. Hodges and Gandevia studied whether the diaphragm activations would interfere with the respiratory cycle phases or with posture[69]. The repeated movements show two changes in the diaphragm which are not correlated to respiration: (1) a tonic contraction during the respiratory cycle, associated with an increase in abdominal pressure. This confirms the diaphragm's role in covering the lower back area during trunk movements; (2) a phasic contraction which demonstrates the diaphragm's role in controlling movements up to the lumbar spine.

Anatomical area 4: Lumbar spine

There are multiple nociceptive information sources involved in lower back pain.

In addition to the posterior facet joints, which may be capable of responding to manipulation treatment[70], other sources of nociceptive irritation have been demonstrated: thoracolumbar fascia[71,72], dura mater[73] and the supraspinous ligaments[74], the experimental stimulation of which causes lower back pain.

Anatomical area 5: Sacroiliac joints

The pelvis represents a connection between the trunk and the lower limbs, and is a key part of the lumbar-pelvic-femoral complex[75]. The sacroiliac joints and the pubic symphysis have a biomechanical role of the absorption joints of this complex by fragmenting gravity[76,77].

On the other hand, the sacroiliac joint has an innervation which, when strained, is prone to leading to lower back pain[78]. Pelvic girdle joint movements would allow for an improvement in lumbar spine strain adaptation and also to act on the nociceptive reflex arcs.

Anatomical area 6: Atlanto-occipital joints

McPartland *et al*.[79] studied the influence of the rectus capitis posterior (RCP) minor muscles and their involvement in postural control due to their high-density neuromuscular spindles. According to these authors, the proprioceptive function of the RCP major and RCP minor muscles is related to those of the spinal postural muscles. A manipulation procedure on the craniocervical junction would aim to reduce the tonicity of the lumbar erector muscles.

Anatomical area 7: Temporomandibular joints (TMJs)

Various authors have identified a direct relationship between temporomandibular and postural disorders which can manifest through chronic lower back pain[80,81,82]. In a case-control study, patients with craniomandibular disorders had a significantly higher number of pain sites, including the lower back[83]. A study by Wiesinger *et al*. showed a statistically significant association between chronic lower back pain and musculoskeletal disorders of the jaw and face, and reported comorbidity between these two symptoms[84].

5.2.2 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 manipulation treatment, and (3) patient comfort. Osteopathic manipulation is therefore not only a matter of spinal manipulation, although this is part of it. Numerous manual techniques are referred to in the Authorized Osteopathic Thesaurus[85] and can be divided into 4 broad categories according to the amount of force, the rhythm and the speed used: (1) rhythmic, (2) high-velocity, low-amplitude (HVLA, the “manipulation” which is accompanied by joint noise), (3) “low-velocity stress”, and (4) visceral[86].

Following the osteopathic examination of each anatomical area, there will be 2 possibilities:
Somatic dysfunction absent: no corrective technique
Somatic dysfunction present: corrective technique carried out by the osteopath

Following the osteopathic examination, to carry out a corrective technique on an anatomical area with somatic dysfunction, there will be 2 possibilities:
Patient free from discomfort and pain: main corrective technique;
Patient with discomfort or pain: alternative corrective technique (same technique carried out with the patient in a different position).

5.2.3 Performance of the techniques

Description of the techniques for each anatomical area: main technique and alternative technique. There will be no cervical spine manipulations. The total treatment time is estimated to be 15 ± 2 minutes.

Anatomical area 1: Talocrural joints - Main technique
Talocrural joint stretching technique[93]
Subject: supine position
Practitioner: standing on the side ipsilateral to the dysfunctional ankle, the practitioner turns their back to the patient. For the right ankle, the practitioner places their bent left knee under the patient's right knee, places their left elbow on the table against their own thigh and holds the patient's right foot between their two hands: the left hand applicator holds the calcaneus, and the right hand applicator is placed towards the dorsal surface of the talus. With the ankle firmly held, the practitioner carries out an elbow-extension movement. With the practitioner's forearm outstretched and stable, a lever arm is created which applies traction in order to stretch the talocrural joint. The practitioner must find a good ankle-positioning angle to carry out the stretching, and alternate between traction and compression by changing the degrees of elbow flexion/extension. The technique may be accompanied by joint noise.

Anatomical area 1: Talocrural joints - Alternative technique
Same principles as the main technique with the patient's leg extended
Subject: supine position
Practitioner: standing at the patient's feet, they hold one ankle while placing the contralateral hand under the calcaneus and the ipsilateral hand on the dorsal side of the talus; with the ankle stabilised by the two hands, the practitioner searches for the best premanipulation tension by changing the degree of flexion/extension of the talocrural joint and carries out repeated tractions of low amplitude in the tibial axis.

Anatomical area 2: Root of mesentery - Main technique
Osteopathic technique on the root of mesentery[87]
Subject: supine position on the table, with the knees bent and the feet on the table.
Practitioner: standing to the left of the patient, with their back towards the patient's head. With the right hand, they palpate the abdomen around the small mass along the axis of the

root of mesentery (little finger around the ileocaecal valve up to the duodenojejunal flexure on the thenar eminence side) and with their left hand in parallel but on the other side of the axis of the root in the left iliac fossa concavity. The technique consists of entering the patient's abdominal mass as deeply as possible without causing severe pain, performing a combination of multiple tensions (backward pressure, clockwise and anticlockwise twists, right and left side tractions, etc.) in the opposite direction to the movement/elasticity restrictions found on examination. The technique must be accompanied by abdominal breathing by the patient.

Anatomical area 2: Root of mesentery - Alternative technique
Subject: right lateral recumbent position, with the hips and the knees bent.
Practitioner: standing at the patient's back, with the left knee bent and placed on the examination table, the left iliac against the patient's pelvis; the practitioner presses the abdomen with both hands around the patient's small mass with the little finger of the left hand pressing deeply in the right iliac fossa concavity. The technique consists of rhythmically raising and mobilising the patient's small mass, with the patient firmly held between the pelvis at the back and the practitioner's hands at the front.

Anatomical area 3: Diaphragm - Main technique
Subject: supine position with the legs bent.
Practitioner: Standing to the right of the patient, they press the lower edge of the right ribcage with the finger pads, with the left forearm against the chest. The patient is asked to breathe deeply while filling the stomach. On inhalation, the practitioner increases the opening movement of the ribcage. On exhalation, the lowering of the ribs is accompanied by their forearm and at the same time enters deeper against the medial side of the ribs accessible under the fingers, around the diaphragmatic insertions (R7 to R10, approximately). Carry out the same procedure in the patient's left hemithorax.

Anatomical area 3: Diaphragm - Alternative technique
Diaphragm lift technique[88]
Subject: supine position with the legs bent.
Practitioner: Standing at the patient's head, they make contact with the lower edge of the ribcage with the finger pads. The patient is asked to breathe deeply while filling the stomach. On inhalation, the practitioner increases the opening movement of the ribcage. On exhalation, they maintain the parameters of tension and abruptly release the tension when the patient takes another deep breath.

Anatomical area 4: Lumbar spine - Main technique

Lumbar joint work technique (ART) known as “general osteopathic treatment”[89],

Technique Subject: right lateral recumbent position then left; Practitioner : standing oblique facing the subject.

The following description uses the example of a patient in the right lateral recumbent position. All parameters should be reversed to carry out the techniques on the other side.

Patient: right lateral recumbent position, with the right leg outstretched and the left leg bent, with the knee at the edge of the table so that it is mobile; the trunk is placed in slight left rotation, and the patient grips their left wrist with their right hand.

Practitioner: squatting position facing the patient, oriented at about 45° towards the patient’s head. The right forearm holds and stabilises the left hemipelvis, and the left forearm passes under the patient’s left arm while holding and stabilising the left hemithorax. Both hands are free and can palpate the lower back area during the technique.

The adjustment is made through mobilisation of the lumbar spine in all joint mobility parameters. The practitioner mobilises the spine using both arms and their body, carrying out an opposite circumduction from the two points of support in order to reproduce a figure 8 at the lumbar level. Mobilisation is carried out by converging the strains on the whole lumbar spine level by level up to the thoracolumbar junction, with emphasis on the areas of dysfunction.

Anatomical area 4: Lumbar spine - Alternative technique

Lumbar joint work technique (ART) known as “general osteopathic treatment”[94],

Patient: supine position with one leg bent and the other outstretched; Practitioner: Sitting next to the subject, on the same side as the bent leg.

Motor hand: medial hand holds the thigh and the arm stabilises the lower limb.

Palpatory hand: the finger pads of the lateral hand press the L5 spinous processes.

Adjustment is done by joint work and circumduction of the lumbar spine from a wide circumduction of the hip using the leg as a lever. The index finger stabilises L4 and the middle finger mobilises L5. We expect tissue release of the posterior soft tissues and a gain in movement among the restricted segments. The lateral hand therefore moves up to L1 under T12. The manoeuvres are carried out on the right and on the left.

Anatomical area 5: Sacroiliac joints – Main technique

Subject: lateral recumbent position

The practitioner makes contact with the lumbosacral junction and pulls the patient's arm contralateral to the sacroiliac joint to be mobilised, to stabilise the spine in neutral rotation.
The practitioner places the patient's crossed hands on the lateral side of the ipsilateral hemithorax.
The practitioner places the ipsilateral foot in the popliteal hollow and extends the contralateral leg.
The practitioner supports the trunk and the spinal segment, with the cephalic forearm which passes under the patient's forearm.
The practitioner places their caudal forearm perpendicular to the posterosuperior iliac spine segment/greater trochanter.
The practitioner applies premanipulation tension with the caudal forearm in the axis of the sacroiliac joint and combines different movements (rotations, sliding and compression). The pulse is carried out using the caudal segment, respecting the plane of the joint surfaces forwards and outwards. The technique is carried out for both sacroiliac joints.

Anatomical area 5: Sacroiliac joints – Alternative technique
High-velocity, low-amplitude technique on the sacroiliac joints, known as the "Chicago technique".[63]
Subject: supine position on the table, hands joined behind the neck, legs outstretched and crossed (the leg on the side of the mobilised sacroiliac joint is on top).
Practitioner: Standing next to the table opposite the sacroiliac joint to be mobilised.
The practitioner moves the patient's torso towards them, and the patient's feet.
The caudal hand presses on the anterior superior iliac spine ipsilateral to the sacroiliac joint.
The practitioner raises the patient by the elbow ipsilateral to the sacroiliac joint, passing the cephalic forearm in the patient's elbow from top to bottom, from back to front and moving towards the anterior superior iliac spine contralateral to the sacroiliac joint. The premanipulation tension is applied by combining flexion/extension parameters and trunk rotation.
The practitioner applies mobilisation with a thrust, and the pulse is given by the caudal arm in the axis of the joint going backwards and inwards. The technique is carried out for both sacroiliac joints.

Anatomical area 6: Atlanto-occipital joints - Main technique
MET (muscle energy technique) craniocervical manipulation technique[94]
Subject: supine position

Practitioner: standing at the patient's head

The caudal anterior hand presses the chin between the index finger and the middle finger, bringing flexion of the dysfunctional atlanto-occipital joint. The cephalic posterior hand presses the occiput, with the index finger and the middle finger positioned around the occipital condyles, and causes a slight cephalic traction up to the restriction of joint mobility by combining a slight rotation with a contralateral tilt.

In this position, the patient is asked to look upwards to contract the small and large right posterior muscles for 3 seconds. During this time, the practitioner maintains resistance with the caudal hand. While the patient releases the contraction, the practitioner slightly increases the parameters of slight rotation combined with contralateral tilt and repeats this manoeuvre 3 times in order to gradually recover the joint mobility that had been lost.

Anatomical area 6: Atlanto-occipital joints - Alternative technique

Strain-counterstrain craniocervical manipulation technique

Subject: supine position

Practitioner: standing at the patient's head

The caudal anterior hand presses the chin between the index finger and the middle finger, bringing flexion of the craniocervical junction. The cephalic posterior hand palpates around the muscle hypertonia of the suboccipital muscles found in the examination. The osteopath searches for a comfortable position in muscular shortening, and this non-painful position is held for 30 seconds, before making a slow and passive return to the neutral position. The manoeuvre is repeated 3 times.

Anatomical area 7: Temporomandibular joints - Main technique

Temporomandibular joint (TMJ) technique

Subject: supine position on the table

Practitioner: seated at the patient's head, they place the thumbs along the rising branches, with the finger pads around the mandibular angle, with the other fingers coming to press the jaw towards its medial side. The technique consists of rubbing, mobilising and pulling the jaw and the masticatory muscles in order to achieve a circumduction of the TMJ.

Anatomical area 7: Temporomandibular joints - Alternative technique

Mandibular osteopathic technique[90]

Subject: supine position on the table

Practitioner: standing next to the table, with an examining fingertip on each thumb, they press the horizontal branches of the patient's jaw by placing the anterior side of the thumbs on the lower dental arches. With the other fingers holding the lower edge of the jaw, with 5 close to the gnathion, 4 around the mandibular insertion of the digastric muscle, 3 around the mylohyoid muscle, and 2 around the medial pterygoid muscle insertion. The practitioner applies a slight caudal traction force before carrying out a soft circumduction movement aimed at mobilising the TMJ in its restricted mobility parameters and relaxing the masticatory muscles (medial and lateral pterygoids, masseters and temporal).

5.2.4 Recommendations given to patients

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[91].

5.2.5 Consultation time

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

6 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[92].

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.

7 Endpoints

All of the endpoints will be collected or verified by an evaluator, a clinical study technician, who will have no knowledge of the treatment given to the patient.

7.1 Primary endpoint

The primary endpoint will be functional capacity at 3 months according to the Quebec questionnaire[93]. 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. The metrological properties have largely been assessed: the acceptability is highly satisfactory and the duration is short (5 mins); accuracy is excellent: internal coherence (alpha coefficient = 0.95 to 0.96) and test-retest

reproducibility (r = 0.88 to 0.93); the validity of the construct is supported by strong correlations with other disability questionnaires: the Roland-Morris Disability Questionnaire (r = 0.77 to 0.81), the Oswestry Low Back Pain Disability Questionnaire (r = 0.80 to 0.83), and the SF-36 physical scale (r = 0.67 to 0.77) and pain intensity scale (r = 0.54 to 0.74), and the scale appears to be adapted to the various levels found in lower back pain[94].

7.2 Secondary endpoints

The secondary endpoints will be as follows:

- Pain assessed using a numeric scale from 1 to 10 at 3 and 12 months;
- Number and duration of sick leave periods at 12 months;
- Functional capacity (Quebec) at 12 months;
- Number of recurrences at 12 months;
- Quality of life assessed using the SF-12 questionnaire[95] 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 allows 8 aspects of quality of life to be measured: general and mental health condition, physical and social functioning, physical and emotional health, pain and vitality;
- Consumption of painkillers and NSAIDs at 3, 6 and 12 months.

8 Expected number of subjects to be enrolled and justification

The primary objective of the study is to assess the functional capacity in patients with sub-acute or chronic common lower back pain using the Quebec score at 3 months. The p-value is 0.05. The desired power is equal to 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.

9 Statistical analysis

The statistical analysis will be provided by the Prof. Ravaud Clinical Epidemiology Centre (Hôpital Hôtel Dieu) in the frozen databases, using SAS® statistics software.

A Statistical Analysis Plan will be prepared and validated prior to the blinded review of data. It will be proposed by the Clinical Epidemiology Centre and reviewed by the Sponsor and the Investigator.

The Statistical Analysis Plan may be revised during the study, in order to take into account any changes made to the protocol or any changes in the conduct of the study which have an impact on the originally planned statistical analyses.

The Statistical Analysis Plan will be edited prior to the blinded review of data. The analyses to be performed may be completed at this review. The final version of the Statistical Analysis Plan will be prepared before unblinding takes place. All versions will be kept in the study file.

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.

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;
- Compliance.

For each group, and at each of the assessment 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 and standard deviation. In the event of quantitative endpoints with asymmetrical behaviour, these will be presented with their median and interquartile range (25^{th} percentile; 75^{th} percentile).

The primary endpoint is the variation in the Quebec score between the baseline and 3 months. The statistical analysis of the primary endpoint will be done in terms of the intention-to-treat (i.e., all randomised patients will be analysed in their group of origin). 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 linear mixed model for repeated measurements

(MMRM), taking into account the correlation of repeated measurements in the same subject (random effect on the patient with an unstructured variance-covariance matrix) under the hypothesis of randomly missing data. The fixed effects will particularly be the randomisation arm, time, initial endpoint value (centred), the interaction between the time and the randomisation arm. The model will allow us to compare the means adjusted to the baseline value of the absolute variations between the Month 3 visit and the enrolment visit (as well as between the other visits and the enrolment visit).

A site effect will also be added and possibly an interaction between the site and the treatment (if significant) in order to take into account on the one hand the differences between the sites and on the other hand the heterogeneity of the treatment effect between the sites. Furthermore, a therapist effect (osteopathic intervention or osteopathic placebo) based on the site will be added to take into account the correlation between the parents undergoing treatment with the same therapist. The MMRM technique is consistent with the principle of the intention-to-treat analysis provided that all patients have a baseline value for the endpoint. The model parameters will be estimated with the restricted maximum likelihood (REML) method, using the Newton-Raphson method. The degrees of freedom will be calculated using the Satterthwaite approach. In order to confirm the results obtained, a sensitivity analysis will be carried out: an analysis of covariance (ANCOVA) approach will be used to confirm the results of the primary analysis. The endpoint to be studied will once again be the difference in pain score between randomisation (D0) and the M6 visit: Δ = value at M6 – value at D0. The difference in Δ between the groups will be analysed with an analysis of covariance (ANCOVA) with the variable group as a fixed factor and the pain at D0 as a quantitative covariate (centred variable). A site effect and a therapeutic (group) effect will be included in the model.

The secondary analyses will be:

1) Comparison of the percentage of relapses: Wald test using a logistic regression model with random effects for the site and the therapist.

2) The repeated measurements of the following criteria will be analysed using mixed-effect linear models with random intercept and slope (the aim will be to compare the progress over time between the 2 groups using an F test with adjustment for the site and the therapist):

- Numeric pain scale
- SF-12

3) Comparison of the number and duration of sick leave periods using a linear mixed model with a random effect on the site and the therapist (F test).

The tests carried out will be considered significant if levels of significance are below 5%.

10 Diagram and conduct of the research

10.1 Sites

The recruiting sites are large CHUs in Ile-de-France, within Assistance Publique des Hôpitaux de Paris, the head office of the AP-HP, and a provincial site at the Grenoble CHU, which is also a large structure, in order to optimise the eligible patient rate. A summary table is attached with the sample sizes of individuals monitored by occupational medicine per hospital with an estimation of the number of patients monitored per occupational physician.

Sites	**Total sample size of individuals monitored by Occupational Medicine**
Pitié-Salpêtrière	11,464
Grenoble	7,600
Saint-Antoine	4,361
Avicenne	2,702
Beaujon	2,633
Paul Brousse	2,513
Louis Mourier	2,241
Head Office of the AP-HP	1,847

Data provided by the AP-HP Occupational Medicine Central Department (July 2010) and estimation per occupational physician provided by the Grenoble CHU.

10.2 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 sample letters 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 lower 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 done 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 participating in this study will be done as follows:

-either directly in their "active files" of individuals already monitored for this condition, either working or on sick leave, and either with or without having rearranged their work position;

-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.).

Physician at the site (name)	**Hospital Centre address**
Dr Amiel-Taieb	Beaujon CHU
Dr Bignebat	Saint-Antoine CHU
Dr Dupre	Louis Mourier CHU
Dr Eudes	Avicenne CHU
Dr Glomot	Paul Brousse CHU
Dr Gorodetzky	Head Office of the AP-HP
Dr Lecieux	Pitié-Salpêtrière CHU (HAD)
Dr Louet	Pitié-Salpêtrière CHU

Dr Michel	Grenoble CHU

Patients recruited by different methods will be referred to the Physical Medicine and Rehabilitation Department at Cochin Hospital or the Occupational Medicine Department at Grenoble CHU for an enrolment visit, which will be centralised at two establishments: Cochin CHU and Grenoble CHU. The latter will also take care of the enrolment and management of its potential patients.

The investigator responsible for enrolment will inform the patient about the study objectives using an information sheet, fill in the patient's informed consent form, collect data, randomise the patient using a computerised tool and provide the patient with an appointment for the manual therapy.

Enrolled patients will be assessed at M3, M6 and M12. The assessment 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.

10.3 Conduct of the research 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;
  - pain on a numeric scale from 1 to 10;
  - number and duration of sick leave periods since the start of the common lower back pain;
  - number of relapses since the first episode of common lower back pain;
  - quality of life questionnaire SF-12;
  - 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;
- pain on a numeric scale from 1 to 10;
- number and duration of sick leave periods since D0;
- number of relapses since D0;
- quality of life questionnaire SF-12;
- 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;
- pain on a numeric 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;
- quality of life questionnaire SF-12;
- consumption of painkillers and NSAIDs;
- adverse events.

M12: End-of-study visit

The end-of-study visit will be carried out by the investigating physician in order to collect the following information:

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

- adverse events.

10.4 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.

10.5 Place where the manual therapy sessions are carried out

The manual therapy sessions will be carried out at Grenoble CHU for patients enrolled at this site, and at the Cochin CHU for all other patients. At Cochin Hospital, we have 8 consultation cubicles 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 mins for each half-day in the morning and 6 in the afternoon.

10.6 Expected duration of participation for each patient

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

10.7 Expected duration of the research

Recruitment will span 18 months. Follow-up until the end of the study will span 12 months for each patient enrolled in the study. The total study duration will therefore be 2.5 years.

10.8 Methods for limiting missing data

The following procedures will be implemented in order to limit missing data.

1) The clinical study technician will systematically confirm the quality of filling in the questionnaires and will contact the patients in the event of missing information.
2) Patients will be contacted by phone and by post one week before the date of the Month 12 visit; if they fail to respond on the visit day, a second letter will be sent.

11 Rules for stopping the research

11.1 Early withdrawal of patients

Patients can withdraw from the study at any time and for any reason, or due to an investigator's decision. All cases of patients withdrawing from the study must be documented and the investigator must indicate the reason (e.g., patient failure to attend the visits after a reminder, lack of cooperation by the patient, etc.).

11.2 Methods for replacing these patients, where applicable

Patients withdrawing from the trial early or excluded from the research will not be replaced.
The analysis will be carried out in terms of the intention-to-treat, including failures, subjects lost-to-follow-up or with missing data, deceased patients and those who stopped the treatment due to intolerance or side effects.

Patient withdrawing from the trial early cannot be enrolled again in the study. Their enrolment and treatment numbers must not be reused.

11.3 Follow-up methods for these individuals

In the event of early withdrawal from the manual therapy sessions, these patients will continue to be monitored until the end of the study, at least for the visits planned as part of the protocol, and the investigator will continue to fill in the electronic CRF until M12.
For subjects lost-to-follow-up, the case report form will be filled in up until the last visit carried out. The investigator and his or her collaborators will endeavour to specify the reasons for the patient's failure to attend the visit and the condition of his or her health.

12 Data management

The clinical and paraclinical signs will be collected and entered into an electronic case report form (eCRF CleanWEB), with restricted access using an individual username and password for each study physician in charge of a patient. The data entered will by anonymised and secured, with data encryption when transferred.

