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The effect of a six-week osteopathic visceral manipulation in patients with non-specific chronic low back pain and functional constipation: study protocol for a randomized controlled trial

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Abstract

Background

The aim of the proposed study is to analyze the effect of a six-week osteopathic visceral manipulation (OVM) program on the flexion-relaxation phenomenon in individuals with non-specific chronic low back pain (LBP) and functional constipation.

Methods/Design

An assessor-blinded, two-arm, randomized, placebo-controlled trial will be conducted. The sample will comprise 76 individuals with non-specific chronic LBP who have functional intestinal constipation, aged 18–65 years. The participants will be randomly allocated to two groups: (1) OVM and (2) sham OVM (SOVM). Evaluations will involve an interview, the Oswestry Disability Index, Fear-Avoidance Beliefs Questionnaire, functional constipation according to Rome III criteria, Biering-Sorensen test to normalize electromyographic (EMG) data, T12–L1 paraspinal level of the EMG signal during the flexion-relaxation phenomenon, 11-point numeric pain rating scale and fingertip-to-floor test. OVM and SOVM will be performed once per week for six weeks. Group 1 will receive OVM for 15 min and Group 2 will receive a sham visceral technique. Evaluations will be performed before and after the first session, after six weeks of treatment, and three months after randomization (follow-up). The findings will be analyzed statistically considering a 5% significance level ($p \leq 0.05$). The limitation of the study is that the therapist will not be blinded.

Discussion

This will be the first trial to analyze the clinical response and electromyographic signals during the flexion-relaxation phenomenon after OVM.

Trial registration

Brazilian Clinical Trial Registry, RBR-7sx8j3. Registered on 26 October 2017.

Keywords

Visceral manipulationLow back painConstipationFlexion-relaxationElectromyography

Background

Recent research shows that low back pain (LBP) can cause more years of disability than any other health condition [1]. Chronic pain is a public health problem, as it is an important cause of morbidity, work absenteeism, and temporary or persistent incapacity, generating high costs for healthcare systems [2]. There is an increasing demand for the treatment of chronic LBP [3] and researchers report that 80–90% [4, 5, 6] of cases are classified as non-specific LBP.

LBP is considered the second most common reason for visits to first-contact practitioners, such as chiropractors and osteopaths [7]. Besides using spinal manipulation [8, 9, 10], these professionals also employ visceral techniques [11] with a conservative approach. The theory is that visceral disorders could potentially trigger or exacerbate LBP symptoms due to impaired movement between internal organs and respective supporting tissues. This could manifest as LBP through two possible mechanisms: referred visceral pain and central sensitization [11].

Studies have shown that visceral techniques applied to healthy individuals lead to an immediate increase in the pain threshold of the low back compared to placebo application [12]. Researchers have also studied specific visceral disorders, such as refractory irritable bowel syndrome [13] and chronic constipation in women [14], and found better results after visceral treatment. While some researchers have performed visceral techniques on patients with LBP [11, 15, 16], the physiological and biomechanical mechanisms remain untested.

There is evidence that patients with LBP have deficits in the neuromuscular control of the spine [17, 18, 19] and that electrical activity of the trunk muscles can be used to evaluate the effects of therapeutic interventions [19, 20, 21] as well as differentiate individuals with LBP, as such individuals have higher electromyographic signals compared to asymptomatic individuals [17, 18, 22, 23, 24]. However, it is not known whether the abnormal electromyographic (EMG) activity in the paraspinal muscles of patients with LBP is the cause or consequence of pain [24, 25].

Individuals with chronic LBP do not reach the flexion-relaxation phenomenon (FRP), which is the decrease in or absence of electromyographic activity in the paraspinal muscles found during full trunk flexion in asymptomatic individuals [17, 18, 19]. In patients with LBP, the absence of this phenomenon may be due to muscle spasms, decreased range of motion, exaggerated stretch reflexes, or the protection of injured passive structures [26].

Based on the literature, there are indications that the FRP may be a valuable clinical tool to assist in the diagnosis and treatment of patients with LBP [17, 18, 24, 27] and there have been very few studies on the use of visceral techniques for such patients. Thus, the aim of the proposed study is to determine whether osteopathic visceral manipulation (OVM) can modulate stabilizing neuromuscular responses of the lumbar spine and reduce

both pain intensity and disability in individuals with non-specific chronic LBP and functional intestinal constipation.

Primary objective

The primary objective of the proposed study is to analyze the effect of a six-week OVM program on pain intensity and the disability index in individuals with non-specific chronic LBP and functional intestinal constipation.

Secondary objective

The secondary objective of the proposed study is to analyze the effect of a six-week OVM program on EMG signals of paraspinal muscles during the FRP, the global flexibility, and the fear-avoidance beliefs in individuals with non-specific chronic LBP and functional intestinal constipation.

Hypothesis

The authors hypothesize that the group submitted to OVM will experience more beneficial effects compared with similar individuals who receive placebo visceral techniques.

Study design

An assessor-blinder, two-arm, placebo-controlled RCT will be conducted.

Methods/Design

Sample selection

Individuals with non-specific chronic LBP will be recruited from physical therapy clinics in the city of Rondonópolis, state of Mato Grosso, Brazil and will be selected based on the eligibility criteria listed below.

Inclusion criteria

- Age 18–65 years [28]
- Non-specific LBP for at least three months [28]
- Pain intensity of at least 2 points measured using the Numeric Pain Rating Scale [11]
- Functional constipation according to Rome III criteria [29]

Exclusion criteria

- Any contraindication to OVM or having undergone treatment in the previous six months
- Having undergone spinal surgery in the previous six months
- Serious spinal pathology (e.g. metastasis, spinal fracture, inflammatory, and infective diseases, caudal equine syndrome, canal stenosis)
- Serious cardiovascular or metabolic disease
- Pregnancy
- Red flag signals [5]
- Currently in an acute inflammatory phase of known gastrointestinal or urinary diseases (such as cholecysticis, renal calculi, peritonitis, appendicitis)

Intervention

The participants will be allocated to groups