13 Safety assessment:

Adverse events

13.1 Potential adverse effects of the treatment

An analysis of questionnaires was carried out in 63 new patients who received osteopathic treatment by students at a comprehensive consultation centre at an osteopathic training school[96]. The aim was to determine the main side effects experienced by patients whose main reason for consultation was lower back pain (33%) and neck pain (20%). Local pain (24.3%), local stiffness (18.3%) and an increase in pain leading the patient to seek medical care (11.8%) were the most common side effects, occurring within two days after the consultation. However, 96% of these reactions were considered to be mild or moderate.

The most severe iatrogenic effects of manual techniques are vertebral artery dissection and cerebrovascular accidents following high-velocity, low-amplitude-type cervical spine manipulations[97], techniques which were not chosen for the intervention group.

A systematic review of the literature on the side effects of manual therapies[98] concluded that there were very few severe side effects but that half of patients could experience transient side effects classified as minor to moderate.

13.2 Description of the safety assessment parameters

Adverse event

Any harmful manifestation occurring in an individual taking part in a biomedical research study, regardless of whether or not the manifestation is related to the research.

Adverse event in a research study not involving a product mentioned in Article L. 5311-1 (medicinal products, biomaterials and medical devices, in vitro diagnostic medical devices, labile blood products, organs, tissues, cells and products of human or animal origin, and cellular products for therapeutic purposes).

Any adverse event due to the research.

Serious adverse event or effect

Any adverse event or effect that leads to death, is life-threatening for the individual taking part in the research, involves hospitalisation or an extended hospital stay, causes significant or permanent incapacity or disability, or leads to a congenital abnormality or malformation.

13.3 Expected methods and schedule for measuring, collecting and analysing the assessment and safety parameters

13.3.1 Steering committee

The steering committee will be made up of the Principal Investigator, Prof. Serge Poiraudeau, investigators from the various sites, methodologists in charge of the project, Dr Isabelle Boutron and Prof. Philippe Ravaud, one or more Project Advisers from the Clinical Research Department (DRCD), the heads of the CIC Cochin-Necker Clinical Research Unit (URC), Prof. Jean-Marc Tréluyer, and one or more Project Advisers from the CIC Cochin-Necker Clinical Research Unit (URC).

The roles of the steering committee are as follows:
-To define the general structure and performance of the research and coordinate the information;
-To initially define the methodology and decide on the measures to be taken throughout the course of the research in the event of unexpected events;
-To supervise the performance of the research, particularly in terms of tolerance and adverse events.

13.3.2 Independent monitoring committee

A serious adverse event monitoring committee was not deemed necessary for this study since the high-velocity, low-amplitude manipulations will not be carried out on the cervical spine, due to this having an unacceptable risk-benefit ratio.

13.4 Serious adverse event management procedures

As this is a biomedical research study classified as “risk A”, i.e. for which there is a negligible **additional risk expected from the research**, no **serious** adverse events are expected through the course of the research, as:

- High-velocity, low-amplitude-type cervical spine manipulations are techniques which were not chosen for this study’s intervention group, as these techniques can lead to vertebral artery dissection and cerebrovascular accidents.

Furthermore, there are no suspected unexpected serious adverse reactions (SUSARs).
In these conditions:

- The investigator will not be expected to report any serious adverse events occurring during the research to the sponsor. Should such events occur, these will be related to the patient's condition or their therapeutic management in the context of care, and will not be related to the research (e.g., death related to the disease, hospitalisation or extended hospital stay due to disease progression or concomitant diseases, life-threatening event unrelated to the research, etc.);
- It is not considered necessary to create an independent monitoring committee.

However, in the unlikely event in which the investigator becomes aware of an event that could affect the safety of any individual involved in the research (e.g., therapeutic error or protocol deviation), the investigator will be required to report this to the sponsor using the form provided for this purpose in Annex IX to the protocol.

Finally, any non-serious adverse events occurring through the course of the research, such as pain or local stiffness, and an increase in pain will be reported on the adverse events page of the case report form.

14 Right to access the information and source documents

Individuals with direct access in accordance with the legislative and regulatory provisions in force, in particular Articles L.1121-3 and R.5121-13 of the French Public Health Code (e.g., researchers, individuals in charge of quality control, monitors, clinical research assistants, auditors and all individuals collaborating in clinical trials) will take all the necessary precautions in order to ensure the confidentiality of the information related to the investigational medicinal products, trials, individuals taking part in the research, and in particular any information involving their identity, as well as the results obtained. The data collected by these individuals through the course of quality controls or audits will then be made anonymous.

15 Quality control and assurance

The research will be conducted in accordance with the standard operating procedures of the sponsor, AP-HP, which will be in line with Good Clinical Practice.
The performance of the study at the research sites and the treatment of subjects will be done in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines in force.
The CRAs, the Head of the Project at the DRCD, the Assistant Head of the Project at the DRCD, the Clinical Trial Coordinator at the URC/CIC and the Study Data Manager will also have the opportunity to view the CRFs and ask questions remotely (queries).

15.1 Monitoring procedures

The research is classified as risk level A, with the corresponding monitoring level.
The CRAs representing the sponsor will carry out visits to the research sites according to the follow-up schedule for patients in the protocol, the enrolments at the various research sites and the level of risk assigned to the research study.

- Start-up visit at the site: before enrolment, for implementation of the protocol and familiarisation with the various parties involved in the biomedical research study.
- At the next visits, the case report forms will be reviewed as the research progresses by the CRAs. The principal investigator at each site, as well as the other investigators who enrol or undertake follow-up with individuals participating in the research, agree to receive visits from the CRAs at regular intervals.

In accordance with the Good Clinical Practice guidelines, the following items will be reviewed at the site visits:

· Compliance with the protocol and procedures set out for the research;
· Verification of the patient informed consent forms;
· Examination of the source documents and comparison with the data reported in the case report form in terms of accuracy, missing data, and consistency of the data according to the regulations set out by the procedures of the DRCD.

- Closure visit: collection of case report forms, biomedical research documents, archiving.

15.2 Transcription of information into the case report form

The research data will be collected and monitored using the CleanWEB electronic case report form, within the framework of a public contract between the AP-HP and TELEMEDICINE TECHNOLOGIES S.A., notified on 17/11/2003 (reference no. 033845) and renewed on 21/11/2006 (reference no. 063844). The data will be centralised in a server located at the Operational Services Department (DSO) of AP-HP, 67 boulevard Bessières, 75017 PARIS.

An initial version of the eCRF may be put online and tested after the Research Sponsorship has been accepted by the DRCD and after sending the specific study specifications by fax to the company TELEMEDICINE. Once the Coordinator, the Clinical Trial Coordinator from the URC/CIC, the Data Manager and the Statistician have agreed on the final version of the eCRF, and following the release of the appropriations, and submission of the purchase order to the company TELEMEDICINE by the DRCD, the DRCD will authorise the Coordinator to begin the research (Inv. 14 letter), and the eCRF comes into operation.

In accordance with the Good Clinical Practice guidelines, the case report form on which the research data are transcribed must correspond to at least the following standard presentation:

- At the start of the form, the following are normally included: the title of the research study, the Sponsor's name, the patient's study code, including the initials of the individual taking part in the research (first letter of their surname and first letter of their first name), treatment number, and inclusion and exclusion criteria in the form of a check-list, which allows subject selection to be validated with respect to the study population. At the end of the research, when the research database has been "frozen", the eCRF of each patient will be printed and signed by the investigator. The references of the research and the identification code of the individual taking part in the research will then appear in the form of a slip on each page to allow data to be identified in all cases.
- The visit dates and data transcribed must be reported in this eCRF as well as the time of the research to which they correspond.
- The following items must be included at the end of the eCRF:
    - Concomitant treatments;
    - Non-serious adverse events (AEs);
    - End of study/Early termination;
    - Outside planning, an SAE module.

All the information required by the protocol must be provided in the case report form and an explanation must be provided by the investigator for any missing information.

Information must be transferred to the case report forms as soon as it becomes available, whether clinical or paraclinical information.

Incorrect information detected in the case report forms will be replaced in the form by a registered investigator, who will log in to the software with his or her access information (user name and password). These codes are strictly personal and confidential, and under no circumstances may be passed on to third parties. They help ensure data confidentiality and authenticate the interventions. Access information is associated with an electronic signature system which validates the data entered by the investigator. Each signature is stamped with the date and time and recorded in the research audit trail. Signed information cannot be changed. However, the investigator may void his or her signature if he or she wishes to correct any information. Voiding a signature is also subject to stamping with the date and time.

Subject anonymity will be guaranteed by an alphanumeric identification code consisting of the research site number, the patient's study enrolment number, and the initials of the individual taking part in the research in all documents required for the study, or by erasing any personal information using a suitable method from the source documents to be included in the research documentation.

The computerised data file will be declared to the CNIL in accordance with the appropriate procedure for the case.

16 Legal and ethics aspects

The sponsor is defined by Law 2004-806 of 9 August 2004. AP-HP is the sponsor of this research study and the Clinical Research and Development Department (DRCD) undertakes the regulatory tasks. Before beginning the research, each investigator must provide the sponsor's representative in the research with a signed and dated copy of their curriculum vitae, which must include their French National Medical Council registration number.

16.1 Request for ANSM authorisation

Before beginning the research, the AP-HP, as the sponsor, must submit an authorisation request file to the competent authority (the ANSM). The competent authority, as defined in Article L. 1123-12, makes decisions related to the safety of individuals taking part in a biomedical research study, taking into account the safety and quality of the products used during the research in accordance with the regulations in force, where applicable, their

condition of use and the safety of individuals with regard to procedures carried out and the methods used, as well as the planned methods of patient follow-up.

16.2 Request for Ethics Committee opinion

The sponsor must submit the research protocol to the Ethics Committee. The committee's opinion will be reported to the competent authority by the sponsor before the research begins.

16.3 Amendments

The DRCD must be informed of any planned changes to the protocol by the principal investigator.

Amendments must be classified as substantial or non-substantial.

A substantial amendment is an amendment which may, in one way or another, change the guarantees given to the individuals taking part in the biomedical research (change in inclusion criteria, extension of enrolment period, participation of new sites, etc.).

Once the research has started, any substantial amendments on the sponsor's initiative must receive a favourable opinion from the Ethics Committee and authorisation from the competent authority prior to being implemented. In this case, where necessary, the committee will ensure that a new consent form is duly collected from individuals participating in the research.

Moreover, any extension to the research (radical change in the treatment regimen or populations included, extension of treatments and/or therapeutic procedures not originally foreseen in the protocol) must be considered as a new research study.

Any substantial amendment must be submitted by the sponsor, after payment of the corresponding fee, for authorisation from the ANSM and/or for the Ethics Committee's opinion.

16.4 CNIL declaration

The law provides that the declaration of the computerised file with the personal data collected for the research must be prepared before the effective start of the research.

A reference methodology specific to the processing of personal data carried out in the context of biomedical research, defined by Law 2004-806 of 9 August 2004 as falling within the scope of Articles L.1121-1 et seq. of the French Public Health Code, was established by the CNIL in January 2006.

This methodology allows a simplified declaration procedure when the nature of the data collected in the research is consistent with the list provided by the CNIL in its reference document.
When the protocol undergoes a quality control of the data by a CRA representing the sponsor and falls within the scope of the simplified CNIL procedure, the DRCD as the sponsor will ask the person in charge of the computer file to undertake in writing to comply with the simplified MR001 reference methodology.

16.5 Information sheet and consent form

Written consent must be collected from any individual participating in the research before any procedures related to the biomedical research are performed.
The enrolled patients will be informed orally and with the help of an information sheet (a written document explaining the course of the protocol) and they must sign the consent form if they agree to take part. They reserve the right to withdraw from the study at any time if they or their attending physician or investigator request this for any reason.

16.6 Final report on the research

The final report on the research will be drafted by the principal investigator in collaboration with the biostatistician for this study. This report will be submitted to each of the investigators for their opinion. Once a consensus has been reached, the final version must be approved with the signature of each of the investigators and sent to the sponsor as soon as possible after the effective end of the study. A report prepared in accordance with the competent authority reference plan must be sent to the competent authority and to the Ethics Committee within one year after the end of the study, with the end of the study understood to be the last follow-up visit of the last subject enrolled. This period is set at 90 days if the research is terminated early.

17 Data processing and storage of documents and data relating to the research study

The documents from a research study falling under the scope of the law on biomedical research must be archived by all the parties for a period of 15 years after the end of the research (see GCP, chapter 8: essential documents).

This indexed archive consists of:

- Copies of the ANSM authorisation letter and the mandatory opinion from the Ethics Committee;
- Successive versions of the protocol (identified by the version number and date);
- Letters of correspondence with the sponsor;
- Consent forms signed by the individuals taking part in the research in a sealed envelope with the corresponding enrolment register or list;
- The paper copy of the case report form filled in and validated for each subject enrolled (automatically dated), signed by the Principal Investigator or investigators for individuals taking part in the research;
- The audit trail;
- The Data Handling manual, the document in which the eCRFs are described in detail (data, controls performed, etc.);
- Any specific annexes to the study;
- The final study report from the statistical analysis and the quality control of the study (sent in duplicate to the sponsor);
- Certificates from any audits performed during the course of the research;

At the site close-out visit, the CRA will take an external CD-ROM burner. The following will be burned onto a CD-ROM:

- The CRFs of the patients at the site in PDF format, with any randomisation faxes created by CleanWEB;
- Emails related to the research study;
- Audit trail and electronic correction requests;

This CD-ROM will be archived in the Research site's file, together with the other documents.

The database that gave rise to the statistical analysis must also be archived by the head analyst (hard copy or electronic copy).

18 Insurance, scientific commitment and funding

18.1 Insurance

Assistance Publique - Hôpitaux de Paris is the sponsor of the research. In accordance with the law on biomedical research studies, it has taken out an insurance policy with the company HDI GERLING for the full duration of the research, guaranteeing its own civil liability as well as that of any intervening parties (physicians or staff involved in conducting the research) (Law no. 2004-806, Art. L.1121-10 of the French Public Health Code).

Assistance Publique - Hôpitaux de Paris reserves the right to interrupt the research at any given time for medical or administrative reasons. If this occurs, the investigator will be notified.

18.2 Scientific commitment

Each investigator undertakes to comply with the obligations of the law and to conduct the research in accordance with the GCP guidelines, complying with the principles set forth in the Declaration of Helsinki in force. To this end, a copy of the scientific commitment (DRCD-type document), dated and signed by the principal investigator of each clinical department of the participating sites, will be provided to the sponsor's representative.

19 Rules regarding publication

The AP-HP owns the data and it may not be used or transferred to third parties without the AP-HP's prior agreement.

The individuals who actively participated in the preparation of the protocol and its implementation, as well as the writing of the results, will be named first in the publications.

As a precaution, a writing committee should be set up and the order of the signatories could be defined in advance.

Assistance Publique-Hôpitaux de Paris must be mentioned as the sponsor of the biomedical research study and as a provider of funding. "Assistance Publique-Hôpitaux de Paris" must appear in the address of the authors.

The Cochin-Necker Clinical Research Unit URC/CIC will be mentioned in the acknowledgements.

20 List of annexes

Annex 1: Further information on osteopathy

Description of the therapeutic principles in osteopathy

Osteopathy is a healthcare approach which advocates the influence of musculoskeletal system function both in times of health and during illness, and is based on four principles which were reassessed in 2002: (1) the body is a physiological unit, (2) the body has mechanisms for self-regulation, (3) structure and function are reciprocally related, and (4) rational treatment is based on the preceding principles[99]. Osteopathy belongs to the category of alternative medicines.

The diagnostic approach taken by osteopaths is based on the search for somatic dysfunction; it is therefore centred on the patient and not exclusively on the symptoms presented. Somatic dysfunction is a pathological entity referenced in the International Classification of Diseases, which is defined as "impaired or altered function of related components of the somatic (bodywork) system including: the skeletal, arthrodial, and myofascial structures, and their related vascular, lymphatic, and neural elements"[47]. The clinical signs which have been associated with joint somatic dysfunction have traditionally been described with the acronym "SART" (Sensitivity/pain on palpation; Asymmetry of the bony landmarks; Restriction in passive joint movement; changes in the Texture of the surrounding soft tissues)[48]. The osteopath determines the severity of the somatic dysfunction according to the significance and concomitant presence of the palpated clinical signs which can be improved and reduced following a suitable manual treatment[14].

A prolonged inflammatory reaction, a chronic change in reflex neurological mechanisms and a chronic change in posture are thought to be the main mechanisms responsible for the onset of somatic dysfunction[100]. Depending on the patient's clinical condition, the somatic dysfunction may be a causal factor, adaptive reflex or a combination of these factors responsible for the symptoms described by the patient[101]. The concept of somatic dysfunction is therefore one of the main elements that is typical of osteopathy, which differentiates it from other manual therapies.

The French Register of Osteopaths (ROF) has set up a Multidisciplinary Council for the management of the risks related to the practice of osteopathy[102], which defined manipulation as a specific, controlled gesture that restores mobility in the impaired minor movement(s) within the limits of their physiological amplitudes and which restores the functional qualities of the surrounding soft tissues.

This is a non-forced manual response to the osteopathic diagnosis of somatic dysfunction. The choice of technique is guided by (1) a previously suggested diagnosis, (2) compliance with contraindications in terms of manipulation treatment, (3) the patient's condition, and (4) the practitioner's experience. Osteopathic manipulation is therefore not only a matter of spinal manipulation, although this is part of it. Numerous manual techniques are referred to in the Authorized Osteopathic Thesaurus[85] and are used by both professional categories (osteopaths and osteopathic physicians) in order to treat somatic dysfunction. These techniques can be divided into 4 broad categories according to the amount of force, the rhythm and the speed used: (1) rhythmic, (2) high-velocity, low-amplitude (HVLA, the previously described "manipulation"), (3) low-velocity stress, and (4) visceral[86]. At the international level, it is possible to differentiate between osteopaths who only practice OMT and osteopathic physicians who practice OMT as part of their medical practice[103]. These two professional categories have a professional status of first contact in all countries in which the practice of osteopathy is regulated.

In France, the French Society of Manual Medicine - Orthopedic and Osteopathic (SOFMMOO) recommends a record of spine techniques applied to treat minor intervertebral derangement (MID), which is defined as reversible, painful dysfunction of the mobile segment of the spine[104]. Spinal manipulation is a therapeutic procedure that is still often related to OMT in the medical world4,[105]. Maigne[21] defined manipulation as a forced movement, applied either directly or indirectly to a joint which abruptly moves the joint elements beyond their usual physiological range, without exceeding the limit imposed on their movement by the anatomy. This is a short, sharp, single push which must be applied from the end of the normal passive range. This movement is generally accompanied by a cracking sound. These spinal manipulations are only applied to the painful spinal level in the opposite direction to that which triggers the pain[106].

The osteopath assesses the various manual therapy options according to their assessment of the patient's physiological response capacities to the treatment, based on their interpretation of the theoretical pathophysiological mechanisms associated with the physical signs found in the clinical examination[107]. Among the physiological models which have been proposed to describe the onset, maintenance and correction of somatic dysfunction, the neurological model based on the function of nociceptors is the one most commonly described in the scientific literature[108].

Changes in a somatic or visceral structure would lead to excessive and discordant afferent neurological impulses up to the posterior horn of the spinal cord. It is assumed that this mechanism would lower the depolarisation thresholds of the spinal inter-neurons of the

medullary segment involved and would therefore allow an exaggerated response of the different neurons that synapse at this level (increased sensation of pain, sympathetic influx and muscle tone)[109]. A nociceptive stimulation which is maintained over time, generated by chronic somatic dysfunction, would lead to a form of central sensitisation (secondary hyperalgesia) and would favour locoregional allodynia and hyperalgesia of the periarticular soft tissues[110].

This description of somatic dysfunction, including a biomechanical dysfunction found on palpation, which could be associated with reflex neurological dysfunction, could be easily integrated into the most recent models which are used to describe the pathophysiology of lower back pain. There are currently two main descriptive models: the End-Organ Dysfunction Model and the Altered Nervous System Processing Models[111].

Diagnostic and therapeutic approaches in osteopathy patients with lower back pain

Somatic dysfunction in patients with lower back pain

The diagnostic approach taken by osteopaths is based on the search for somatic dysfunction; it is therefore centred on the patient and not exclusively on the symptoms presented. Current university training for osteopaths is mainly based on a nociceptive model for describing the clinical phenomena diagnosed on palpation in order to assess any potential links between the somatic dysfunction found in patients mainly through reflex neurological phenomena (viscerosomatic, somatovisceral, somatosomatic and viscerovisceral[86,108]), which could theoretically be involved. The gold-standard physiological models used by osteopaths are therefore based on an interpretation of the various reflex neurological interactions, based on the biomechanical elements found on palpation, and not based on a strictly biomechanical understanding of the painful area described by the patient[112].

In the USA, the Agency for Healthcare Research and Quality has recently validated and published recommendations by the American Osteopathic Association regarding the management of patients with lower back pain using OMT[113] by assigning it the best level of scientific evidence (1), and recommending OMT for the management of lower back pain of musculoskeletal origin by treating somatic dysfunction in relation to the lower back pain. These recommendations are based on the results of an epidemiological study by Snider *et al.*[114], in which they observed that somatic dysfunction in patients with lower back pain was more common and more severe compared to an asymptomatic population with significantly more common clinical signs: tissue changes in periarticular soft tissues, asymmetry in spinous

processes on static palpation, increase in tissue resistance on anterior passive movement of the lumbar spine and pain on palpation of the L1 to L4 spinous processes.

Specific features of osteopathic treatment of patients with lower back pain

Osteopathic treatment is developed specifically according to the patient's complaint and the somatic dysfunction found by the practitioner. The rationale behind osteopathic treatment would therefore correspond to treatment of somatic dysfunction in the context of its contribution to the symptoms described by the patient[115]. The osteopath manually treats the anatomical areas with somatic dysfunction in the whole body (viscera, cranium and musculoskeletal system) to change the neurophysiological and biomechanical interactions in order to reduce the symptoms described by the patient,[116], and frequently ends their consultations by providing the patient with specific dietary-hygiene advice.

The osteopath establishes a privileged-care relationship with the patient based on a longer consultation time than a regular medical appointment, the attention paid to the patient's aetiopathogenic mechanisms and not only his or her symptoms, and finally on the dominant area as agreed through touching. These specific therapeutic features could have a positive influence on the patient's perception and understanding of the pain, phenomena described as being psychosocial risk factors leading to chronicity of the pain[117]. According to Kuchera[26], the anterior cingulate gyrus is involved in the chronic pain self-maintenance system, and the osteopath, through the privileged interaction established with patients through dialogues and the time spent touching the patient, would act on this area of the brain and defuse the chronic pain self-maintenance mechanism.

Annex 2: Description of the physical examination sequence for the two groups

10 minutes.

The sequence is the same in both groups except for the fact that the tests in the control group are not interpreted by the practitioner but rather presented as such to the patients, and in the osteopathic examination the palpation pressure used for the diagnosis of somatic dysfunction remains light. The practitioner's gestures, the patient's position and the verbalisation are exactly the same.

There is no questioning. The patient undresses at the start. On the other hand, and throughout the whole test sequence, the practitioner creates a dialogue by questioning the patient about their complaint: its history, location, associated signs, and their progress, socio-professional and emotional impact. History, extracurricular activities: sport, hobbies, etc.

The tests are exactly the same for both groups. On the other hand, for the placebo group, the clinical signs of somatic dysfunction will not be studied; the results of this clinical examination must therefore give the impression of being interpreted by the practitioner, as far as the patient is concerned.

1. Patient standing

1.1 Inspection

1.1.1. Overall posture

In the sagittal plane: increase or reduction in curvatures?

In the frontal plane: orientation of the shoulder and pelvic girdle? Curvature of the spine?

Texture of the posterior integuments around the joints of the spine and the pelvic girdle?

1.1.2. Active movement assessment

Assessment of the amplitudes, movement asymmetries, and search for pain reproduction in active movements of the spine.

The practitioner is behind the patient, guiding them in their movements.

The patient carries out the following movements: flexion, extension, right and left rotation, right and left lateral tilt.

Assessment of the amplitudes, asymmetries and search for pain reproduction in movement of the sacroiliac joints.

Finger test[118],[119]: the practitioner asks the patient to indicate the site of their pain with their index finger twice. The patient should indicate on two occasions with one single finger a point at less than a centimetre from the posterior superior iliac spine.
Gillet Test: the practitioner is behind the patient, who holds onto the wall. The practitioner's thumbs are placed on both sides of a sulcus (first sacral spine and anterior superior iliac spine), and the patient is asked to carry out a flexion of the hip ipsilateral to the sacroiliac joint assessed. The practitioner assesses sacroiliac joint movement by the descent of the posterior superior iliac spine.

1.2 Palpation:
Search by palpation of the spine for signs associated with somatic dysfunction: asymmetry of the bony landmarks in movement, spontaneous or provoked pain on pressure of the bony landmarks and periarticular soft tissues.
Palpation of the bony landmarks while standing: iliac crests, anterior superior and posterior superior iliac spines, greater trochanter, ischial tuberosities, sulcus.
On the whole of the spine: spinous processes, transverse processes, posterior facet joints, posterior angles of the ribs.
Palpation of the soft tissues in search of paravertebral muscle hypertonia, assessment of subcutaneous tissue flexibility around the joints.

2. Patient in the seated position
Passive movement test of the whole spine in search of joint movement restrictions; determine the hypomobile vertebral rib and level.

2.1 Cervical spine.
The practitioner is behind the patient, supporting the patient's head with the anterior hand.
With the posterior hand, the practitioner palpates around the posterior joints of the spine level being assessed with the thumb and index finger.
The anterior hand carries out the main movements of flexion, extension, right and left rotations, and right and left tilts; then the accessory movements of right and left lateral transfer.
The practitioner analyses the tissue response and the change in soft-tissue texture with the forces applied during this test; with the posterior hand, the practitioner assesses the restrictions in movement and elasticity of the joints in the parameters tested, as well as any

muscle hypertonia, sensitivity or pain on palpation and asymmetry of the anatomical landmarks.

2.2 Thoracic spine: (T1-T2 to T12-L1 posterior facet joints)

The practitioner is behind the patient, supporting the patient's chest by grasping at the front with the upper limb.

With the posterior hand, the practitioner palpates both sides of the spinous process with the index finger and middle finger, around the posterior joints of the spine level tested. Using the body, a rhythm is induced in the thoracic vertebrae in the parameters of flexion, extension, right and left rotations, and right and left tilts; and then the accessory movements of right and left lateral transfer.

The practitioner analyses the tissue response and the change in soft-tissue texture with the forces applied during this test; with the posterior hand, the practitioner assesses the restrictions in movement and elasticity of the joints in the parameters tested, as well as any muscle hypertonia, sensitivity or pain on palpation and asymmetry of the anatomical landmarks in movement.

3. Patient lying down on the table

3.1 Lateral recumbent position - Passive movement tests in search of any restrictions in joint mobility, palpation of bony landmarks and periarticular soft tissues, sensitivity on palpation and movement, or changes in soft-tissue texture.

Lumbar spine

Flexion/extension: the practitioner is in front of the patient, holding the patient's bent lower limbs in the caudal hand, while the cephalic hand palpates the spinous processes of the lumbar spine. The practitioner successively moves the hips in flexion/extension and assesses the spacing and alignment of the spinous processes, in order to assess the presence of any mobility restrictions in flexion/extension parameters, as well as any changes in soft-tissue texture, sensitivity on palpation and asymmetry of the anatomical landmarks in movement.

Tilt: the patient keeps the outstretched leg in contact with the table and places the foot of the leg that is on top in the popliteal hollow of the leg that is in contact with the table.

The practitioner is in front of the patient, holding the patient's trunk with the caudal upper limb, while the cephalic hand is positioned around the posterior facet joints. The practitioner

tilts the patient's trunk with the caudal upper limb, while the cephalic hand analyses the opening of the vertebral compartment contralateral to the tilt, as well as any possible muscular hypertonia and changes in the flexibility of the subcutaneous tissues.

Rotations: the patient and practitioner are in exactly the same position. The practitioner induces rotations in the patient's trunk with the caudal upper limb, while the cephalic hand analyses the presence of any mobility restrictions in the rotation parameters, as well as any changes in soft-tissue texture, sensitivity on palpation and asymmetry of the anatomical landmarks in movement.

Sacroiliac joints

With the caudal hand, the practitioner palpates around the lumbosacral junction and uses the cephalic upper limb to lift the patient's arm contralateral to the sacroiliac joint to be tested, to stabilise the spine in neutral rotation.

The patient is asked to cross their hands on the lateral side of the ipsilateral hemithorax.

The practitioner places the ipsilateral foot in the popliteal hollow and extends the contralateral leg.

The practitioner supports the trunk and the spinal segment with the cephalic forearm which passes under the patient's forearm.

The practitioner places the caudal forearm on the patient's pelvis, perpendicular to the posterior superior iliac spine segment/greater trochanter.

Using the caudal forearm, the practitioner searches for lever forces to test the movement restrictions in the axis of the sacroiliac joint in the following parameters: anterior and posterior rotation, compression and spacing.

With the posterior hand, the practitioner assesses the movement restrictions in the parameters tested, as well as any changes in the soft-tissue texture, sensitivity on palpation and asymmetry of the anatomical landmarks in movement.

3.2 Prone position

Spring test on the lumbar and thoracic spine and the ribs

While standing, the practitioner applies one hand to the spinal processes, and the other hand reinforces the support and induces a sagittal forward thrust, (vertical support towards the table) analysing with the weight of the body the movement restrictions in the sagittal plane, as well as any changes in soft-tissue texture, sensitivity on palpation and asymmetry of anatomical landmarks in movement.

Sacroiliac joint

Palpation of the bony landmarks (posterior superior iliac spine and sacral spine) in search of any pain or asymmetry.

Sacral thrust test[120,121]: while standing, the practitioner applies both hands to the sacrum, which induce a sagittal forward thrust, with the 2 iliac bones being stabilised on the plane of the table.

The practitioner initially attempts to retrigger any pain.

With the weight of the body, the practitioner analyses the movement restrictions in the sagittal plane, as well as any changes in soft-tissue texture, sensitivity on palpation and asymmetry of the anatomical landmarks in movement.

3.3 Supine position

Talocrural joints

The practitioner is standing, facing the patient's feet. They hold the calcaneus and place their forearm against the plantar surface of the patient's foot; the other hand is placed on the patient's tibia in order to palpate the joint space. The practitioner analyses the patient's tissue response to the forces applied during this test; they search for any movement restrictions in the flexion/extension and anterior posterior shift parameters tested, as well as any changes in the soft-tissue texture, sensitivity on palpation and asymmetry of the anatomical landmarks in movement.

Sacroiliac joints: Thigh thrust test[130,131] (pain reproduction test)

The patient has the hip bent at 90 degrees. With the practitioner standing on the side of the sacroiliac joint to be assessed, they hold the patient's knee between their forearm and chest.

The practitioner applies a force in the axis of the patient's femur by also combining an adduction.

The practitioner searches to retrigger the pain.

Coxofemoral joints

The patient has the hip bent at 90 degrees.

With the practitioner standing on the side of the sacroiliac joint to be assessed, they hold the patient's knee between their forearm and chest. The cephalic hand palpates the sulcus to control it so that movements do not occur in the sacroiliac joint. The practitioner searches for any movement restrictions on the parameters of medial and lateral rotation, flexion/extension,

and abduction/adduction. They search for any changes in soft-tissue texture, sensitivity on palpation and asymmetry of the anatomical landmarks in movement.

Root of mesentery test (V test)

The patient's knees are bent.

The practitioner stands to the left of the patient, with their back towards the patient's head. With the right hand, the practitioner holds the small mass along the axis of the root of mesentery (of the ileocaecal valve on V side up to the duodenojejunal flexure on the hypothenar eminence side) and with their left hand in parallel but on the other side of the axis of the root, in the concavity of the left iliac fossa.

The practitioner searches for restrictions in movement/elasticity in up/down, right/left and forward/backward shift patterns, changes in soft-tissue texture and sensitivity or pain on palpation.

Diaphragm test

The patient's legs are bent.

The practitioner is standing sideways to the patient and uses the two columns of the thumbs/thenar eminences to palpate the lower edge of the ribcage on both sides of the xiphoid process of the sternum in order to surround the diaphragmatic cupolae.

During an inhalation and exhalation cycle, the practitioner analyses the restrictions in movement and elasticity of the cupolae, as well as any changes in the soft-tissue texture, sensitivity on palpation and asymmetry of the anatomical landmarks in movement.

Passive movement test of the upper cervical spine

The practitioner is behind the patient, supporting the patient's head with the abdomen and both hands.

The practitioner makes contact with either the atlanto-occipital joints or the atlanto-axial joints with the metacarpophalangeal joint of the index fingers, while the body performs the flexion, extension, right and left rotation, right and left tilt movements in the spine area; the practitioner uses the applicator to analyse the restrictions in movement and elasticity in the parameters tested, as well as any changes in soft-tissue texture, sensitivity on palpation and asymmetry of anatomical landmarks in movement.

Cranial palpation (C test)[122]

The practitioner palpates the cranial vault and the face around the cranial sutures then around each bone on both sides of each suture with a light force in the opposite direction. The practitioner then assesses the presence of any changes in soft-tissue texture, sensitivity/pain on palpation, restriction in movement/elasticity when applying force, and asymmetry of the anatomical landmarks. The assessment of this anatomical area is part of the general osteopathic examination as described in the Outpatient Osteopathic SOAP Note Form. It is therefore assessed even though it has not been chosen as part of the anatomical areas included in the standard osteopathic treatment.

Temporomandibular joint (TMJ)

Passive movement test and palpation of the masticatory muscles

The practitioner is seated at the patient's head. The practitioner places the thumbs behind the rising branches of the jaw and tests for changes in texture and any pain on palpation of the masticatory muscles. The practitioner then places the middle finger at the opening of the ear around the TMJ and asks the patient to open and close their mouth. The practitioner searches for any restrictions in condyloid joint movement or tissue elasticity in the opening/closing parameters, anterior posterior shift or lateral shift, or any changes in soft-tissue texture, sensitivity or pain on palpation, or asymmetry of the anatomical landmarks in movement.

Annex 3: Table of validation criteria for the training of osteopaths taking part in the study in the intervention and control group

General topics assessed	Knowledge	Acquired =1 Not acquired = 0
Practitioner compliance with inclusion criteria	Submission of administrative documents: Osteopathy Diploma, appendices to the diploma, in accordance with the WHO international standards (4,200 hours of training, of which at least 600 hours must be in clinical practice), the right to practice, RCP up-to-date to practice osteopathy.	
	Weekly availability over 6 months according to schedule.	
Understanding of the study and its implications	1/ Knowledge of the basic aspects of clinical research in general (groups, semi-blinding, procedures, standardisation); 2/ Knowledge of the specific features of studies related to complex interventions (examples, criteria studied and compared); 3/ Knowledge of the chronic lower back pain study protocol in particular: criteria studied and compared, with the criteria being similar between the two groups, the number and frequency of sessions, patient enrolment, obligations, etc.	
	Commitment to comply with the procedures and standardisation.	
	Detailed knowledge of the performance of both types of session (treatment and control) and performance of each session (tests, techniques, verbalisation and attitude, duration, etc.)	
	Knowledge of osteopathic semiology: somatic dysfunction and clinical criteria, modulations chosen for the study compared to the SNF (7 functional anatomical areas, SD scoring of 1 or 0).	
Tests	7 tests: technical practice (rigour in gestures and positioning of the patient), respecting the time (10 mins), verbalisation quality (introducing the session, taking the patient's history, etc.).	
Treatment	Quality of each of the 14 techniques (patient handling, positioning and body gestures), accuracy of the gestures, clarity in explaining the expected physiological effects, knowledge of the choices between each pair of techniques.	
	Respecting the time to put the chosen 7 techniques into practice, good performance over the 15 mins of treatment.	
	Quality of the verbalisation and attitude towards the patient: general verbalisation, quality of listening and dialogue, empathy and trust in the favourable outcome of the symptoms.	

Placebo	Proper application of the gestures and changes in the patient's position, compliance with "light-touch" instructions (light contact, not lasting over 5 seconds, with the whole body covered).	
	Compliance with the 15 minutes for putting the whole procedure into practice while using general verbalisation, the quality of listening and dialogue, empathy and trust in the favourable outcome of the symptoms.	
End of sessions	End-of-session quality: redressing, verbalisation, general healthy lifestyle advice (physical/practical, nutritional, hydration, sleep, careful attitude in the workplace, etc.)	
Explanation of the follow-up clinical forms	Quality of explanation of the forms (scoring, somatic dysfunction clinical signs found, related systems, etc.)	
Total / 14	0 to 11: not validated: 12 or 13: not validated, to be reassessed; 14 = validated	**0**

Annex 4: Light-touch treatment sequence

Patient in the supine position

Feet

The practitioner places their hands on the dorsal surface of the foot first of all, then on the plantar surface, then on the medial edge, and then on the lateral edge. The same gestures are performed on the other foot.

Legs

The practitioner places their hands on the medial side of the right leg first of all, then on the lateral side, and then on the anterior side. The same gestures are performed on the other leg.

Knees

The practitioner places their hands on the medial side of the right knee first of all, then on the lateral side, and then on the anterior side. The same gestures are performed on the other knee.

Thighs

The practitioner places their hands on the medial side of the right thigh first of all, then on the lateral side, and then on the anterior side. The same gestures are performed on the other thigh.

Pelvis

Successive application of the hands on the lateral side of the right and left greater trochanters, and the right and left iliac crests.

Abdomen

The practitioner successively places their hands on the various anatomical points of the abdomen (right and left iliac fossa, hypogastrium, epigastrium, right and left flanks, and right and left hypochondrium).

Chest

Successive application of the hands on the anterior side of the right and left lower ribcage, the right and left upper ribcage, and the sternum.

Shoulder girdle

Successive application of the hands on the anterior side of the stump of the right and left shoulder, then on the lateral sides, then on the upper sides.

Neck

The practitioner presses the lateral sides of the neck with both hands, then presses the anterior and posterior sides of the neck.

Cranium

Successive application of the hands on the right and left lateral sides, on the lower jaw, on the upper jaw, and then on the cranial vault.

Patient in the prone position

Feet

The practitioner places their hands on the plantar surface first of all, then on the medial edge, and then on the lateral edge. The same gestures are performed on the other foot.

Legs

The practitioner places their hands on the medial side of the right leg first of all, and then on the posterior side. The same gestures are performed on the other leg.

Knees

The practitioner places their hands on the medial side of the right knee first of all, then on the lateral side, and then on the posterior side. The same gestures are performed on the other knee.

Thighs

The practitioner places their hands on the medial side of the right thigh first of all, then on the lateral side, and then on the posterior side. The same gestures are performed on the other thigh.

Pelvic girdle

Successive application of the hands on the posterior side of the sacrum, the right and left sacroiliac joints, the lateral side of the right and left greater trochanters, the right and left iliac crests, and folds under the right and left buttocks.

Lumbar spine

Successive application of the hands on the dorsal side of the right and left lower trunk, and the right and left upper trunk.

Central application of the hands on the lumbar spine

Thoracic spine

Successive application of the hands on the dorsal side of the right and left lower thoracic ribcage, the right and left mid thoracic ribcage, and the right and left upper thoracic ribcage.

Central application of the hands on the lower then upper thoracic spine.

Shoulder girdle and upper limb

Successive application of the hands on the posterior side of the right shoulder, then the lateral side of the right shoulder, then the lateral side of the arm, medial side of the arm, posterior side of the arm, then the lateral side of the right elbow, medial side of the elbow, posterior side of the elbow, then the lateral side of the forearm, medial side of the forearm, posterior side of the forearm, and then palpates the palmar surface of the right hand.

The same gestures are performed on the other shoulder girdle and upper limb.

Atlanto-occipital joint

Successive application of the hands on the posterior side of the right and left craniocervical junction.

Annex 5: Summary table for osteopathic assessment: methodology and example

• The musculoskeletal table includes several endpoints which can either be combined or not. These criteria are grouped under the acronym "TART":

T: tissue texture change;

A: asymmetry of anatomical landmarks;

R: range of motion;

T: tenderness;

∑: all the criteria are present.

• The musculoskeletal examination includes 6 areas to be studied:

Head, face and neck;
Spine, ribs and pelvis;
Right upper limb;
Left upper limb;
Right lower limb;
Left lower limb.

The abdominal/other part is for other dysfunctions such as any visceral repercussions associated with thoracic dysfunction.

• 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 indicated 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. These dysfunctions are generally asymptomatic;
3 (severe): major dysfunction, including somatic dysfunction endpoints, which are usually symptomatic.

• The somatic dysfunction and other systems section allows us to note any links between the somatic dysfunction found and the following systems:

MS: musculoskeletal;
SNS: sympathetic nervous system;
PNS: parasympathetic nervous system;
LYM: lymphatic;
CV: cardiovascular;
RESP: respiratory;
GI: gastrointestinal;
FAS: fascial.

• Treatment yes/no: mark Y (yes) for an area examined and treated or N (no) if this is not the case.

- Techniques: the abbreviations correspond to the various osteopathic treatment methods:

  ART: Articular techniques

  BLT: Balanced ligamentous tension technique

  CR: Cranial/Osteopathic techniques in the cranial vault

  CS: Counterstrain techniques

  DIR: Direct techniques

  FPR: Facilitated positional release

  HVLA: High-velocity, low-amplitude techniques (thrust)

  IND: Indirect techniques

  INR: Integrated neuromuscular release

  LAS: Ligamentous articular strain

  MET: Muscle energy techniques

  MFR: Myofascial release

  ST: Soft-tissue techniques

  VIS: Visceral techniques

  OTH: Other techniques

- Treatment response: the area is tested again after the treatment.

  R: resolved, there is no more dysfunction

  Imp.: improved, dysfunction is still present but less significant

  U: unchanged

  Inc.: dysfunction has increased.

Table 2. Osteopathic Outpatient SOAP Note Form

Clinical signs					Anatomical area	Severity				Somatic dysfunction(s) / system(s)	Treatment		Techniques*	Progress			
Σ	S	A	R	T	Tested	0	1	2	3	MS / SNS / SNP / LYM / CV / RESP / GI / FASCIAL / Other	O	N		R	Imp.	U	Inc.
					Cranium and Face												
					Neck												
					Thoracic T1-T4												
					Thoracic T5-T9												
					Thoracic T10-T12												
					Ribs												
					Lumbar												
					Sacrum/pelvis												
					Pelvis/iliac												
					Abdomen												
					Right upper limb												
					Left upper limb												
					Right lower limb												
					Left lower limb												

*ART / BLT / CR / CS / DIR / FPR / HVLA / IND / INR / LAS / ME / MFR / ST / VIS.

Annex 6: Quebec functional capacity questionnaire

QUEBEC BACK PAIN DISABILITY SCALE

This questionnaire is about the way your back pain is affecting your daily life. People with back problems may find it difficult to perform some of their daily activities. We would like to know if you find it difficult to perform any of the activities listed below, **because of your back pain**. For each activity there is a scale from 0 to 5. Please choose one response for each activity (do not skip any activities).

Today, do you find it difficult to perform the following activities **because of your back pain**?

	Not difficult at all	Minimally difficult	Somewhat difficult	Fairly difficult	Very difficult	Unable to do it
1 – Get out of bed	☐	☐	☐	☐	☐	☐
2 – Sleep through the night	☐	☐	☐	☐	☐	☐
3 – Turn over in bed	☐	☐	☐	☐	☐	☐
4 – Ride in a car	☐	☐	☐	☐	☐	☐
5 – Stand up for 20 to 30 minutes	☐	☐	☐	☐	☐	☐
6 – Sit in a chair for several hours	☐	☐	☐	☐	☐	☐
7 – Climb one flight of stairs	☐	☐	☐	☐	☐	☐
8 – Walk a few blocks (300-400 m)	☐	☐	☐	☐	☐	☐
9 – Walk several kilometres	☐	☐	☐	☐	☐	☐
10 – Reach up to high shelves	☐	☐	☐	☐	☐	☐
11 – Throw a ball	☐	☐	☐	☐	☐	☐
12 – Run one block (about 100 m)	☐	☐	☐	☐	☐	☐
13 – Take food out of the refrigerator	☐	☐	☐	☐	☐	☐
14 – Make your bed	☐	☐	☐	☐	☐	☐
15 – Put on socks (pantyhose)	☐	☐	☐	☐	☐	☐
16 – Bend over to clean the bathtub	☐	☐	☐	☐	☐	☐
17 – Move a chair	☐	☐	☐	☐	☐	☐
18 – Pull or push heavy doors	☐	☐	☐	☐	☐	☐

19 – Carry two bags of groceries	☐	☐	☐	☐	☐	☐
20 – Lift and carry a heavy suitcase	☐	☐	☐	☐	☐	☐

Annex 7

MOS SF-12 QUALITY OF LIFE QUESTIONNAIRE

The following questions ask for your views about your health. Your answers will help monitor the condition of your health and to know how well you are able to do your usual activities.

Answer all of the following questions by following the instructions you have been given. If you are unsure, please give the best answer you can.

1. **In general, would you say your health is:**

..... *(mark one answer only)*

- Excellent..... ☐
- Very good ..... ☐
- Good..... ☐
- Fair ..... ☐
- Poor ..... ☐

➢ The following is a list of activities you might do during a typical day. For each of these, indicate whether your health now limits you in these activities.

(mark one answer only per line)

	limited a lot	**limited a little**	**not limited at all**
2. **Moderate physical activities** such as moving a table, pushing a vacuum cleaner, bowling	☐	☐	☐
3. Climbing **several flights** of stairs	☐	☐	☐

➢ **During the <u>past 4 weeks,</u> due to your <u>physical condition</u>,**

(mark one answer only per line)

	YES	**NO**
4. have you **accomplished less** than you would like?	☐	☐
5. have you had to stop doing certain things?	☐	☐

➢ **During the <u>past 4 weeks</u>, due to your <u>emotional state</u> (such as feeling sad, nervous or depressed)**

(mark one answer only per line)

	YES	**NO**
6. have you **accomplished less** than you would like?	☐	☐
7. have you had **difficulties** in doing what you had to do **with as much care and attention as usual?** ☐	☐	

8. **During the past 4 weeks, how much did your physical pain interfere with your work or housework?**

(mark one answer only)

- Not at all..... ☐
- A little bit ..... ☐

- Moderately ..... ☐
- Quite a bit ..... ☐
- Extremely ..... ☐

➢ The following questions are related to how you have felt over the past 4 weeks. For each question, please indicate the response you feel is most appropriate.

➢ **During the past 4 weeks, have there been times when:**

(mark one answer only per line)

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
9. Have you felt calm & peaceful?	☐	☐	☐	☐	☐	☐
10. Have you felt full of energy?	☐	☐	☐	☐	☐	☐
11. Have you felt down-hearted and blue?	☐	☐	☐	☐	☐	☐

12. **During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities and relationships with others (family, friends, etc.)?**

(mark one answer only)

All the of time..... ☐
Most of the time ..... ☐
From time to time ..... ☐
Rarely ..... ☐
Never ..... ☐

Annex 8: SAE Form

REPORT FORM FOR A SERIOUS ADVERSE EVENT (SAE) OCCURRING DURING A BIOMEDICAL RESEARCH STUDY NOT RELATED TO A PRODUCT MENTIONED IN ARTICLE L.5311-1 OF THE FRENCH PUBLIC HEALTH CODE

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

DÉPARTEMENT de la RECHERCHE CLINIQUE et du DEVELOPPEMENT DIRC Ile-de-FRANCE

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|__|__| - |__|__| - *DRCD* - |__|__|__|__| - |__|__|__|__|

This form must be returned duly completed (2 pages) to the DRCD by fax: +33 (0)1 44 84 17 99

For the attention of *Didier Bouton*

Date reported: |__|__| |__|__| |__|__|__|__|
dd mm yyyy

Research code: **P110142**

IDRCB no.: 2012-A00167-36 **Initial report** ☐ **Follow-up on reported SAE** ☐ **Follow-up no.** |__|

Title of the Biomedical Research LC-OSTEO:

Comparison of the Effectiveness of 2 Manual Therapies Administered by Osteopaths on Functional Outcome in Sub-acute and Chronic Low Back Pain Less Than 1 Year Duration: a Randomised Controlled Trial

1) Site name and address: _____

Site no.: |__|__| Investigator (Role - Surname - First Name): _____

2) Patient identification:

Surname: |__| First name: |__|

Patient no.: |__|__|__|__|__|

Sex: Male ☐ Female ☐

Date of birth: |__|__||__|__| |__|__|__|__|

Age: |__|__| years

Weight: |__|__|__| kg

Height: |__|__|__| cm

Enrolment date: |__|__||__|__| |__|__|__|__|

Randomisation date: |__|__||__|__| |__|__|__|__|

Intervention arm ☐ Control arm ☐

Date of manual therapy

Start: |__|__||__|__| |__|__|__|__|

End: |__|__||__|__| |__|__|__|__|

3) Serious adverse event:

Death ☐

Life-threatening event ☐

Required hospitalisation or extended hospital stay ☐

From |__|__||__|__| |__|__| *to* |__|__||__|__| |__|__| ☐ *ongoing*

Incapacity or disability ☐

Pregnancy ☐

Other medically significant criteria (please specify): ☐

_____

_____

History (allergy, renal failure, etc.): _____

_____

4) Full description of the adverse event (diagnosis made, anatomical location, criteria leading to the event being considered as serious):

Intensity: Mild ☐ Moderate ☐ Severe ☐

Date of event: |__|__| |__|__| |__|__|__|__| and time of event: |__|__| |__|__|

Dd Mm yyyy hh min

_____

_____

Time before occurrence: _____

5) <u>Concomitant</u> medicinal product(s) excluding those used to treat the adverse event:

Brand name (preferably) or International Non-proprietary Name	Route	Dose/ 24 hrs	Start date	On-going	End date	Indication	Causality *(1, 2, 3 or 4)
			|__|__|__|__| |__|__|	☐	|__|__|__|__| |__|__|		
			|__|__|__|__| |__|__|	☐	|__|__|__|__| |__|__|		
			|__|__|__|__| |__|__|	☐	|__|__|__|__| |__|__|		
			|__|__|__|__| |__|__|	☐	|__|__|__|__| |__|__|		

** 1 = Likely 2 = Possible 3 = Unrelated 4 = Unknown*

Patient identification: Surname |__| **First name:** |__| **Site:** |__|__| **Research code: P110142**

6) Progress (indicate whether any symptomatic measures were taken: no ☐ yes ☐*If yes, please specify*) :

_____

_____

_____

_____

7) Date of disappearance: |__|__| |__|__| |__|__|__|__| and time of disappearance: |__|__| |__|__|

Dd Mm yyyy hh min

8) Other aetiology(ies) considered: no ☐yes☐ *If yes, please specify:*

_____

_____

9) Complementary examination(s) performed: no ☐ yes☐ *If yes, please specify date, nature and results:*

_____

_____

10) According to the investigator, the serious adverse event is most likely related to:

☐ a medical device in place

☐ one or more medicinal product(s) administered: which: _____

☐ the biomedical research procedures

☐ a concomitant disease

☐ the disease progression

☐ other: _____ ___

Date: |__|__| |__|__| |__|__| **Department stamp:** **Investigator's name:** _____ **Signature:**

Name and role of the Reporting Party: _____ **Phone no.** _____ **Signature:**

20.1.1.1.1 SECTION RESERVED FOR THE SPONSOR: DO NOT FILL IN

20.1.1.1.2 **Event identification number:** ***EV I__I__I__I***

Date received by the sponsor: |__|__| |__|__| |__|__|__|__|

Date of this report: |__|__| |__|__| |__|__|__|__| ☐ initial ☐ follow-up no. |__|__|

According to the sponsor, the adverse event is most likely related to:

☐ a medical device in place

☐ one or more medicinal product(s) administered: which: _____

☐ the biomedical research procedures

☐ concomitant disease

☐ the disease progression

☐ other: _____

If, according to the sponsor, the event is more likely to be related to the biomedical research:

☐ The serious adverse event is expected

☐ The serious adverse event is unexpected

Sponsor's comments:

_____

_____

_____

_____

Name and role of the sponsor's representative: **Signature:**

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Method Supplement 2. **English translation of the study's final full protocol and summary of changes.**

COMPARISON OF THE EFFECTIVENESS OF 2 MANUAL THERAPIES ON FUNCTIONAL OUTCOME IN SUB-ACUTE AND CHRONIC LOW BACK PAIN: A RANDOMISED CONTROLLED TRIAL.

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

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Biomedical research PROTOCOL SIGNATURE page

for the PRINCIPAL Investigator and the SPONSOR's representative

Biomedical research no. P110142 – IDRCB 2012-A 167-36

"COMPARISON OF THE EFFECTIVENESS OF 2 MANUAL THERAPIES ADMINISTERED BY OSTEOPATHS ON FUNCTIONAL OUTCOME IN SUB-ACUTE AND CHRONIC LOW BACK PAIN: A RANDOMISED CONTROLLED TRIAL"

Version no. 7.0 dated 02/08/2018

Principal Investigator:

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Date:

Signature:

NB: This version corresponds to the protocol text and annexes sent to the Ethics Committee (CPP) and the competent authority for a request for opinion and authorisation, respectively, and to other parties involved in the research (hospital directors, etc.).

List of research sites

No.	Principal Investigator at the site (name, title, role)	Department	Site address	Telephone Fax
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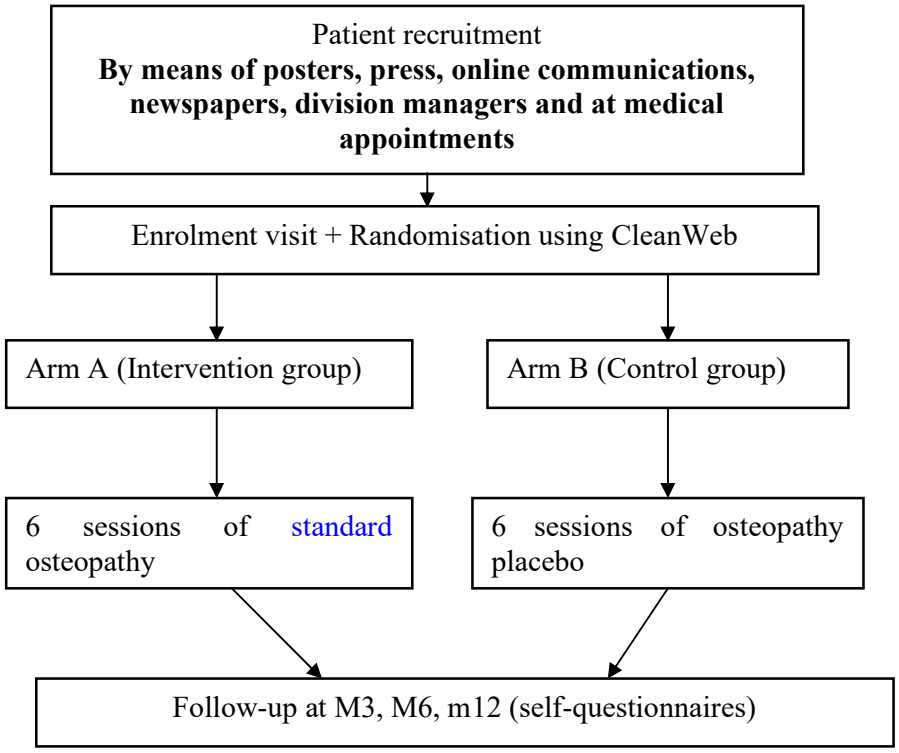
Protocol Summary

Study Title	Comparison of the Effectiveness of 2 Manual Therapies Administered by Osteopaths on Functional Outcome in Sub-acute and Chronic Low Back Pain: a Randomised Controlled Trial
Sponsor	AP-HP
Principal Investigator Scientific Leaders	Prof. François Rannou Dr Peggy Krief Mr Rafael Zegarra-Parodi
Introduction and hypothesis	Alternative 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 assess the effectiveness of two manual therapies on improving functional capacity at 3 months after randomization in patients who have had sub-acute or chronic common lower back pain.
Secondary objectives	To assess the effectiveness of standard manual therapy on: - Low back 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 non-steroidal anti-inflammatory drugs (NSAIDs) (at 3 and 12 months).
Study type	A randomised, controlled, multicentre trial comparing a manual therapy treatment with an osteopathic placebo treatment.
Inclusion criteria	- Patients with sub-acute or chronic common lower back pain as the main reason for consultation; - Patient 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.
- Exclusion criteria	- Any chronic lower back pain secondary to an inflammatory (rheumatic disorders), tumour (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 clinical trial therapeutic protocol.
Intervention	Six sessions of manual therapy at 15-day intervals.
Comparator	Six sessions of manual placebo therapy at 15-day intervals.
Primary endpoint	Assessment of average change in functional capacity using the Quebec Back Pain Disability Scale 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 after

	randomization.
Secondary endpoints	- Average change in pain using the numeric pain scale from 0 to 100, at 3 and 12 months; - Number and duration of sick leave periods at 12 months; - Number of recurrences at 12 months; - Average change in functional capacity using the Quebec questionnaire at 12 months; - Average change in quality of life assessment using the physical and mental components of the SF-12 questionnaire at 3 and 12 months; - Consumption of painkillers and NSAIDs (yes/no) (at 3 and 12 months).
Total number of patients expected	400 patients
Study duration	42 months
Patient observation duration	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 assess the effectiveness of manual therapy treatment in sub-acute or chronic common lower back pain.

GENERAL OUTLINE OF THE STUDY



Visits	D0	D15	M1	M1.5	M2	M2.5	M3	M6	M12
Inclusion/exclusion criteria, Information	X								
Information – Consent	X								
Enrolment Randomisation	X								
Examination and osteopathic treatment (intervention group) or placebo (control group)		X	X	X	X	X	X		
Assessment *Quebec* *Numeric pain scale* *Number and duration of sick leave periods* *Relapses* *SF-12*	 X X X X X						 X X X X X	 X X X X X	 X X X X X
Treatment credibility assessment							X		
Consumption of painkillers and NSAIDs	X						X	X	X
Adverse events / Serious adverse events		X	X	X	X	X	X	X	X

1 What is known about the issue

Chronic common lower back pain represents a public health problem, particularly at the socio-professional and economic level. Beyond the human suffering, they lead to functional disorders which disrupt professional activity. They account for a heavy financial burden on society as they lead to significant employee absenteeism and therefore a loss in efficiency for the company[3,4]. Numerous treatments have been proposed for this condition, but they have not been effective enough to reduce its incidence. Osteopathy, one example of manual therapy, belongs to the category of emerging alternative medicines which patients may resort to, although few scientific studies have been implemented to demonstrate their effectiveness[1,19,26,28]. We aim to assess the effectiveness of two manual therapies administered by osteopaths in patients who have had sub-acute or chronic common lower back pain; this is particularly relevant as the assessment of alternative medicines is part of the AP-HP's 2010-2014 Strategic Plan.

1.1 Definition and epidemiology of sub-acute and chronic common lower back pain

1.1.1 Definition

Sub-acute and chronic common lower back pain is defined as a regular pain in the lower back area which can radiate as far as the knee without surpassing it, with sub-acute pain lasting between 4 and 12 weeks and chronic pain lasting more than 3 months, and for which secondary causes (infectious, inflammatory, tumour or traumatic causes) are ruled out from being at the origin of lower back pain, known as symptomatic causes[2].

1.1.2 Epidemiology

According to Llorca[3], lower back pain is the leading cause of disability in the under-45 population working in the industrial sector, the leading cause of restricted activity in individuals between the ages of 45 and 65, and the third leading cause of chronic disability. Its incidence is between 60% and 90% and its prevalence varies depending on the age and definition adopted. In France, it accounts for almost one-quarter of the reasons for rheumatology consultations and between 2% and 4% of general medical consultations. It has a considerable annual cost, amounting to around 1.5 billion euros in France.

Lumbar radicular pain (Table 98) and osteoarticular diseases (Table 57) account for the vast majority of the occupational diseases reported and recognised at the AP-HP. Osteoarticular diseases account for around 75% of sick leave causes at the AP-HP. Musculoskeletal disorders (MSDs) accounted for around 49% of all workplace accidents at the AP-HP in 2008 and 77% of workplace accidents involving sick leave. MSDs accounted for 85.5% of all sick leave days (workplace accidents or illness), which was around 44,000 days in total in 2008. (Source: Statutory Medicine and Control Department of the AP-HP 2008).

Sub-acute and chronic common lower back pain is extremely common. It will only become chronic in 8% of patients, but they account for over 85% of the costs incurred. The factors leading to chronicity and non-return to work are essentially a history of lower back pain, the presence of sciatica, the severity of the functional impairment, age and dissatisfaction at work[4].

1.2 Therapeutic methods and the limitations of their effectiveness

1.2.1 Medicinal treatments

Level 1, 2 and 3 analgesics act on lower back pain but these alone cannot solve the problem of chronic pain and the resulting disability[3]. Their use must comply with the contraindications and be limited to acute or short-lasting episodes, to prevent dependency.

NSAIDs at inflammatory doses may be prescribed for analgesic purposes in the short-term, in accordance with the contraindications. NSAIDs have proven to be effective particularly in acute episodes[5].

Muscle relaxants have not proven to be effective in chronic lower back pain compared to placebo[5]. They are essentially prescribed to patients with resurgence of pain over a period which must not exceed 2 weeks.

Antidepressants seem to develop an actual analgesic effect in chronic lower back pain[5], independent of their antidepressant effect.

Epidural corticosteroid injections appear to have a short-term analgesic effect in patients with lower back pain or sciatica [6].

1.2.2 Non-medicinal treatments

Physical therapy combined with physical exercises appears to be effective in terms of pain reduction and functional improvement in chronic lower back pain[7,8].

Multidisciplinary management, combining education and advice sessions, intense physical exercises either supervised or not by a physical therapist, and psychological management (at proportions yet to be determined), essentially allow for an improvement in functional capacity, leading to an earlier and longer-lasting return to work[9]. The improvement in terms of pain has not been demonstrated[10].

Spinal traction has not proven to be effective[11].

Spinal manipulations are slightly effective in terms of pain but studies are controversial: their effectiveness in terms of pain does not appear to be better than other existing treatments (physical therapy, painkillers, etc.)[12,13].

Acupuncture appears to have a short-term and long-term effect in terms of pain and functional capacity in chronic lower back pain[14,15]. This is likely to be a placebo effect (decorum)[16].

Percutaneous electrical stimulation treatment has not yet demonstrated its effectiveness. The 2005 literature review by Khadilkar was not able to reach any conclusions regarding the effectiveness of transcutaneous electrical nerve stimulation (TENS) due to the low number of randomised controlled studies and the contradictory results[17,18].

The choice of literature on the management of sub-acute and chronic common lower back pain was limited to randomised controlled trials. Most of the studies identified involve multiple and partial endpoints (pain, return to work, functional score, subjective improvement assessed by the patient, etc.). This means that the studies cannot be compared to each other and the results are very mixed. As a result of these methodological limitations, a gold-standard treatment cannot be recommended; all that can be recommended are proposals aimed at helping healthcare professionals manage these patients.

The following table provides a summary of the treatments and therapeutic effectiveness according to the levels of scientific evidence on sub-acute or chronic common lower back pain.

Treatment	Endpoint	Level of evidence	Therapeutic effectiveness
Physical therapy	Pain, function	1	Slightly effective in terms of pain Slightly effective in terms of function
Multidisciplinary programmes	Pain, function, return to work	1	Effective in terms of function and return to work Not proven to be effective in terms of pain
Acupuncture	Pain, function	1	Slightly effective in terms of pain and function
Spinal manipulation	Pain, function	1	Slightly effective in terms of pain Not proven to be effective in terms of function
Corticosteroid injection	Pain	2	Effective in the short-term
Antidepressant	Pain	2	Slightly effective
NSAID	Pain	2	Effective in the short-term
Analgesic	Pain	2	Moderately effective
Paracetamol	Pain	2	Slightly effective
Muscle relaxant	Pain	2	Not proven to be effective
TENS	Pain	2	Not proven to be effective
Spinal traction	Pain	2	Not proven to be effective

Table 1: Summary table of the treatments and their effectiveness in chronic lower back pain. Slightly effective = $5 \leq \Delta$ VAS < 15; moderately effective = $15 \leq \Delta$ VAS < 25; highly effective = Δ VAS ≥ 25.

These treatment methods are adapted to each patient according to the objectives set with them: the aim is to prevent excessive use of medication while ensuring therapeutic accompaniment which comforts the patient.

Allopathic medicine has its limitations: while it has proven to be effective in acute common lower back pain (continued activity + paracetamol), the situation is quite different for sub-acute (4 to 12 weeks) and chronic (> 3 months) lower back pain.

1.3 Data published on the effects of an osteopathic treatment on patients with lower back pain

(See Annexe 1 page 60 for further information on osteopathy.)

Considering that sub-acute and chronic common lower back pain represent a significant public health problem and that allopathic medicine has its limitations, patients are resorting to osteopathy, which belongs to the category of emerging alternative medicines, although few scientific studies have been conducted. Furthermore, the assessment of alternative medicines is part of the AP-HP's 2010-2014 Strategic Plan.

1.3.1 Effects on pain

A meta-analysis of randomised clinical studies assessing the effects of osteopathic manipulative treatment (OMT) in patients with chronic lower back pain showed that this treatment significantly reduced the pain, with better effects compared to the placebo and which last at least 3 months[19]. This meta-analysis published by Licciardone *et al*. in 2005 studied the results of 6 randomised clinical studies conducted in the USA and in the UK[20,21,22,23,24,25]. A total of 525 subjects with lower back pain were enrolled in the various randomised clinical studies. There was a significant reduction ($p = 0.001$) in the chronic lower back pain treated with OMT, and the effect size was modest at -0.30 (95% CI=[-0.47;-0.13]), which corresponds to a reduction of 6.5 mm on the VAS. There is also a significant reduction ($p = 0.02$) in pain in these randomised clinical studies in patients treated with OMT versus active treatment or versus placebo, with an effect size of -0.26 (95% CI=[-0.48;-0.05]).

1.3.2 Effects on functional capacity

In 2004, the "United Kingdom back pain exercise and manipulation (UK BEAM) Trial" team [26] published a study on 1,334 patients with chronic common lower back pain on the effects of spinal manipulations compared to the "best care", either with or without a therapeutic exercise programme. The comparator treatment ("best care") consisted of higher quality care than that of routine practice, as the general practitioners had received specific training in patients with lower back pain before the study. The main measurement instrument was the Roland-Morris Disability Questionnaire, which was used at the start of the study, at 3 months then at 12 months. There was a significant difference between the spinal manipulation and "best care" scores compared to "best care" alone at 3 months ($p = 0.001$) and at 12 months ($p = 0.01$).

The authors also used the SF-36 questionnaire to compare these same therapeutic approaches and observed a very significant difference at 3 months (p = 0.001) and a significant difference at 12 months (p = 0.01).
Throughout the whole study, the management method providing the best results was spinal manipulation (8 sessions of 20 minutes carried out by osteopaths, chiropractors and physiotherapists) combined with muscle reinforcement sessions (8 group sessions each lasting 60 minutes in the 6 weeks after the manipulations).

While the treatments assessed are not used in routine practice by osteopaths, as these professionals include other technical approaches, the authors concluded that the spinal manipulative treatment together with the treatment by the attending physician improves the patient's back function and quality of life more effectively than the treatment by the attending physician alone[27].
There are few osteopathic studies and they have significant methodological bias, as osteopathy belongs to the category of "complex interventions"[28] and it is difficult to implement blinding.

2 Research objectives

2.1 Primary objective

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

2.2 Secondary objectives

To assess the effectiveness of standard osteopathic treatment on:

- low back 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).

3 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.

This study will be planned, implemented, analysed and reported in accordance with the recommendations of the 2010 CONSORT Statement[29] and the CONSORT Statement extension for the assessment of non-pharmacological treatments[30,31].

The randomised, controlled trial is considered the gold standard for therapeutic assessment. However, the assessment of non-pharmacological treatments raises specific methodological issues related to the choice of comparator, difficulties in achieving blinding, the complexity of the intervention and the therapist's influence on the intervention's success[32].

The planning of this study took these difficulties into account.

3.1 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.

3.2 Choice of comparator

For this trial, we chose to use an osteopathic placebo as the comparator. This choice was motivated by the important 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[33] demonstrated that blinding is particularly important for subjective endpoints, with an overestimation of 25% in terms of the treatment effect.

The other comparators which were not chosen were as follows:

1) Standard medical treatment. However, in this situation, the blinding of patients and therefore the assessors was not possible, with a risk of disappointment in the patients randomised into the standard treatment group.
2) Physical therapy treatment. However, this choice would not allow us to respond to the question put forward.

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.

3.3 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. A modified Zelen design was not chosen as some of the patients will be recruited by occupational and rehabilitation physicians, and patients would have the opportunity to discuss this with each other, leading to a significant risk of this design failing.
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 lower 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 the other manual treatment is 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 the study.
The success of the blinding will not be assessed during the study as several methodology studies have shown this not to be useful and that such procedures involve a risk in terms of the methodological plan[34,35]. On the other hand, the credibility of the treatment received will be systematically assessed[36].
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-administered printed questionnaires).

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.

3.4 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[37], this intervention will be standard, the therapists will be trained and the level of accuracy in terms of the protocol will be assessed.

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.

The osteopaths will be trained to both experimental and sham interventions before starting the study, in order to standardise the treatment (see 4.5.2 to 4.5.5). They will therefore have a total of 3 training/assessment days, among which 2 will take place at the Rehabilitation Department of Cochin Hospital with 3 instructors in osteopathic practice, and will receive the detailed procedure in the form of a DVD. Accuracy in terms of the protocol will be assessed through audio recordings of the sessions; 30 recordings will be chosen at random from 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.

In order to ensure maximum transparency at all stages, the making of the DVD as well as the recruitment, training and assessment of practitioners will go through a non-profit association.

3.5 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.

Special attention will also be paid to the style of communication of all the study practitioners, due to their placebo effect on patients with chronic musculoskeletal pain and treated with a complex intervention[16].

All practitioners must therefore follow the same style of communication during their treatments. Phrases or key words, expressing a more positive message on the issue of treatment, will also be emphasised[16]. The treatment sessions will be recorded (audio) in both groups (see 3.6 Comparator standardisation, page 24-25/92).

Osteopath expertise

Performance of the practitioner recruitment procedure in accordance with the inclusion criteria

Justification for choosing a high level of professional qualification for the practitioners

The European Qualifications Framework for Lifelong Learning (EQF) is the benchmark system created to standardise professional training and professional practice in Europe[38], [39], [40]. As of 2012, all the professional qualifications issued by higher education establishments in Europe should theoretically refer to a qualification level as described in the EQF[41]. Despite the current context in France in terms of the lack of qualifications for manual therapies, in January 2011, 10 private osteopathy teaching establishments obtained the highest level of professional qualification: level 1 of the French National Professional Qualifications Framework (RNCP)[42]. Eight of these 10 osteopathy teaching centres made a joint request mainly referring to the EQF procedures to define a professional qualification for the practice of osteopathy in France.

These 8 establishments issue the osteopath diploma after a 5-year full-time course in accordance with the recommendations made by the WHO on the subject[38]. For osteopathic practitioners who are already practising, they have the possibility of obtaining level 1 of the RNCP by undertaking a personal validation of prior experience (VAE) at any of these 10 establishments.

Inclusion criteria for study practitioners

The study practitioners must therefore be able to demonstrate the following points:

1/ Holders of an Osteopath Diploma issued: in France by one of the 10 establishments registered with level 1 of the RNCP, or abroad in a country where osteopathy is recognised and regulated;

2/ Holders of authorisation to practice osteopathy in France, issued by the competent authorities (Regional Health Agency, ARS);

3/ Holders of appendices to their training diplomas (“competency log”), in accordance with the European regulations on professional qualifications, who are able to demonstrate osteopathic training of at least 4,200 hours in accordance with the WHO Benchmarks and the

existing professional competency regulations: General Osteopathic Council – GOsC (UK)[43], Forum for Osteopathic Regulation in Europe – FORE (Europe)[44], and Switzerland[45]);
4/ Up-to-date Individual Professional Liability and Legal Protection.

Selection of 24 study practitioners

The study will be structured around 3 6-month sessions (additional session in case of extended inclusion period). 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, among which 2 will take place at the Department of Rehabilitation of Cochin Hospital with 3 instructors in osteopathic practice. Quality control will be continuously carried out by the 3 instructors in osteopathic practice, in conjunction with the clinical study technicians of the study, in order to answer the questions of the osteopathic practitioners and ensure the standardization of all procedures throughout 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 1 6-month session. The practitioners of a group will have the possibility of participating in a following one provided that they follow the evaluation process for instructors in osteopathic practice again.

Each group of 10 practitioners will be made up 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 the placebo, so that they are able to provide both approaches depending on patient allocation.

Overview of the training and assessment

The practitioner preparation and assessment phase will be carried out on 3 days over the course of a month, among which 2 will take place at the Department of Rehabilitation of Cochin Hospital with 3 instructors in osteopathic practice. The assessment must be carried out each time, one month before the start of the first patient enrolments (the first training day will therefore be two months before the first enrolment):

Training and assessment

Dates: 2 days at a 15-day interval in the presence of 15 practitioners for the 6-month session and a quality control of all procedures ensured electronically by the 3 instructors in

osteopathic practice to ensure the standardization of all of the procedures by osteopathic practitioners.
Qualification of the trainers: Professional osteopaths and practising teachers, who hold a university diploma or a Master's in Education.
Role of the trainers: to provide criteria for verbalisation in accordance with the study requirements.
Assessment: 1 day, 15 days after the second training session carried out by 3 certifying osteopaths who will be different from the trainers.
The training and assessment will take place at the Rehabilitation Department of Cochin Hospital.

Summary of the practitioner training procedure

Day 1

Presentation of the study as well as the basic methodological principles for assessment of a complex intervention, presentation and detailed description of the clinical procedures for the treatment group and the osteopathic placebo group, presentation of the assessment table and distribution of the DVD showing the techniques.
Aim: to acquire knowledge of the techniques and procedures in a sequenced manner. Group self-assessment with the help of a video tool.

Day 2

Recap on knowledge and sequencing, work on the specific parameters described in the literature regarding manual therapies for improving the intra- and inter-practitioner accuracy of the study's diagnostic procedures, description and validation by the osteopath supervisors of the different stages to reproduce the tests, their interpretation as well as the manipulation techniques, and then the implementation of all the clinical procedures in a timed manner.
Aim: understanding of the criteria to be worked on to improve the accuracy of the tests, their interpretation and the performance of the techniques so that the treatment will be standard and personalised, acquisition of the implementation of intervention and placebo sessions from start to finish in 30 mins facing the patient, then proper explanation of the follow-up form in 10 mins. Group self-assessment including the video tool.

Teaching sheets for the training

1/ Understanding of the study

Detailed presentation of the study and its implications; complex interventions; specific features of the study compared to a doctor's surgery situation.

Role of the practitioners, rights and duties, relationships with the investigators.

Data from the literature on the reproducibility of the osteopathic tests and the methods for improvement.

The point on the osteopathic semiology, the somatic dysfunction study criteria and treatment.

2/ Test section

Presentation and demonstration of the tests by the osteopath supervisors.

Patient set-up and practitioner positioning.

Direction and amount of force used for the tests.

Interpretation of the tissue response to pressure applied.

Patient handling.

Verbalisation (main key words) for describing to the patient what the practitioner is doing.

3/ Standard osteopathic treatment

Presentation and demonstration of the 14 techniques by the osteopath supervisors one by one at first (Day 1) then in sequence (Day 2).

Patient set-up and practitioner positioning.

Direction and amount of force used for the techniques.

Interpretation of the tissue response to pressure applied.

Patient handling.

Verbalisation (main key words) for describing to the patient what the practitioner is doing.

4/ Osteopathic placebo treatment

Presentation and demonstration of the standardised procedure by the osteopath supervisors.

Patient set-up and practitioner positioning.

Direction and amount of force used for the techniques.

Patient handling.

Verbalisation (main key words) for describing to the patient what the practitioner is doing.

5/ Management of general verbalisation and end of the session

Presentation and detailed description of the verbalisation to be used according to the various

phases of the consultation: questioning, physical examination, presentation of diagnosis, presentation of techniques, presentation of the issue of manual treatment.
Standardisation of key words to be used according to each phase of the consultation.
Advice and supervision by a clinical psychologist.
Presentation and detailed description of the standard healthy lifestyle advice to be given to patients for the next session: job, nutrition and hydration, “stay active”, etc.

6/ Filling in of clinical forms

Presentation and explanation of the documents to be entered in the Outpatient Osteopathic SOAP Note Form: location and severity of the somatic dysfunction, techniques used, standardised abbreviations and specific points.

Performance of the practitioner assessment procedure at the end of the second day of training

Day 3

Assessment in front of the certifying osteopaths who must fill in the assessment table (Annex 3) and in the presence of the other candidates. Two jurors, each having taken part in the training. Debriefing of the assessment in front of the other candidates, for training purposes.

For the record, each candidate is assessed over an hour, structured as follows:

- Presentation of the study and its key points (5 mins)
- Information collection practice (tests and symptom history) (10 mins)
- Standard osteopathic treatment practice (15 mins) for the osteopaths dedicated to the intervention group
- Osteopathic placebo treatment practice (15 mins) for the osteopaths dedicated to the control group
- End of consultation and advice (5 mins)
- Information regarding the form and time for any questions (10 mins)

In other words, 15 hours of assessment split between the two jurors (one full day).
The 8 chosen practitioners as well as the 2 substitute practitioners will be appointed.

A total of 3 training sessions will be carried out at approximately 6-month intervals.

An audio recording will be made of the patients' sessions; 30 recordings will be chosen at random from 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 the Grenoble CHU Occupational Medicine Department, which allows the number of osteopaths to be reduced. Eight osteopaths as well as 2 substitute osteopaths will be involved in this study, every 6 months.

3.6 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 therefore 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 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.

4 Eligibility criteria of the population

4.1 Inclusion criteria for patients

- Patients with sub-acute or chronic common lower 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.

4.2 Exclusion criteria

- Any chronic lower back pain secondary to an inflammatory (rheumatic disorders), tumour (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 clinical trial therapeutic protocol.

5 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.

5.1 Standardisation of the diagnostic part – 4 items

5.1.1 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.
Somatic dysfunction is a pathological entity referenced in the International Classification of Diseases, which is defined as “impaired or altered function of related components of the somatic (bodywork) system including: the skeletal, arthrodial, and myofascial structures, and

their related vascular, lymphatic, and neural elements"[46]. The clinical signs which have been associated with joint somatic dysfunction have traditionally been described with the acronym "SART" (Sensitivity/pain on palpation; Asymmetry of the bony landmarks; Restriction in passive joint movement; changes in the Texture of the surrounding soft tissues)[47]. The osteopath determines the severity of the somatic dysfunction according to the significance and concomitant presence of the palpated clinical signs which can be improved and reduced following suitable manual treatment.

There are three main categories of osteopathic tests according to the anatomical areas being assessed: cranial[48], neuromusculoskeletal[49] and visceral[50]. The clinical signs associated with somatic dysfunction will be studied and interpreted according to the criteria set out in Table 1 in terms of presence (which will require a manipulation technique) and absence (no manipulation technique performed).

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 mobility/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 signs symptoms found	0 to 1 sign(s) symptom found	McPartland
Neuromusculoskeletal (NMS test)	Restricted movement and at least 2 other signs symptoms found	0 to 1 sign(s) symptom found	Hartmann
Visceral (V test)	Restricted movement and at least 2 other signs symptoms found	0 to 1 sign(s) symptom 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[51].

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 in the 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 7 have not been chosen as part of the anatomical areas included in the standard osteopathic treatment.

5.1.2 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)[47,52,53], 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 file provide good intra- and inter-examiner accuracy when the recommendations of the authors are followed[54].

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.

5.2 Standardisation of the treatment part – 5 items

5.2.1 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 lower back pain (the most common ones). The patients would therefore receive treatment in an identical number of anatomical areas in neurological and biomechanical terms with 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 lower back pain by changing the altered neurological reflexes: somatosomatic (posture), viscerosomatic and somatovisceral, in addition to their locoregional biomechanical action.[55]

The locoregional effects of the osteopathic techniques which will be used are similar to the effects already described in the scientific literature[56]:

- Reduction in muscle spasms;
- General relaxation;
- Improvement in movement;
- Drainage of cell exudates;
- Reduction in adherences;

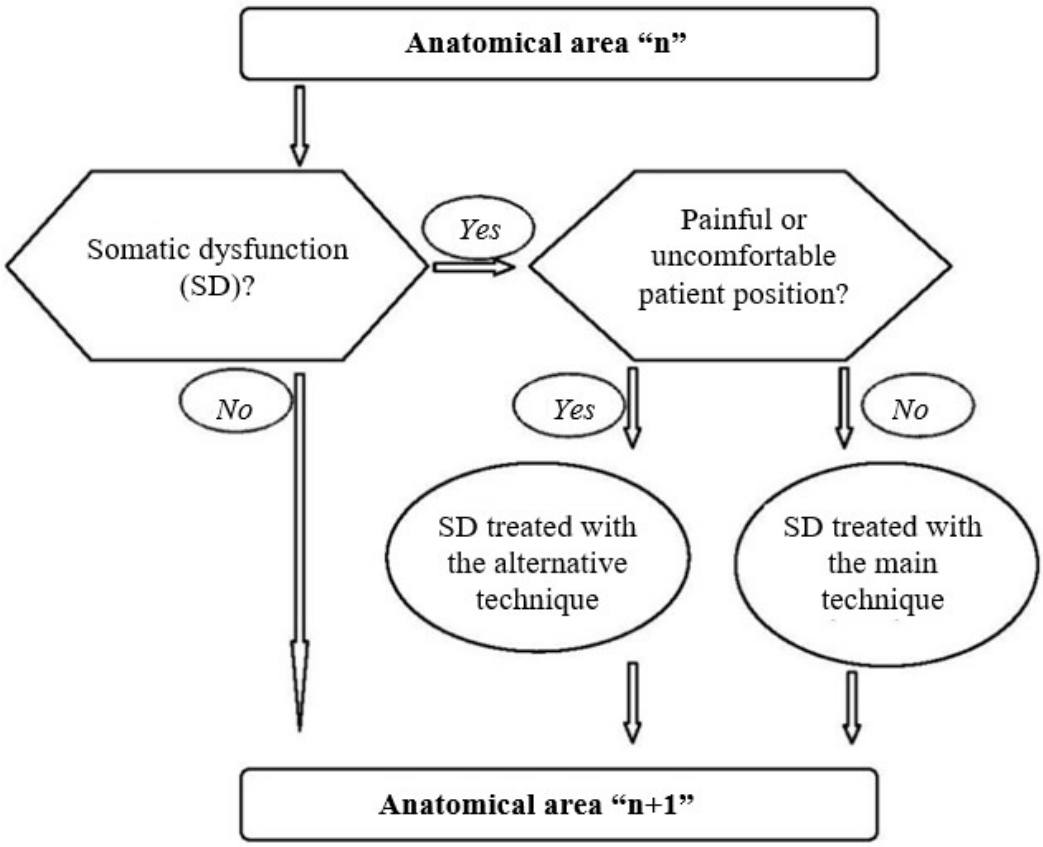
- Improvement in microcirculation and drainage;
- Changes in the levels of serotonin and beta-endorphins in the blood[27];
- Changes in the levels of endogenous cannabinoids in the blood[57].

The osteopathic treatment will be standard and will include 7 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 algorithm for the techniques according to the presence of somatic dysfunction and patient pain/discomfort.



Description of the 7 anatomical areas for standard and personalised osteopathic treatment

Anatomical area 1: Talocrural joint

It is advisable to assess the overall biomechanical function of the lower limbs in the understanding of chronic lower back pain mechanisms[58], as these pains can be associated with adaptation impairment in terms of trunk rotation when walking. Functional instability of the ankle has also been recognised as a predisposing factor for lower back pain due to impaired trunk-stability muscle reflexes which have been associated with this, although no cause-effect link has ever been proven[59].

Anatomical area 2: Root of mesentery

The mesentery is rich in mechanoreceptors and graviceptors[60,61], the reflex neurological paths of which electively borrow those of the orthosympathetic system through the splanchnic nerves and transit through the middle vertebral levels (T9-T10-T11)[62,63]. The release of

visceral connective tissue tension would allow the intra-abdominal pressure to be better distributed and to restore better flexibility to the serous mesenteric joint. These two factors are involved in the construction of the composite beam of the lumbar spine[64]. In order to relieve the pressure on the intervertebral discs, this stabilises on the intra-abdominal cavity, which varies in geometry and pressure[65]. As such, the mechanical information originating from the mesentery could influence the spinal posture by directly modulating the sensitivity thresholds of the musculature of the lumbar spine and the lower limbs.

Anatomical area 3: Diaphragm

Chronic discogenic pain is conveyed by the sinuvertebral nerve[66], which also conveys the nociceptive influx of the anterior longitudinal ligament. In the lower back area, the anterior longitudinal ligament would be the extension of the pillars of the diaphragm[67]. The manual techniques on the diaphragm could therefore theoretically act on the nociceptive reflex arcs. Hodges and Gandevia studied whether the diaphragm activations would interfere with the respiratory cycle phases or with posture[68]. The repeated movements show two changes in the diaphragm which are not correlated to respiration: (1) a tonic contraction during the respiratory cycle, associated with an increase in abdominal pressure. This confirms the diaphragm's role in covering the lower back area during trunk movements; (2) a phasic contraction which demonstrates the diaphragm's role in controlling movements up to the lumbar spine.

Anatomical area 4: Lumbar spine

There are multiple nociceptive information sources involved in lower back pain.

In addition to the posterior facet joints, which may be capable of responding to manipulation treatment[69], other sources of nociceptive irritation have been demonstrated: thoracolumbar fascia[70,71], dura mater[72] and the supraspinous ligaments[73], the experimental stimulation of which causes lower back pain.

Anatomical area 5: Sacroiliac joints

The pelvis represents a connection between the trunk and the lower limbs, and is a key part of the lumbar-pelvic-femoral complex[74]. The sacroiliac joints and the pubic symphysis have a biomechanical role of the absorption joints of this complex by fragmenting gravity[75,76].

On the other hand, the sacroiliac joint has an innervation which, when strained, is prone to leading to lower back pain[77]. Pelvic girdle joint movements would allow for an improvement in lumbar spine strain adaptation and also to act on the nociceptive reflex arcs.

Anatomical area 6: Atlanto-occipital joints

McPartland *et al*.[78] studied the influence of the rectus capitis posterior (RCP) minor muscles and their involvement in postural control due to their high-density neuromuscular spindles. According to these authors, the proprioceptive function of the RCP major and RCP minor muscles is related to those of the spinal postural muscles. A manipulation procedure on the craniocervical junction would aim to reduce the tonicity of the lumbar erector muscles.

Anatomical area 7: Temporomandibular joints (TMJs)

Various authors have identified a direct relationship between temporomandibular and postural disorders which can manifest through chronic lower back pain[79,80,81]. In a case-control study, patients with craniomandibular disorders had a significantly higher number of pain sites, including the lower back[82]. A study by Wiesinger *et al*. showed a statistically significant association between chronic lower back pain and musculoskeletal disorders of the jaw and face, and reported comorbidity between these two symptoms[83].

5.2.2 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 manipulation treatment, and (3) patient comfort. Osteopathic manipulation is therefore not only a matter of spinal manipulation, although this is part of it. Numerous manual techniques are referred to in the Authorized Osteopathic Thesaurus[84] and can be divided into 4 broad categories according to the amount of force, the rhythm and the speed used: (1) rhythmic, (2) high-velocity, low-amplitude (HVLA, the "manipulation" which is accompanied by joint noise), (3) "low-velocity stress", and (4) visceral[85].

Following the osteopathic examination of each anatomical area, there will be 2 possibilities:
Somatic dysfunction absent: no corrective technique
Somatic dysfunction present: corrective technique carried out by the osteopath

Following the osteopathic examination, to carry out a corrective technique on an anatomical area with somatic dysfunction, there will be 2 possibilities:
Patient free from discomfort and pain: main corrective technique;
Patient with discomfort or pain: alternative corrective technique (same technique carried out with the patient in a different position).

5.2.3 Performance of the techniques

Description of the techniques for each anatomical area: main technique and alternative technique. There will be no cervical spine manipulations. The total treatment time is estimated to be 15 ± 2 minutes.

Anatomical area 1: Talocrural joints - Main technique
Talocrural joint stretching technique[93]
Subject: supine position
Practitioner: standing on the side ipsilateral to the dysfunctional ankle, the practitioner turns their back to the patient. For the right ankle, the practitioner places their bent left knee under the patient's right knee, places their left elbow on the table against their own thigh and holds the patient's right foot between their two hands: the left hand applicator holds the calcaneus, and the right hand applicator is placed towards the dorsal surface of the talus. With the ankle firmly held, the practitioner carries out an elbow-extension movement. With the practitioner's forearm outstretched and stable, a lever arm is created which applies traction in order to stretch the talocrural joint. The practitioner must find a good ankle-positioning angle to carry out the stretching, and alternate between traction and compression by changing the degrees of elbow flexion/extension. The technique may be accompanied by joint noise.

Anatomical area 1: Talocrural joints - Alternative technique
Same principles as the main technique with the patient's leg extended
Subject: supine position
Practitioner: standing at the patient's feet, they hold one ankle while placing the contralateral hand under the calcaneus and the ipsilateral hand on the dorsal side of the talus; with the ankle stabilised by the two hands, the practitioner searches for the best premanipulation tension by changing the degree of flexion/extension of the talocrural joint and carries out repeated tractions of low amplitude in the tibial axis.

Anatomical area 2: Root of mesentery - Main technique
Osteopathic technique on the root of mesentery[86]
Subject: supine position on the table, with the knees bent and the feet on the table.
Practitioner: standing to the left of the patient, with their back towards the patient's head. With the right hand, they palpate the abdomen around the small mass along the axis of the

root of mesentery (little finger around the ileocaecal valve up to the duodenojejunal flexure on the thenar eminence side) and with their left hand in parallel but on the other side of the axis of the root in the left iliac fossa concavity. The technique consists of entering the patient's abdominal mass as deeply as possible without causing severe pain, performing a combination of multiple tensions (backward pressure, clockwise and anticlockwise twists, right and left side tractions, etc.) in the opposite direction to the movement/elasticity restrictions found on examination. The technique must be accompanied by abdominal breathing by the patient.

Anatomical area 2: Root of mesentery - Alternative technique
Subject: right lateral recumbent position, with the hips and the knees bent.
Practitioner: standing at the patient's back, with the left knee bent and placed on the examination table, the left iliac against the patient's pelvis; the practitioner presses the abdomen with both hands around the patient's small mass with the little finger of the left hand pressing deeply in the right iliac fossa concavity. The technique consists of rhythmically raising and mobilising the patient's small mass, with the patient firmly held between the pelvis at the back and the practitioner's hands at the front.

Anatomical area 3: Diaphragm - Main technique
Subject: supine position with the legs bent.
Practitioner: Standing to the right of the patient, they press the lower edge of the right ribcage with the finger pads, with the left forearm against the chest. The patient is asked to breathe deeply while filling the stomach. On inhalation, the practitioner increases the opening movement of the ribcage. On exhalation, the lowering of the ribs is accompanied by their forearm and at the same time enters deeper against the medial side of the ribs accessible under the fingers, around the diaphragmatic insertions (R7 to R10, approximately). Carry out the same procedure in the patient's left hemithorax.

Anatomical area 3: Diaphragm - Alternative technique
Diaphragm lift technique[87]
Subject: supine position with the legs bent.
Practitioner: Standing at the patient's head, they make contact with the lower edge of the ribcage with the finger pads. The patient is asked to breathe deeply while filling the stomach. On inhalation, the practitioner increases the opening movement of the ribcage. On exhalation, they maintain the parameters of tension and abruptly release the tension when the patient takes another deep breath.

Anatomical area 4: Lumbar spine - Main technique

Lumbar joint work technique (ART) known as “general osteopathic treatment”[88],

Technique Subject: right lateral recumbent position then left; Practitioner : standing oblique facing the subject.

The following description uses the example of a patient in the right lateral recumbent position. All parameters should be reversed to carry out the techniques on the other side.

Patient: right lateral recumbent position, with the right leg outstretched and the left leg bent, with the knee at the edge of the table so that it is mobile; the trunk is placed in slight left rotation, and the patient grips their left wrist with their right hand.

Practitioner: squatting position facing the patient, oriented at about 45° towards the patient’s head. The right forearm holds and stabilises the left hemipelvis, and the left forearm passes under the patient’s left arm while holding and stabilising the left hemithorax. Both hands are free and can palpate the lower back area during the technique.

The adjustment is made through mobilisation of the lumbar spine in all joint mobility parameters. The practitioner mobilises the spine using both arms and their body, carrying out an opposite circumduction from the two points of support in order to reproduce a figure 8 at the lumbar level. Mobilisation is carried out by converging the strains on the whole lumbar spine level by level up to the thoracolumbar junction, with emphasis on the areas of dysfunction.

Anatomical area 4: Lumbar spine - Alternative technique

Lumbar joint work technique (ART) known as “general osteopathic treatment”[94],

Patient: supine position with one leg bent and the other outstretched; Practitioner: Sitting next to the subject, on the same side as the bent leg.

Motor hand: medial hand holds the thigh and the arm stabilises the lower limb.

Palpatory hand: the finger pads of the lateral hand press the L5 spinous processes.

Adjustment is done by joint work and circumduction of the lumbar spine from a wide circumduction of the hip using the leg as a lever. The index finger stabilises L4 and the middle finger mobilises L5. We expect tissue release of the posterior soft tissues and a gain in movement among the restricted segments. The lateral hand therefore moves up to L1 under T12. The manoeuvres are carried out on the right and on the left.

Anatomical area 5: Sacroiliac joints – Main technique

Subject: lateral recumbent position

The practitioner makes contact with the lumbosacral junction and pulls the patient's arm contralateral to the sacroiliac joint to be mobilised, to stabilise the spine in neutral rotation.
The practitioner places the patient's crossed hands on the lateral side of the ipsilateral hemithorax.
The practitioner places the ipsilateral foot in the popliteal hollow and extends the contralateral leg.
The practitioner supports the trunk and the spinal segment, with the cephalic forearm which passes under the patient's forearm.
The practitioner places their caudal forearm perpendicular to the posterosuperior iliac spine segment/greater trochanter.
The practitioner applies premanipulation tension with the caudal forearm in the axis of the sacroiliac joint and combines different movements (rotations, sliding and compression). The pulse is carried out using the caudal segment, respecting the plane of the joint surfaces forwards and outwards. The technique is carried out for both sacroiliac joints.

Anatomical area 5: Sacroiliac joints – Alternative technique
High-velocity, low-amplitude technique on the sacroiliac joints, known as the "Chicago technique".[62]
Subject: supine position on the table, hands joined behind the neck, legs outstretched and crossed (the leg on the side of the mobilised sacroiliac joint is on top).
Practitioner: Standing next to the table opposite the sacroiliac joint to be mobilised.
The practitioner moves the patient's torso towards them, and the patient's feet.
The caudal hand presses on the anterior superior iliac spine ipsilateral to the sacroiliac joint.
The practitioner raises the patient by the elbow ipsilateral to the sacroiliac joint, passing the cephalic forearm in the patient's elbow from top to bottom, from back to front and moving towards the anterior superior iliac spine contralateral to the sacroiliac joint. The premanipulation tension is applied by combining flexion/extension parameters and trunk rotation.
The practitioner applies mobilisation with a thrust, and the pulse is given by the caudal arm in the axis of the joint going backwards and inwards. The technique is carried out for both sacroiliac joints.

Anatomical area 6: Atlanto-occipital joints - Main technique
MET (muscle energy technique) craniocervical manipulation technique[94]
Subject: supine position

Practitioner: standing at the patient's head

The caudal anterior hand presses the chin between the index finger and the middle finger, bringing flexion of the dysfunctional atlanto-occipital joint. The cephalic posterior hand presses the occiput, with the index finger and the middle finger positioned around the occipital condyles, and causes a slight cephalic traction up to the restriction of joint mobility by combining a slight rotation with a contralateral tilt.

In this position, the patient is asked to look upwards to contract the small and large right posterior muscles for 3 seconds. During this time, the practitioner maintains resistance with the caudal hand. While the patient releases the contraction, the practitioner slightly increases the parameters of slight rotation combined with contralateral tilt and repeats this manoeuvre 3 times in order to gradually recover the joint mobility that had been lost.

Anatomical area 6: Atlanto-occipital joints - Alternative technique

Strain-counterstrain craniocervical manipulation technique

Subject: supine position

Practitioner: standing at the patient's head

The caudal anterior hand presses the chin between the index finger and the middle finger, bringing flexion of the craniocervical junction. The cephalic posterior hand palpates around the muscle hypertonia of the suboccipital muscles found in the examination. The osteopath searches for a comfortable position in muscular shortening, and this non-painful position is held for 30 seconds, before making a slow and passive return to the neutral position. The manoeuvre is repeated 3 times.

Anatomical area 7: Temporomandibular joints - Main technique

Temporomandibular joint (TMJ) technique

Subject: supine position on the table

Practitioner: seated at the patient's head, they place the thumbs along the rising branches, with the finger pads around the mandibular angle, with the other fingers coming to press the jaw towards its medial side. The technique consists of rubbing, mobilising and pulling the jaw and the masticatory muscles in order to achieve a circumduction of the TMJ.

Anatomical area 7: Temporomandibular joints - Alternative technique

Mandibular osteopathic technique[89]

Subject: supine position on the table

Practitioner: standing next to the table, with an examining fingertip on each thumb, they press the horizontal branches of the patient's jaw by placing the anterior side of the thumbs on the lower dental arches. With the other fingers holding the lower edge of the jaw, with 5 close to the gnathion, 4 around the mandibular insertion of the digastric muscle, 3 around the mylohyoid muscle, and 2 around the medial pterygoid muscle insertion. The practitioner applies a slight caudal traction force before carrying out a soft circumduction movement aimed at mobilising the TMJ in its restricted mobility parameters and relaxing the masticatory muscles (medial and lateral pterygoids, masseters and temporal).

5.2.4 Recommendations given to patients

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[90].

5.2.5 Consultation time

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

6 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[91].

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.

7 Endpoints

All of the endpoints will be collected in the form of data completed by the patient in a self-assessment booklet.

7.1 Primary endpoint

The primary endpoint will be the average change in functional capacity at 3 months after randomization according to the Quebec questionnaire[92]. 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. The metrological properties have largely been assessed: the acceptability is highly satisfactory and the duration is short (5 mins); accuracy is excellent: internal coherence (alpha coefficient

= 0.95 to 0.96) and test-retest reproducibility (r = 0.88 to 0.93); the validity of the construct is supported by strong correlations with other disability questionnaires: the Roland-Morris Disability Questionnaire (r = 0.77 to 0.81), the Oswestry Low Back Pain Disability Questionnaire (r = 0.80 to 0.83), and the SF-36 physical scale (r = 0.67 to 0.77) and pain intensity scale (r = 0.54 to 0.74), and the scale appears to be adapted to the various levels found in lower back pain[93].

7.2 Secondary endpoints

The secondary endpoints will be as follows:

- Average change in low back pain in the previous 48 hrs assessed using a numeric scale from 0 to 100 at 3 and 12 months;
- Number and duration of sick leave periods at 12 months;
- Average change in functional capacity (Quebec) at 12 months;
- Number of recurrences at 12 months;
- Average change in quality of life assessed using the SF-12 questionnaire[94] 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 allows 2 components of quality of life to be measured: physical and mental components;
- Consumption of painkillers and NSAIDs (yes/no) at 3 and 12 months.

8 Expected number of subjects to be enrolled and justification

The primary objective of the study is to assess the functional capacity in patients with sub-acute or chronic common lower back pain using the Quebec score at 3 months. The p-value is 0.05. The desired power is equal to 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.

9 Statistical analysis

The statistical analysis will be provided by the Prof. Ravaud Clinical Epidemiology Centre (Hôpital Hôtel Dieu) in the frozen databases, using SAS® statistics software.

A Statistical Analysis Plan will be prepared and validated prior to the blinded review of data. It will be proposed by the Clinical Epidemiology Centre and reviewed by the Sponsor and the Investigator.

The Statistical Analysis Plan may be revised during the study, in order to take into account any changes made to the protocol or any changes in the conduct of the study which have an impact on the originally planned statistical analyses.

The Statistical Analysis Plan will be edited prior to the blinded review of data. The analyses to be performed may be completed at this review. The final version of the Statistical Analysis Plan will be prepared before unblinding takes place. All versions will be kept in the study file.

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.

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;
- Compliance.

For each group, and at each of the assessment 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 and standard deviation. In the event of quantitative endpoints with asymmetrical behaviour, these will be presented with their median and interquartile range (25^{th} percentile; 75^{th} percentile).

The primary endpoint is the variation in the Quebec score between the baseline and 3 months. The statistical analysis of the primary endpoint will be done in terms of the intention-to-treat (i.e., all randomised patients will be analysed in their group of origin). 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 linear mixed model for repeated measurements

(MMRM), taking into account the correlation of repeated measurements in the same subject (random effect on the patient with an unstructured variance-covariance matrix) under the hypothesis of randomly missing data. The fixed effects will particularly be the randomisation arm, time, initial endpoint value (centred), the interaction between the time and the randomisation arm. The model will allow us to compare the means adjusted to the baseline value of the absolute variations between the Month 3 visit and the enrolment visit (as well as between the other visits and the enrolment visit).

A site effect will also be added and possibly an interaction between the site and the treatment (if significant) in order to take into account on the one hand the differences between the sites and on the other hand the heterogeneity of the treatment effect between the sites. Furthermore, a therapist effect (osteopathic intervention or osteopathic placebo) based on the site will be added to take into account the correlation between the parents undergoing treatment with the same therapist. The MMRM technique is consistent with the principle of the intention-to-treat analysis provided that all patients have a baseline value for the endpoint. The model parameters will be estimated with the restricted maximum likelihood (REML) method, using the Newton-Raphson method. The degrees of freedom will be calculated using the Satterthwaite approach. In order to confirm the results obtained, a sensitivity analysis will be carried out: an analysis of covariance (ANCOVA) approach will be used to confirm the results of the primary analysis. The endpoint to be studied will once again be the difference in pain score between randomisation (D0) and the M6 visit: Δ = value at M6 – value at D0. The difference in Δ between the groups will be analysed with an analysis of covariance (ANCOVA) with the variable group as a fixed factor and the pain at D0 as a quantitative covariate (centred variable). A site effect and a therapeutic (group) effect will be included in the model.

The secondary analyses will be:

1) Comparison of the percentage of relapses: Wald test using a logistic regression model with random effects for the site and the therapist.

2) The repeated measurements of the following criteria will be analysed using mixed-effect linear models with random intercept and slope (the aim will be to compare the progress over time between the 2 groups using an F test with adjustment for the site and the therapist):

- Numeric pain scale
- SF-12

3) Comparison of the number and duration of sick leave periods using a linear mixed model with a random effect on the site and the therapist (F test).

The tests carried out will be considered significant if levels of significance are below 5%.

10 Diagram and conduct of the research

10.1 Sites

The recruiting sites are large CHUs in Ile-de-France, within Assistance Publique des Hôpitaux de Paris and the head office of the AP-HP in order to optimise the eligible patient rate. A summary table is attached with the sample sizes of individuals monitored by occupational medicine per hospital with an estimation of the number of patients monitored per occupational physician.

Sites	**Total sample size of individuals monitored by Occupational Medicine**
Pitié-Salpêtrière	11,464
Saint-Antoine	4,361
Avicenne	2,702
Beaujon	2,633
Paul Brousse	2,513
Louis Mourier	2,241
Head Office of the AP-HP	1,847

Data provided by the AP-HP Occupational Medicine Central Department (July 2010).

10.2 Recruitment method

A triple recruitment method will be organised:

1) Patient recruitment within Assistance Publique in the Île de France: 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 sample letters 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 lower 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 done 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 participating in this study will be done as follows:

-either directly in their "active files" of individuals already monitored for this condition, either working or on sick leave, and either with or without having rearranged their work position;

-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.).

Physician at the site (name)	**Hospital Centre address**
Dr Amiel-Taieb	Beaujon CHU
Dr Bignebat	Saint-Antoine CHU
Dr Dupre	Louis Mourier CHU
Dr Eudes	Avicenne CHU
Dr Glomot	Paul Brousse CHU
Dr Gorodetzky	Head Office of the AP-HP
Dr Lecieux	Pitié-Salpêtrière CHU (HAD)
Dr Louet	Pitié-Salpêtrière CHU

Patients recruited by different methods will be referred to the Physical Medicine and Rehabilitation Department at Cochin Hospital for an enrolment visit.

The investigator responsible for enrolment will inform the patient about the study objectives using an information sheet, fill in the patient's informed consent form, collect data, randomise the patient using a computerised tool and provide the patient with an appointment for the manual therapy.

Enrolled patients will be assessed at M3, M6 and M12. The assessment 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.

10.3 Conduct of the research 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;
  - pain on a numeric scale from 0 to 100;
  - number and duration of sick leave periods since the start of the common lower back pain;
  - number of relapses since the first episode of common lower back pain;
  - quality of life questionnaire SF-12;
  - 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;
- low back pain in the previous 48 hrs on a numeric scale from 0 to 100;
- number and duration of sick leave periods since D0;
- number of relapses since D0;
- quality of life questionnaire SF-12;
- 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;
- low back pain in the previous 48 hrs on a numeric scale from 0 to 100;
- number and duration of sick leave periods since the Month 3 visit;
- number of relapses since the Month 3 visit;
- quality of life questionnaire SF-12;
- adverse events.

M12: End-of-study follow-up

The end-of-study follow-up will be carried out by the investigating physician during a face-to-face visit. Participants can also choose to send their self-assessment booklet by mail in a T envelope, or choose to be contacted by phone by a clinical study technician. The following informations will be collected:
- Quebec functional capacity questionnaire;
- low back pain in the previous 48 hrs on a numeric scale from 0 to 100;
- number and duration of sick leave periods since the 6-month follow-up;
- number of relapses since the 6-month follow-up;
- quality of life questionnaire SF-12;
- consumption of painkillers and NSAIDs;
- adverse events.

10.4 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.

10.5 Place where the manual therapy sessions are carried out

The manual therapy sessions will be carried out at Grenoble CHU for patients enrolled at this site, and at the Cochin CHU for all other patients. At Cochin Hospital, we have 8 consultation cubicles 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 mins for each half-day in the morning and 6 in the afternoon.

10.6 Expected duration of participation for each patient

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

10.7 Expected duration of the research

Recruitment will span 30 months. Follow-up until the end of the study will span 12 months for each patient enrolled in the study. The total study duration will therefore be 42 months.

10.8 Methods for limiting missing data

The following procedures will be implemented in order to limit missing data.

1) The clinical study technician will systematically confirm the quality of filling in the questionnaires and will contact the patients in the event of missing information.
2) Patients will be contacted by phone and by post one week before the date of the 12-month follow-up; if they fail to respond on the visit day, a second letter will be sent.

11 Rules for stopping the research

11.1 Early withdrawal of patients

Patients can withdraw from the study at any time and for any reason, or due to an investigator's decision. All cases of patients withdrawing from the study must be documented and the investigator must indicate the reason (e.g., patient failure to attend the visits after a reminder, lack of cooperation by the patient, etc.).

11.2 Methods for replacing these patients, where applicable

Patients withdrawing from the trial early or excluded from the research will not be replaced.

The analysis will be carried out in terms of the intention-to-treat, including failures, subjects lost-to-follow-up or with missing data, deceased patients and those who stopped the treatment due to intolerance or side effects.

Patient withdrawing from the trial early cannot be enrolled again in the study. Their enrolment and treatment numbers must not be reused.

11.3 Follow-up methods for these individuals

In the event of early withdrawal from the manual therapy sessions, these patients will continue to be monitored until the end of the study, at least for the visits planned as part of the protocol, and the investigator will continue to fill in the electronic CRF until M12.
For subjects lost-to-follow-up, the case report form will be filled in up until the last visit carried out. The investigator and his or her collaborators will endeavour to specify the reasons for the patient's failure to attend the visit and the condition of his or her health.

12 Data management

The clinical and paraclinical signs will be collected and entered into an electronic case report form (eCRF CleanWEB), with restricted access using an individual username and password for each study physician in charge of a patient. The data entered will by anonymised and secured, with data encryption when transferred.

13 Safety assessment:

Adverse events

13.1 Potential adverse effects of the treatment

An analysis of questionnaires was carried out in 63 new patients who received osteopathic treatment by students at a comprehensive consultation centre at an osteopathic training school[95]. The aim was to determine the main side effects experienced by patients whose main reason for consultation was lower back pain (33%) and neck pain (20%). Local pain (24.3%), local stiffness (18.3%) and an increase in pain leading the patient to seek medical care (11.8%) were the most common side effects, occurring within two days after the consultation. However, 96% of these reactions were considered to be mild or moderate.

The most severe iatrogenic effects of manual techniques are vertebral artery dissection and cerebrovascular accidents following high-velocity, low-amplitude-type cervical spine manipulations[96], techniques which were not chosen for the intervention group.
A systematic review of the literature on the side effects of manual therapies[97] concluded that there were very few severe side effects but that half of patients could experience transient side effects classified as minor to moderate.

13.2 Description of the safety assessment parameters

Adverse event

Any harmful manifestation occurring in an individual taking part in a biomedical research study, regardless of whether or not the manifestation is related to the research.

Adverse event in a research study not involving a product mentioned in Article L. 5311-1 (medicinal products, biomaterials and medical devices, in vitro diagnostic medical devices, labile blood products, organs, tissues, cells and products of human or animal origin, and cellular products for therapeutic purposes).

Any adverse event due to the research.

Serious adverse event or effect

Any adverse event or effect that leads to death, is life-threatening for the individual taking part in the research, involves hospitalisation or an extended hospital stay, causes significant or permanent incapacity or disability, or leads to a congenital abnormality or malformation.

13.3 Expected methods and schedule for measuring, collecting and analysing the assessment and safety parameters

13.3.1 Steering committee

The steering committee will be made up of the Principal Investigator, Prof. François Rannou, investigators from the various sites, methodologists in charge of the project, Prof. Isabelle Boutron and Prof. Philippe Ravaud, one or more Project Advisers from the DRCI, the heads of the CIC Paris Descartes Necker / Cochin Clinical Research Unit (URC), Prof. Jean-Marc Tréluyer, and one or more Project Advisers from the CIC Paris Descartes Necker / Cochin Clinical Research Unit (URC).

The roles of the steering committee are as follows:

-To define the general structure and performance of the research and coordinate the information;

-To initially define the methodology and decide on the measures to be taken throughout the course of the research in the event of unexpected events;

-To supervise the performance of the research, particularly in terms of tolerance and adverse events.

13.3.2 Independent monitoring committee

A serious adverse event monitoring committee was not deemed necessary for this study since the high-velocity, low-amplitude manipulations will not be carried out on the cervical spine, due to this having an unacceptable risk-benefit ratio.

13.4 Serious adverse event management procedures

As this is a biomedical research study classified as "risk A", i.e. for which there is a negligible **additional risk expected from the research**, no **serious** adverse events are expected through the course of the research, as:

- High-velocity, low-amplitude-type cervical spine manipulations are techniques which were not chosen for this study's intervention group, as these techniques can lead to vertebral artery dissection and cerebrovascular accidents.

Furthermore, there are no suspected unexpected serious adverse reactions (SUSARs).

In these conditions:

- The investigator will not be expected to report any serious adverse events occurring during the research to the sponsor. Should such events occur, these will be related to the patient's condition or their therapeutic management in the context of care, and will not be related to the research (e.g., death related to the disease, hospitalisation or extended hospital stay due to disease progression or concomitant diseases, life-threatening event unrelated to the research, etc.);
- It is not considered necessary to create an independent monitoring committee.

However, in the unlikely event in which the investigator becomes aware of an event that could affect the safety of any individual involved in the research (e.g., therapeutic error or

protocol deviation), the investigator will be required to report this to the sponsor using the form provided for this purpose in Annex IX to the protocol.

Finally, any non-serious adverse events occurring through the course of the research, such as pain or local stiffness, and an increase in pain will be reported on the adverse events page of the case report form.

14 Right to access the information and source documents

Individuals with direct access in accordance with the legislative and regulatory provisions in force, in particular Articles L.1121-3 and R.5121-13 of the French Public Health Code (e.g., researchers, individuals in charge of quality control, monitors, clinical research assistants, auditors and all individuals collaborating in clinical trials) will take all the necessary precautions in order to ensure the confidentiality of the information related to the investigational medicinal products, trials, individuals taking part in the research, and in particular any information involving their identity, as well as the results obtained. The data collected by these individuals through the course of quality controls or audits will then be made anonymous.

15 Quality control and assurance

The research will be conducted in accordance with the standard operating procedures of the sponsor, AP-HP, which will be in line with Good Clinical Practice.
The performance of the study at the research sites and the treatment of subjects will be done in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines in force.
The CRAs, the Head of the Project at the DRCI, the Assistant Head of the Project at the DRCI, the Clinical Trial Coordinator at the URC/CIC and the Study Data Manager will also have the opportunity to view the CRFs and ask questions remotely (queries).

15.1 Monitoring procedures

The research is classified as risk level A, with the corresponding monitoring level.

The CRAs representing the sponsor will carry out visits to the research sites according to the follow-up schedule for patients in the protocol, the enrolments at the various research sites and the level of risk assigned to the research study.

- Start-up visit at the site: before enrolment, for implementation of the protocol and familiarisation with the various parties involved in the biomedical research study.
- At the next visits, the case report forms will be reviewed as the research progresses by the CRAs. The principal investigator at each site, as well as the other investigators who enrol or undertake follow-up with individuals participating in the research, agree to receive visits from the CRAs at regular intervals.

In accordance with the Good Clinical Practice guidelines, the following items will be reviewed at the site visits:

· Compliance with the protocol and procedures set out for the research;

· Verification of the patient informed consent forms;

· Examination of the source documents and comparison with the data reported in the case report form in terms of accuracy, missing data, and consistency of the data according to the regulations set out by the procedures of the DRCI.

- Closure visit: collection of case report forms, biomedical research documents, archiving.

15.2 Transcription of information into the case report form

The research data will be collected and monitored using the CleanWEB electronic case report form, within the framework of a public contract between the AP-HP and TELEMEDICINE TECHNOLOGIES S.A., notified on 17/11/2003 (reference no. 033845) and renewed on 21/11/2006 (reference no. 063844). The data will be centralised in a server located at the Operational Services Department (DSO) of AP-HP, 67 boulevard Bessières, 75017 PARIS.

An initial version of the eCRF may be put online and tested after the Research Sponsorship has been accepted by the DRCI and after sending the specific study specifications by fax to the company TELEMEDICINE. Once the Coordinator, the Clinical Trial Coordinator from the URC/CIC, the Data Manager and the Statistician have agreed on the final version of the eCRF, and following the release of the appropriations, and submission of the purchase order to the company TELEMEDICINE by the DRCI, the DRCI will authorise the Coordinator to begin the research (Inv. 14 letter), and the eCRF comes into operation.

In accordance with the Good Clinical Practice guidelines, the case report form on which the research data are transcribed must correspond to at least the following standard presentation:

- At the start of the form, the following are normally included: the title of the research study, the Sponsor's name, the patient's study code, including the initials of the individual taking part in the research (first letter of their surname and first letter of their first name), treatment number, and inclusion and exclusion criteria in the form of a check-list, which allows subject selection to be validated with respect to the study population. At the end of the research, when the research database has been "frozen", the eCRF of each patient will be printed and signed by the investigator. The references of the research and the identification code of the individual taking part in the research will then appear in the form of a slip on each page to allow data to be identified in all cases.
- The visit dates and data transcribed must be reported in this eCRF as well as the time of the research to which they correspond.
- The following items must be included at the end of the eCRF:
    - Concomitant treatments;
    - Non-serious adverse events (AEs);
    - End of study/Early termination;
    - Outside planning, an SAE module.

All the information required by the protocol must be provided in the case report form and an explanation must be provided by the investigator for any missing information.

Information must be transferred to the case report forms as soon as it becomes available, whether clinical or paraclinical information.

Incorrect information detected in the case report forms will be replaced in the form by a registered investigator, who will log in to the software with his or her access information (user name and password). These codes are strictly personal and confidential, and under no circumstances may be passed on to third parties. They help ensure data confidentiality and authenticate the interventions. Access information is associated with an electronic signature system which validates the data entered by the investigator. Each signature is stamped with the date and time and recorded in the research audit trail. Signed information cannot be changed. However, the investigator may void his or her signature if he or she wishes to correct any information. Voiding a signature is also subject to stamping with the date and time.

Subject anonymity will be guaranteed by an alphanumeric identification code consisting of the research site number, the patient's study enrolment number, and the initials of the individual taking part in the research in all documents required for the study, or by erasing

any personal information using a suitable method from the source documents to be included in the research documentation.
The computerised data file will be declared to the CNIL in accordance with the appropriate procedure for the case.

16 Legal and ethics aspects

The sponsor is defined by Law 2004-806 of 9 August 2004. AP-HP is the sponsor of this research study and the DRCI undertakes the regulatory tasks. Before beginning the research, each investigator must provide the sponsor's representative in the research with a signed and dated copy of their curriculum vitae, which must include their French National Medical Council registration number.

16.1 Request for ANSM authorisation

Before beginning the research, the AP-HP, as the sponsor, must submit an authorisation request file to the competent authority (the ANSM). The competent authority, as defined in Article L. 1123-12, makes decisions related to the safety of individuals taking part in a biomedical research study, taking into account the safety and quality of the products used during the research in accordance with the regulations in force, where applicable, their condition of use and the safety of individuals with regard to procedures carried out and the methods used, as well as the planned methods of patient follow-up.

16.2 Request for Ethics Committee opinion

The sponsor must submit the research protocol to the Ethics Committee. The committee's opinion will be reported to the competent authority by the sponsor before the research begins.

16.3 Amendments

The DRCI must be informed of any planned changes to the protocol by the principal investigator.
Amendments must be classified as substantial or non-substantial.

A substantial amendment is an amendment which may, in one way or another, change the guarantees given to the individuals taking part in the biomedical research (change in inclusion criteria, extension of enrolment period, participation of new sites, etc.).
Once the research has started, any substantial amendments on the sponsor's initiative must receive a favourable opinion from the Ethics Committee and authorisation from the competent authority prior to being implemented. In this case, where necessary, the committee will ensure that a new consent form is duly collected from individuals participating in the research.
Moreover, any extension to the research (radical change in the treatment regimen or populations included, extension of treatments and/or therapeutic procedures not originally foreseen in the protocol) must be considered as a new research study.
Any substantial amendment must be submitted by the sponsor, after payment of the corresponding fee, for authorisation from the ANSM and/or for the Ethics Committee's opinion.

16.4 CNIL declaration

The law provides that the declaration of the computerised file with the personal data collected for the research must be prepared before the effective start of the research.
A reference methodology specific to the processing of personal data carried out in the context of biomedical research, defined by Law 2004-806 of 9 August 2004 as falling within the scope of Articles L.1121-1 et seq. of the French Public Health Code, was established by the CNIL in January 2006.
This methodology allows a simplified declaration procedure when the nature of the data collected in the research is consistent with the list provided by the CNIL in its reference document.
When the protocol undergoes a quality control of the data by a CRA representing the sponsor and falls within the scope of the simplified CNIL procedure, the DRCI as the sponsor will ask the person in charge of the computer file to undertake in writing to comply with the simplified MR001 reference methodology.

16.5 Information sheet and consent form

Written consent must be collected from any individual participating in the research before any procedures related to the biomedical research are performed.
The enrolled patients will be informed orally and with the help of an information sheet (a written document explaining the course of the protocol) and they must sign the consent form

if they agree to take part. They reserve the right to withdraw from the study at any time if they or their attending physician or investigator request this for any reason.

16.6 Final report on the research

The final report on the research will be drafted by the principal investigator in collaboration with the biostatistician for this study. This report will be submitted to each of the investigators for their opinion. Once a consensus has been reached, the final version must be approved with the signature of each of the investigators and sent to the sponsor as soon as possible after the effective end of the study. A report prepared in accordance with the competent authority reference plan must be sent to the competent authority and to the Ethics Committee within one year after the end of the study, with the end of the study understood to be the last follow-up visit of the last subject enrolled. This period is set at 90 days if the research is terminated early.

17 Data processing and storage of documents and data relating to the research study

The documents from a research study falling under the scope of the law on biomedical research must be archived by all the parties for a period of 15 years after the end of the research (see GCP, chapter 8: essential documents).

This indexed archive consists of:

- Copies of the ANSM authorisation letter and the mandatory opinion from the Ethics Committee;
- Successive versions of the protocol (identified by the version number and date);
- Letters of correspondence with the sponsor;
- Consent forms signed by the individuals taking part in the research in a sealed envelope with the corresponding enrolment register or list;
- The paper copy of the case report form filled in and validated for each subject enrolled (automatically dated), signed by the Principal Investigator or investigators for individuals taking part in the research;
- The audit trail;
- The Data Handling manual, the document in which the eCRFs are described in detail (data, controls performed, etc.);

- Any specific annexes to the study;
- The final study report from the statistical analysis and the quality control of the study (sent in duplicate to the sponsor);
- Certificates from any audits performed during the course of the research;

At the site close-out visit, the CRA will take an external CD-ROM burner. The following will be burned onto a CD-ROM:

- The CRFs of the patients at the site in PDF format, with any randomisation faxes created by CleanWEB;
- Emails related to the research study;
- Audit trail and electronic correction requests;

This CD-ROM will be archived in the Research site's file, together with the other documents. The database that gave rise to the statistical analysis must also be archived by the head analyst (hard copy or electronic copy).

18 Insurance, scientific commitment and funding

18.1 Insurance

Assistance Publique - Hôpitaux de Paris is the sponsor of the research. In accordance with the law on biomedical research studies, it has taken out an insurance policy with the company HDI GERLING for the full duration of the research, guaranteeing its own civil liability as well as that of any intervening parties (physicians or staff involved in conducting the research) (Law no. 2004-806, Art. L.1121-10 of the French Public Health Code).

Assistance Publique - Hôpitaux de Paris reserves the right to interrupt the research at any given time for medical or administrative reasons. If this occurs, the investigator will be notified.

18.2 Scientific commitment

Each investigator undertakes to comply with the obligations of the law and to conduct the research in accordance with the GCP guidelines, complying with the principles set forth in the Declaration of Helsinki in force. To this end, a copy of the scientific commitment (DRCI-type document), dated and signed by the principal investigator of each clinical department of the participating sites, will be provided to the sponsor's representative.

19 Rules regarding publication

The AP-HP owns the data and it may not be used or transferred to third parties without the AP-HP's prior agreement.

The individuals who actively participated in the preparation of the protocol and its implementation, as well as the writing of the results, will be named first in the publications.

As a precaution, a writing committee should be set up and the order of the signatories could be defined in advance.

Assistance Publique-Hôpitaux de Paris must be mentioned as the sponsor of the biomedical research study and as a provider of funding. "Assistance Publique-Hôpitaux de Paris" must appear in the address of the authors.

The Clinical Research Unit URC/CIC Paris Descartes Necker / Cochin will be mentioned in the acknowledgements.

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Annex 1: Further information on osteopathy

Description of the therapeutic principles in osteopathy

Osteopathy is a healthcare approach which advocates the influence of musculoskeletal system function both in times of health and during illness, and is based on four principles which were reassessed in 2002: (1) the body is a physiological unit, (2) the body has mechanisms for self-regulation, (3) structure and function are reciprocally related, and (4) rational treatment is based on the preceding principles[98]. Osteopathy belongs to the category of alternative medicines.

The diagnostic approach taken by osteopaths is based on the search for somatic dysfunction; it is therefore centred on the patient and not exclusively on the symptoms presented. Somatic dysfunction is a pathological entity referenced in the International Classification of Diseases, which is defined as "impaired or altered function of related components of the somatic (bodywork) system including: the skeletal, arthrodial, and myofascial structures, and their related vascular, lymphatic, and neural elements"[46]. The clinical signs which have been associated with joint somatic dysfunction have traditionally been described with the acronym "SART" (Sensitivity/pain on palpation; Asymmetry of the bony landmarks; Restriction in passive joint movement; changes in the Texture of the surrounding soft tissues)[47]. The osteopath determines the severity of the somatic dysfunction according to the significance and

concomitant presence of the palpated clinical signs which can be improved and reduced following a suitable manual treatment[14].

A prolonged inflammatory reaction, a chronic change in reflex neurological mechanisms and a chronic change in posture are thought to be the main mechanisms responsible for the onset of somatic dysfunction[99]. Depending on the patient's clinical condition, the somatic dysfunction may be a causal factor, adaptive reflex or a combination of these factors responsible for the symptoms described by the patient[100]. The concept of somatic dysfunction is therefore one of the main elements that is typical of osteopathy, which differentiates it from other manual therapies.

The French Register of Osteopaths (ROF) has set up a Multidisciplinary Council for the management of the risks related to the practice of osteopathy[101], which defined manipulation as a specific, controlled gesture that restores mobility in the impaired minor movement(s) within the limits of their physiological amplitudes and which restores the functional qualities of the surrounding soft tissues.

This is a non-forced manual response to the osteopathic diagnosis of somatic dysfunction. The choice of technique is guided by (1) a previously suggested diagnosis, (2) compliance with contraindications in terms of manipulation treatment, (3) the patient's condition, and (4) the practitioner's experience. Osteopathic manipulation is therefore not only a matter of spinal manipulation, although this is part of it. Numerous manual techniques are referred to in the Authorized Osteopathic Thesaurus[84] and are used by both professional categories (osteopaths and osteopathic physicians) in order to treat somatic dysfunction. These techniques can be divided into 4 broad categories according to the amount of force, the rhythm and the speed used: (1) rhythmic, (2) high-velocity, low-amplitude (HVLA, the previously described "manipulation"), (3) low-velocity stress, and (4) visceral[85]. At the international level, it is possible to differentiate between osteopaths who only practice OMT and osteopathic physicians who practice OMT as part of their medical practice[102]. These two professional categories have a professional status of first contact in all countries in which the practice of osteopathy is regulated.

In France, the French Society of Manual Medicine - Orthopedic and Osteopathic (SOFMMOO) recommends a record of spine techniques applied to treat minor intervertebral derangement (MID), which is defined as reversible, painful dysfunction of the mobile segment of the spine[103]. Spinal manipulation is a therapeutic procedure that is still often related to OMT in the medical world4,[104]. Maigne[21] defined manipulation as a forced movement, applied either directly or indirectly to a joint which abruptly moves the joint elements beyond their usual physiological range, without exceeding the limit imposed on their

movement by the anatomy. This is a short, sharp, single push which must be applied from the end of the normal passive range. This movement is generally accompanied by a cracking sound. These spinal manipulations are only applied to the painful spinal level in the opposite direction to that which triggers the pain[105].

The osteopath assesses the various manual therapy options according to their assessment of the patient's physiological response capacities to the treatment, based on their interpretation of the theoretical pathophysiological mechanisms associated with the physical signs found in the clinical examination[106]. Among the physiological models which have been proposed to describe the onset, maintenance and correction of somatic dysfunction, the neurological model based on the function of nociceptors is the one most commonly described in the scientific literature[107].

Changes in a somatic or visceral structure would lead to excessive and discordant afferent neurological impulses up to the posterior horn of the spinal cord. It is assumed that this mechanism would lower the depolarisation thresholds of the spinal inter-neurons of the medullary segment involved and would therefore allow an exaggerated response of the different neurons that synapse at this level (increased sensation of pain, sympathetic influx and muscle tone)[108]. A nociceptive stimulation which is maintained over time, generated by chronic somatic dysfunction, would lead to a form of central sensitisation (secondary hyperalgesia) and would favour locoregional allodynia and hyperalgesia of the periarticular soft tissues[109].

This description of somatic dysfunction, including a biomechanical dysfunction found on palpation, which could be associated with reflex neurological dysfunction, could be easily integrated into the most recent models which are used to describe the pathophysiology of lower back pain. There are currently two main descriptive models: the End-Organ Dysfunction Model and the Altered Nervous System Processing Models[110].

Diagnostic and therapeutic approaches in osteopathy patients with lower back pain

Somatic dysfunction in patients with lower back pain

The diagnostic approach taken by osteopaths is based on the search for somatic dysfunction; it is therefore centred on the patient and not exclusively on the symptoms presented. Current university training for osteopaths is mainly based on a nociceptive model for describing the clinical phenomena diagnosed on palpation in order to assess any potential links between the somatic dysfunction found in patients mainly through reflex neurological phenomena (viscerosomatic, somatovisceral, somatosomatic and viscerovisceral[85,107]), which could theoretically be involved. The gold-standard physiological models used by osteopaths are

therefore based on an interpretation of the various reflex neurological interactions, based on the biomechanical elements found on palpation, and not based on a strictly biomechanical understanding of the painful area described by the patient[111].

In the USA, the Agency for Healthcare Research and Quality has recently validated and published recommendations by the American Osteopathic Association regarding the management of patients with lower back pain using OMT[112] by assigning it the best level of scientific evidence (1), and recommending OMT for the management of lower back pain of musculoskeletal origin by treating somatic dysfunction in relation to the lower back pain. These recommendations are based on the results of an epidemiological study by Snider *et al.*[113], in which they observed that somatic dysfunction in patients with lower back pain was more common and more severe compared to an asymptomatic population with significantly more common clinical signs: tissue changes in periarticular soft tissues, asymmetry in spinous processes on static palpation, increase in tissue resistance on anterior passive movement of the lumbar spine and pain on palpation of the L1 to L4 spinous processes.

Specific features of osteopathic treatment of patients with lower back pain

Osteopathic treatment is developed specifically according to the patient's complaint and the somatic dysfunction found by the practitioner. The rationale behind osteopathic treatment would therefore correspond to treatment of somatic dysfunction in the context of its contribution to the symptoms described by the patient[114]. The osteopath manually treats the anatomical areas with somatic dysfunction in the whole body (viscera, cranium and musculoskeletal system) to change the neurophysiological and biomechanical interactions in order to reduce the symptoms described by the patient,[115], and frequently ends their consultations by providing the patient with specific dietary-hygiene advice.

The osteopath establishes a privileged-care relationship with the patient based on a longer consultation time than a regular medical appointment, the attention paid to the patient's aetiopathogenic mechanisms and not only his or her symptoms, and finally on the dominant area as agreed through touching. These specific therapeutic features could have a positive influence on the patient's perception and understanding of the pain, phenomena described as being psychosocial risk factors leading to chronicity of the pain[116]. According to Kuchera[26], the anterior cingulate gyrus is involved in the chronic pain self-maintenance system, and the osteopath, through the privileged interaction established with patients through dialogues and the time spent touching the patient, would act on this area of the brain and defuse the chronic pain self-maintenance mechanism.

Annex 2: Description of the physical examination sequence for the two groups

10 minutes.

The sequence is the same in both groups except for the fact that the tests in the control group are not interpreted by the practitioner but rather presented as such to the patients, and in the osteopathic examination the palpation pressure used for the diagnosis of somatic dysfunction remains light. The practitioner's gestures, the patient's position and the verbalisation are exactly the same.

There is no questioning. The patient undresses at the start. On the other hand, and throughout the whole test sequence, the practitioner creates a dialogue by questioning the patient about their complaint: its history, location, associated signs, and their progress, socio-professional and emotional impact. History, extracurricular activities: sport, hobbies, etc.

The tests are exactly the same for both groups. On the other hand, for the placebo group, the clinical signs of somatic dysfunction will not be studied; the results of this clinical examination must therefore give the impression of being interpreted by the practitioner, as far as the patient is concerned.

1. Patient standing

1.1 Inspection

1.1.1. Overall posture

In the sagittal plane: increase or reduction in curvatures?

In the frontal plane: orientation of the shoulder and pelvic girdle? Curvature of the spine?

Texture of the posterior integuments around the joints of the spine and the pelvic girdle?

1.1.2. Active movement assessment

Assessment of the amplitudes, movement asymmetries, and search for pain reproduction in active movements of the spine.

The practitioner is behind the patient, guiding them in their movements.

The patient carries out the following movements: flexion, extension, right and left rotation, right and left lateral tilt.

Assessment of the amplitudes, asymmetries and search for pain reproduction in movement of the sacroiliac joints.

Finger test[117],[118]: the practitioner asks the patient to indicate the site of their pain with their index finger twice. The patient should indicate on two occasions with one single finger a point at less than a centimetre from the posterior superior iliac spine.
Gillet Test: the practitioner is behind the patient, who holds onto the wall. The practitioner's thumbs are placed on both sides of a sulcus (first sacral spine and anterior superior iliac spine), and the patient is asked to carry out a flexion of the hip ipsilateral to the sacroiliac joint assessed. The practitioner assesses sacroiliac joint movement by the descent of the posterior superior iliac spine.

1.2 Palpation:
Search by palpation of the spine for signs associated with somatic dysfunction: asymmetry of the bony landmarks in movement, spontaneous or provoked pain on pressure of the bony landmarks and periarticular soft tissues.
Palpation of the bony landmarks while standing: iliac crests, anterior superior and posterior superior iliac spines, greater trochanter, ischial tuberosities, sulcus.
On the whole of the spine: spinous processes, transverse processes, posterior facet joints, posterior angles of the ribs.
Palpation of the soft tissues in search of paravertebral muscle hypertonia, assessment of subcutaneous tissue flexibility around the joints.

2. Patient in the seated position
Passive movement test of the whole spine in search of joint movement restrictions; determine the hypomobile vertebral rib and level.

2.1 Cervical spine.
The practitioner is behind the patient, supporting the patient's head with the anterior hand.
With the posterior hand, the practitioner palpates around the posterior joints of the spine level being assessed with the thumb and index finger.
The anterior hand carries out the main movements of flexion, extension, right and left rotations, and right and left tilts; then the accessory movements of right and left lateral transfer.
The practitioner analyses the tissue response and the change in soft-tissue texture with the forces applied during this test; with the posterior hand, the practitioner assesses the restrictions in movement and elasticity of the joints in the parameters tested, as well as any

muscle hypertonia, sensitivity or pain on palpation and asymmetry of the anatomical landmarks.

2.2 Thoracic spine: (T1-T2 to T12-L1 posterior facet joints)

The practitioner is behind the patient, supporting the patient's chest by grasping at the front with the upper limb.

With the posterior hand, the practitioner palpates both sides of the spinous process with the index finger and middle finger, around the posterior joints of the spine level tested. Using the body, a rhythm is induced in the thoracic vertebrae in the parameters of flexion, extension, right and left rotations, and right and left tilts; and then the accessory movements of right and left lateral transfer.

The practitioner analyses the tissue response and the change in soft-tissue texture with the forces applied during this test; with the posterior hand, the practitioner assesses the restrictions in movement and elasticity of the joints in the parameters tested, as well as any muscle hypertonia, sensitivity or pain on palpation and asymmetry of the anatomical landmarks in movement.

3. Patient lying down on the table

3.1 Lateral recumbent position - Passive movement tests in search of any restrictions in joint mobility, palpation of bony landmarks and periarticular soft tissues, sensitivity on palpation and movement, or changes in soft-tissue texture.

Lumbar spine

Flexion/extension: the practitioner is in front of the patient, holding the patient's bent lower limbs in the caudal hand, while the cephalic hand palpates the spinous processes of the lumbar spine. The practitioner successively moves the hips in flexion/extension and assesses the spacing and alignment of the spinous processes, in order to assess the presence of any mobility restrictions in flexion/extension parameters, as well as any changes in soft-tissue texture, sensitivity on palpation and asymmetry of the anatomical landmarks in movement.

Tilt: the patient keeps the outstretched leg in contact with the table and places the foot of the leg that is on top in the popliteal hollow of the leg that is in contact with the table.

The practitioner is in front of the patient, holding the patient's trunk with the caudal upper limb, while the cephalic hand is positioned around the posterior facet joints. The practitioner

tilts the patient's trunk with the caudal upper limb, while the cephalic hand analyses the opening of the vertebral compartment contralateral to the tilt, as well as any possible muscular hypertonia and changes in the flexibility of the subcutaneous tissues.

Rotations: the patient and practitioner are in exactly the same position. The practitioner induces rotations in the patient's trunk with the caudal upper limb, while the cephalic hand analyses the presence of any mobility restrictions in the rotation parameters, as well as any changes in soft-tissue texture, sensitivity on palpation and asymmetry of the anatomical landmarks in movement.

Sacroiliac joints

With the caudal hand, the practitioner palpates around the lumbosacral junction and uses the cephalic upper limb to lift the patient's arm contralateral to the sacroiliac joint to be tested, to stabilise the spine in neutral rotation.

The patient is asked to cross their hands on the lateral side of the ipsilateral hemithorax.

The practitioner places the ipsilateral foot in the popliteal hollow and extends the contralateral leg.

The practitioner supports the trunk and the spinal segment with the cephalic forearm which passes under the patient's forearm.

The practitioner places the caudal forearm on the patient's pelvis, perpendicular to the posterior superior iliac spine segment/greater trochanter.

Using the caudal forearm, the practitioner searches for lever forces to test the movement restrictions in the axis of the sacroiliac joint in the following parameters: anterior and posterior rotation, compression and spacing.

With the posterior hand, the practitioner assesses the movement restrictions in the parameters tested, as well as any changes in the soft-tissue texture, sensitivity on palpation and asymmetry of the anatomical landmarks in movement.

3.2 Prone position

Spring test on the lumbar and thoracic spine and the ribs

While standing, the practitioner applies one hand to the spinal processes, and the other hand reinforces the support and induces a sagittal forward thrust, (vertical support towards the table) analysing with the weight of the body the movement restrictions in the sagittal plane, as well as any changes in soft-tissue texture, sensitivity on palpation and asymmetry of anatomical landmarks in movement.

Sacroiliac joint

Palpation of the bony landmarks (posterior superior iliac spine and sacral spine) in search of any pain or asymmetry.

Sacral thrust test[119,120]: while standing, the practitioner applies both hands to the sacrum, which induce a sagittal forward thrust, with the 2 iliac bones being stabilised on the plane of the table.

The practitioner initially attempts to retrigger any pain.

With the weight of the body, the practitioner analyses the movement restrictions in the sagittal plane, as well as any changes in soft-tissue texture, sensitivity on palpation and asymmetry of the anatomical landmarks in movement.

3.3 Supine position

Talocrural joints

The practitioner is standing, facing the patient's feet. They hold the calcaneus and place their forearm against the plantar surface of the patient's foot; the other hand is placed on the patient's tibia in order to palpate the joint space. The practitioner analyses the patient's tissue response to the forces applied during this test; they search for any movement restrictions in the flexion/extension and anterior posterior shift parameters tested, as well as any changes in the soft-tissue texture, sensitivity on palpation and asymmetry of the anatomical landmarks in movement.

Sacroiliac joints: Thigh thrust test[130,131] (pain reproduction test)

The patient has the hip bent at 90 degrees. With the practitioner standing on the side of the sacroiliac joint to be assessed, they hold the patient's knee between their forearm and chest.

The practitioner applies a force in the axis of the patient's femur by also combining an adduction.

The practitioner searches to retrigger the pain.

Coxofemoral joints

The patient has the hip bent at 90 degrees.

With the practitioner standing on the side of the sacroiliac joint to be assessed, they hold the patient's knee between their forearm and chest. The cephalic hand palpates the sulcus to control it so that movements do not occur in the sacroiliac joint. The practitioner searches for any movement restrictions on the parameters of medial and lateral rotation, flexion/extension,

and abduction/adduction. They search for any changes in soft-tissue texture, sensitivity on palpation and asymmetry of the anatomical landmarks in movement.

Root of mesentery test (V test)

The patient's knees are bent.

The practitioner stands to the left of the patient, with their back towards the patient's head. With the right hand, the practitioner holds the small mass along the axis of the root of mesentery (of the ileocaecal valve on V side up to the duodenojejunal flexure on the hypothenar eminence side) and with their left hand in parallel but on the other side of the axis of the root, in the concavity of the left iliac fossa.

The practitioner searches for restrictions in movement/elasticity in up/down, right/left and forward/backward shift patterns, changes in soft-tissue texture and sensitivity or pain on palpation.

Diaphragm test

The patient's legs are bent.

The practitioner is standing sideways to the patient and uses the two columns of the thumbs/thenar eminences to palpate the lower edge of the ribcage on both sides of the xiphoid process of the sternum in order to surround the diaphragmatic cupolae.

During an inhalation and exhalation cycle, the practitioner analyses the restrictions in movement and elasticity of the cupolae, as well as any changes in the soft-tissue texture, sensitivity on palpation and asymmetry of the anatomical landmarks in movement.

Passive movement test of the upper cervical spine

The practitioner is behind the patient, supporting the patient's head with the abdomen and both hands.

The practitioner makes contact with either the atlanto-occipital joints or the atlanto-axial joints with the metacarpophalangeal joint of the index fingers, while the body performs the flexion, extension, right and left rotation, right and left tilt movements in the spine area; the practitioner uses the applicator to analyse the restrictions in movement and elasticity in the parameters tested, as well as any changes in soft-tissue texture, sensitivity on palpation and asymmetry of anatomical landmarks in movement.

Cranial palpation (C test)[121]

The practitioner palpates the cranial vault and the face around the cranial sutures then around each bone on both sides of each suture with a light force in the opposite direction. The practitioner then assesses the presence of any changes in soft-tissue texture, sensitivity/pain on palpation, restriction in movement/elasticity when applying force, and asymmetry of the anatomical landmarks. The assessment of this anatomical area is part of the general osteopathic examination as described in the Outpatient Osteopathic SOAP Note Form. It is therefore assessed even though it has not been chosen as part of the anatomical areas included in the standard osteopathic treatment.

Temporomandibular joint (TMJ)

Passive movement test and palpation of the masticatory muscles

The practitioner is seated at the patient's head. The practitioner places the thumbs behind the rising branches of the jaw and tests for changes in texture and any pain on palpation of the masticatory muscles. The practitioner then places the middle finger at the opening of the ear around the TMJ and asks the patient to open and close their mouth. The practitioner searches for any restrictions in condyloid joint movement or tissue elasticity in the opening/closing parameters, anterior posterior shift or lateral shift, or any changes in soft-tissue texture, sensitivity or pain on palpation, or asymmetry of the anatomical landmarks in movement.

Annex 3: Table of validation criteria for the training of osteopaths taking part in the study in the intervention and control group

General topics assessed	Knowledge	Acquired =1 Not acquired = 0
Practitioner compliance with inclusion criteria	Submission of administrative documents: Osteopathy Diploma, appendices to the diploma, in accordance with the WHO international standards (4,200 hours of training, of which at least 600 hours must be in clinical practice), the right to practice, RCP up-to-date to practice osteopathy.	
	Weekly availability over 6 months according to schedule.	
Understanding of the study and its implications	1/ Knowledge of the basic aspects of clinical research in general (groups, semi-blinding, procedures, standardisation); 2/ Knowledge of the specific features of studies related to complex interventions (examples, criteria studied and compared); 3/ Knowledge of the chronic lower back pain study protocol in particular: criteria studied and compared, with the criteria being similar between the two groups, the number and frequency of sessions, patient enrolment, obligations, etc.	
	Commitment to comply with the procedures and standardisation.	
	Detailed knowledge of the performance of both types of session (treatment and control) and performance of each session (tests, techniques, verbalisation and attitude, duration, etc.)	
	Knowledge of osteopathic semiology: somatic dysfunction and clinical criteria, modulations chosen for the study compared to the SNF (7 functional anatomical areas, SD scoring of 1 or 0).	
Tests	7 tests: technical practice (rigour in gestures and positioning of the patient), respecting the time (10 mins), verbalisation quality (introducing the session, taking the patient's history, etc.).	
Treatment	Quality of each of the 14 techniques (patient handling, positioning and body gestures), accuracy of the gestures, clarity in explaining the expected physiological effects, knowledge of the choices between each pair of techniques.	
	Respecting the time to put the chosen 7 techniques into practice, good performance over the 15 mins of treatment.	
	Quality of the verbalisation and attitude towards the patient: general verbalisation, quality of listening and dialogue, empathy and trust in the favourable outcome of the symptoms.	

Placebo	Proper application of the gestures and changes in the patient's position, compliance with "light-touch" instructions (light contact, not lasting over 5 seconds, with the whole body covered).	
	Compliance with the 15 minutes for putting the whole procedure into practice while using general verbalisation, the quality of listening and dialogue, empathy and trust in the favourable outcome of the symptoms.	
End of sessions	End-of-session quality: redressing, verbalisation, general healthy lifestyle advice (physical/practical, nutritional, hydration, sleep, careful attitude in the workplace, etc.)	
Explanation of the follow-up clinical forms	Quality of explanation of the forms (scoring, somatic dysfunction clinical signs found, related systems, etc.)	
Total / 14	0 to 11: not validated: 12 or 13: not validated, to be reassessed; 14 = validated	**0**

Annex 4: Light-touch treatment sequence

Patient in the supine position

Feet

The practitioner places their hands on the dorsal surface of the foot first of all, then on the plantar surface, then on the medial edge, and then on the lateral edge. The same gestures are performed on the other foot.

Legs

The practitioner places their hands on the medial side of the right leg first of all, then on the lateral side, and then on the anterior side. The same gestures are performed on the other leg.

Knees

The practitioner places their hands on the medial side of the right knee first of all, then on the lateral side, and then on the anterior side. The same gestures are performed on the other knee.

Thighs

The practitioner places their hands on the medial side of the right thigh first of all, then on the lateral side, and then on the anterior side. The same gestures are performed on the other thigh.

Pelvis

Successive application of the hands on the lateral side of the right and left greater trochanters, and the right and left iliac crests.

Abdomen

The practitioner successively places their hands on the various anatomical points of the abdomen (right and left iliac fossa, hypogastrium, epigastrium, right and left flanks, and right and left hypochondrium).

Chest

Successive application of the hands on the anterior side of the right and left lower ribcage, the right and left upper ribcage, and the sternum.

Shoulder girdle

Successive application of the hands on the anterior side of the stump of the right and left shoulder, then on the lateral sides, then on the upper sides.

Neck

The practitioner presses the lateral sides of the neck with both hands, then presses the anterior and posterior sides of the neck.

Cranium

Successive application of the hands on the right and left lateral sides, on the lower jaw, on the upper jaw, and then on the cranial vault.

Patient in the prone position

Feet

The practitioner places their hands on the plantar surface first of all, then on the medial edge, and then on the lateral edge. The same gestures are performed on the other foot.

Legs

The practitioner places their hands on the medial side of the right leg first of all, and then on the posterior side. The same gestures are performed on the other leg.

Knees

The practitioner places their hands on the medial side of the right knee first of all, then on the lateral side, and then on the posterior side. The same gestures are performed on the other knee.

Thighs

The practitioner places their hands on the medial side of the right thigh first of all, then on the lateral side, and then on the posterior side. The same gestures are performed on the other thigh.

Pelvic girdle

Successive application of the hands on the posterior side of the sacrum, the right and left sacroiliac joints, the lateral side of the right and left greater trochanters, the right and left iliac crests, and folds under the right and left buttocks.

Lumbar spine

Successive application of the hands on the dorsal side of the right and left lower trunk, and the right and left upper trunk.

Central application of the hands on the lumbar spine

Thoracic spine

Successive application of the hands on the dorsal side of the right and left lower thoracic ribcage, the right and left mid thoracic ribcage, and the right and left upper thoracic ribcage.

Central application of the hands on the lower then upper thoracic spine.

Shoulder girdle and upper limb

Successive application of the hands on the posterior side of the right shoulder, then the lateral side of the right shoulder, then the lateral side of the arm, medial side of the arm, posterior side of the arm, then the lateral side of the right elbow, medial side of the elbow, posterior side of the elbow, then the lateral side of the forearm, medial side of the forearm, posterior side of the forearm, and then palpates the palmar surface of the right hand.

The same gestures are performed on the other shoulder girdle and upper limb.

Atlanto-occipital joint

Successive application of the hands on the posterior side of the right and left craniocervical junction.

Annex 5: Summary table for osteopathic assessment: methodology and example

• The musculoskeletal table includes several endpoints which can either be combined or not. These criteria are grouped under the acronym "TART":

T: tissue texture change;

A: asymmetry of anatomical landmarks;

R: range of motion;

T: tenderness;

∑: all the criteria are present.

• The musculoskeletal examination includes 6 areas to be studied:

Head, face and neck;
Spine, ribs and pelvis;
Right upper limb;
Left upper limb;
Right lower limb;
Left lower limb.

The abdominal/other part is for other dysfunctions such as any visceral repercussions associated with thoracic dysfunction.

• 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 indicated 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. These dysfunctions are generally asymptomatic;
3 (severe): major dysfunction, including somatic dysfunction endpoints, which are usually symptomatic.

• The somatic dysfunction and other systems section allows us to note any links between the somatic dysfunction found and the following systems:

MS: musculoskeletal;
SNS: sympathetic nervous system;
PNS: parasympathetic nervous system;
LYM: lymphatic;
CV: cardiovascular;
RESP: respiratory;
GI: gastrointestinal;
FAS: fascial.

• Treatment yes/no: mark Y (yes) for an area examined and treated or N (no) if this is not the case.

- Techniques: the abbreviations correspond to the various osteopathic treatment methods:

  ART: Articular techniques

  BLT: Balanced ligamentous tension technique

  CR: Cranial/Osteopathic techniques in the cranial vault

  CS: Counterstrain techniques

  DIR: Direct techniques

  FPR: Facilitated positional release

  HVLA: High-velocity, low-amplitude techniques (thrust)

  IND: Indirect techniques

  INR: Integrated neuromuscular release

  LAS: Ligamentous articular strain

  MET: Muscle energy techniques

  MFR: Myofascial release

  ST: Soft-tissue techniques

  VIS: Visceral techniques

  OTH: Other techniques

- Treatment response: the area is tested again after the treatment.

  R: resolved, there is no more dysfunction

  Imp.: improved, dysfunction is still present but less significant

  U: unchanged

  Inc.: dysfunction has increased.

Table 2. Osteopathic Outpatient SOAP Note Form

Clinical signs					Anatomical area	Severity				Somatic dysfunction(s) / system(s)	Treatment		Techniques*	Progress			
Σ	S	A	R	T	Tested	0	1	2	3	MS / SNS / SNP / LYM / CV / RESP / GI / FASCIAL / Other	O	N		R	Imp.	U	Inc.
					Cranium and Face												
					Neck												
					Thoracic T1-T4												
					Thoracic T5-T9												
					Thoracic T10-T12												
					Ribs												
					Lumbar												
					Sacrum/pelvis												
					Pelvis/iliac												
					Abdomen												
					Right upper limb												
					Left upper limb												
					Right lower limb												
					Left lower limb												

*ART / BLT / CR / CS / DIR / FPR / HVLA / IND / INR / LAS / ME / MFR / ST / VIS.

Annex 6: Quebec functional capacity questionnaire

QUEBEC BACK PAIN DISABILITY SCALE

This questionnaire is about the way your back pain is affecting your daily life. People with back problems may find it difficult to perform some of their daily activities. We would like to know if you find it difficult to perform any of the activities listed below, **because of your back pain**. For each activity there is a scale from 0 to 5. Please choose one response for each activity (do not skip any activities).

Today, do you find it difficult to perform the following activities **because of your back pain**?

	Not difficult at all	Minimally difficult	Somewhat difficult	Fairly difficult	Very difficult	Unable to do it
1 – Get out of bed	☐	☐	☐	☐	☐	☐
2 – Sleep through the night	☐	☐	☐	☐	☐	☐
3 – Turn over in bed	☐	☐	☐	☐	☐	☐
4 – Ride in a car	☐	☐	☐	☐	☐	☐
5 – Stand up for 20 to 30 minutes	☐	☐	☐	☐	☐	☐
6 – Sit in a chair for several hours	☐	☐	☐	☐	☐	☐
7 – Climb one flight of stairs	☐	☐	☐	☐	☐	☐
8 – Walk a few blocks (300-400 m)	☐	☐	☐	☐	☐	☐
9 – Walk several kilometres	☐	☐	☐	☐	☐	☐
10 – Reach up to high shelves	☐	☐	☐	☐	☐	☐
11 – Throw a ball	☐	☐	☐	☐	☐	☐
12 – Run one block (about 100 m)	☐	☐	☐	☐	☐	☐
13 – Take food out of the refrigerator	☐	☐	☐	☐	☐	☐
14 – Make your bed	☐	☐	☐	☐	☐	☐
15 – Put on socks (pantyhose)	☐	☐	☐	☐	☐	☐
16 – Bend over to clean the bathtub	☐	☐	☐	☐	☐	☐
17 – Move a chair	☐	☐	☐	☐	☐	☐
18 – Pull or push heavy doors	☐	☐	☐	☐	☐	☐

19 – Carry two bags of groceries	☐	☐	☐	☐	☐	☐
20 – Lift and carry a heavy suitcase	☐	☐	☐	☐	☐	☐

Annex 7

MOS SF-12 QUALITY OF LIFE QUESTIONNAIRE

The following questions ask for your views about your health. Your answers will help monitor the condition of your health and to know how well you are able to do your usual activities.

Answer all of the following questions by following the instructions you have been given. If you are unsure, please give the best answer you can.

1. **In general, would you say your health is:**

..... *(mark one answer only)*

- Excellent..... ☐
- Very good ..... ☐
- Good..... ☐
- Fair ..... ☐
- Poor ..... ☐

➢ The following is a list of activities you might do during a typical day. For each of these, indicate whether your health now limits you in these activities.

(mark one answer only per line)

	limited a lot	**limited a little**	**not limited at all**
2. **Moderate physical activities** such as moving a table, pushing a vacuum cleaner, bowling	☐	☐	☐
3. Climbing **several flights** of stairs	☐	☐	☐

➢ **During the <u>past 4 weeks,</u> due to your <u>physical condition</u>,**

(mark one answer only per line)

	YES	**NO**
4. have you **accomplished less** than you would like?	☐	☐
5. have you had to stop doing certain things?	☐	☐

➢ **During the <u>past 4 weeks</u>, due to your <u>emotional state</u> (such as feeling sad, nervous or depressed)**

(mark one answer only per line)

	YES	**NO**
6. have you **accomplished less** than you would like?	☐	☐
7. have you had **difficulties** in doing what you had to do **with as much care and attention as usual?** ☐	☐	

8. **During the past 4 weeks, how much did your physical pain interfere with your work or housework?**

(mark one answer only)

- Not at all..... ☐
- A little bit ..... ☐

- Moderately ..... ☐
- Quite a bit ..... ☐
- Extremely ..... ☐

➢ The following questions are related to how you have felt over the past 4 weeks. For each question, please indicate the response you feel is most appropriate.

➢ **During the past 4 weeks, have there been times when:**

(mark one answer only per line)

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
9. Have you felt calm & peaceful?	☐	☐	☐	☐	☐	☐
10. Have you felt full of energy?	☐	☐	☐	☐	☐	☐
11. Have you felt down-hearted and blue?	☐	☐	☐	☐	☐	☐

12. **During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities and relationships with others (family, friends, etc.)?**

(mark one answer only)

All the of time..... ☐
Most of the time ..... ☐
From time to time ..... ☐
Rarely ..... ☐
Never ..... ☐

Annex 8: SAE Form

REPORT FORM FOR A SERIOUS ADVERSE EVENT (SAE) OCCURRING DURING A BIOMEDICAL RESEARCH STUDY NOT RELATED TO A PRODUCT MENTIONED IN ARTICLE L.5311-1 OF THE FRENCH PUBLIC HEALTH CODE

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

DÉPARTEMENT de la RECHERCHE CLINIQUE et du DEVELOPPEMENT DIRC Ile-de-FRANCE

SECTION RESERVED FOR THE SPONSOR: DO NOT FILL IN

|__|__| - |__|__| - *DRCD* - |__|__|__|__| - |__|__|__|__|

This form must be returned duly completed (2 pages) to the DRCD by fax: +33 (0)1 44 84 17 99

For the attention of *Didier Bouton*

Date reported: |__|__| |__|__| |__|__|__|__|
dd mm yyyy

Research code: **P110142**

IDRCB no.: 2012-A00167-36 **Initial report** ☐ **Follow-up on reported SAE** ☐ **Follow-up no.** |__|

Title of the Biomedical Research LC-OSTEO:

Comparison of the Effectiveness of 2 Manual Therapies on Functional Outcome in Sub-acute and Chronic Low Back Pain: a Randomised Controlled Trial

1) Site name and address: _____

Site no.: |__|__| Investigator (Role - Surname - First Name): _____

2) Patient identification:

Surname: |__| First name: |__|

Patient no.: |__|__|__|__|__|

Sex: Male ☐ Female ☐

Date of birth: |__|__||__|__| |__|__|__|__|

Age: |__|__| years

Weight: |__|__|__| kg

Height: |__|__|__| cm

Enrolment date: |__|__||__|__| |__|__|__|__|

Randomisation date: |__|__||__|__| |__|__|__|__|

Intervention arm ☐ Control arm ☐

Date of manual therapy

Start: |__|__||__|__| |__|__|__|__|

End: |__|__||__|__| |__|__|__|__|

3) Serious adverse event:

Death ☐

Life-threatening event ☐

Required hospitalisation or extended hospital stay ☐

From |__|__||__|__| |__|__| *to* |__|__||__|__| |__|__| ☐ *ongoing*

Incapacity or disability ☐

Pregnancy ☐

Other medically significant criteria (please specify): ☐

_____

_____

History (allergy, renal failure, etc.): _____

_____

4) Full description of the adverse event (diagnosis made, anatomical location, criteria leading to the event being considered as serious):

Intensity: Mild ☐ Moderate ☐ Severe ☐

Date of event: |__|__| |__|__| |__|__|__|__| and time of event: |__|__| |__|__|

Dd Mm yyyy hh min

_____

_____

Time before occurrence: _____

5) <u>Concomitant</u> medicinal product(s) excluding those used to treat the adverse event:

Brand name (preferably) or International Non-proprietary Name	Route	Dose/ 24 hrs	Start date	On-going	End date	Indication	Causality *(1, 2, 3 or 4)
			|__|__|__|__| |__|__|	☐	|__|__|__|__| |__|__|		
			|__|__|__|__| |__|__|	☐	|__|__|__|__| |__|__|		
			|__|__|__|__| |__|__|	☐	|__|__|__|__| |__|__|		
			|__|__|__|__| |__|__|	☐	|__|__|__|__| |__|__|		

** 1 = Likely 2 = Possible 3 = Unrelated 4 = Unknown*

Patient identification: Surname |__| **First name:** |__| **Site:** |__|__| **Research code: P110142**

6) Progress (indicate whether any symptomatic measures were taken: no ☐ yes ☐*If yes, please specify*) :

_____

_____

_____

_____

7) Date of disappearance: |__|__| |__|__| |__|__|__|__| and time of disappearance: |__|__| |__|__|

Dd Mm yyyy hh min

8) Other aetiology(ies) considered: no ☐yes☐ *If yes, please specify:*

_____

_____

9) Complementary examination(s) performed: no ☐ yes☐ *If yes, please specify date, nature and results:*

_____

_____

10) According to the investigator, the serious adverse event is most likely related to:

☐ a medical device in place

☐ one or more medicinal product(s) administered: which: _____

☐ the biomedical research procedures

☐ a concomitant disease

☐ the disease progression

☐ other: _____ ___

Date: |__|__| |__|__| |__|__| **Department stamp:** **Investigator's name:** _____ **Signature:**

Name and role of the Reporting Party: _____ **Phone no.** _____ **Signature:**

20.1.1.1.1 SECTION RESERVED FOR THE SPONSOR: DO NOT FILL IN

20.1.1.1.2 **Event identification number:** ***EV I__I__I__I***

Date received by the sponsor: |__|__| |__|__| |__|__|__|__|

Date of this report: |__|__| |__|__| |__|__|__|__| ☐ initial ☐ follow-up no. |__|__|

According to the sponsor, the adverse event is most likely related to:

☐ a medical device in place

☐ one or more medicinal product(s) administered: which: _____

☐ the biomedical research procedures

☐ concomitant disease

☐ the disease progression

☐ other: _____

If, according to the sponsor, the event is more likely to be related to the biomedical research:

☐ The serious adverse event is expected

☐ The serious adverse event is unexpected

Sponsor's comments:

_____

_____

_____

_____

Name and role of the sponsor's representative: **Signature:**

Summary of changes between study's original and final full protocols.

Changes in outcomes after trial commencement

- Change in the primary objective "to assess the efficacy of two manual therapies on improving the functional capacity at 3 months in patients with subacute or chronic common lower back pain" following the deletion of an inclusion criterion and an exclusion criterion (Amendment no. 1, version 2.0 dated 05/06/2014).
- A better definition of the outcome "pain" assessed at 3 and 12 months was provided: it was low back pain and not leg pain intensity (Amendment no. 6, version 7.0 dated 08/02/2018).
- The assessment of consumption of pain killers and non-steroidal anti-inflammatory drugs at 6 was removed because it added little information to the 3- and 12-month assessments (Amendment no. 6, version 7.0 dated 08/02/2018).

Changes in eligibility or inclusion or exclusion criteria after trial commencement

- Deletion of the inclusion criterion "common lower back pain for which the current episode has been progressing for between 1 month and 1 year" and the exclusion criteria "chronic common lower back pain for which the current episode has been progressing for over 1 year". The epidemiological and clinical justifications for maintaining these criteria are weak, and they are a significant limitation in terms of enrolment (Amendment no. 1, version 2.0 dated 05/06/2014).
- Deletion of the inclusion criterion "in activity or in sick leave" because it was inconsistent with other sections of the protocol (Amendment no. 5, version 6.0 dated 24/07/2017).

Other changes

- Enrolment period extended by 12 months, meaning that the study duration is 42 months, in order to reach the target number of expected patients (Amendment no. 2, version 3.0 dated 10/02/2015).
- Addition of details on the methods of structuring the manual therapist training sessions and the logistical aspects (Amendment no. 2, version 3.0 dated 10/02/2015). Possible addition of a manual therapist training session if the enrolment period is extended (Amendment no. 3, version 4.0 dated 12/01/2016).
- Deletion of the treatment assessment method by a clinical study technician. The assessment is carried out by patients who complete the self-reporting questionnaires themselves (self-assessment logs) (Amendment no. 2, version 3.0 dated 10/02/2015).
- Change of principal investigator following the passing of Prof. Serge Poiraudeau. Prof. François Rannou replaces him as the principal investigator of the study (Amendment no. 4, version 5.0 dated 03/04/2017).

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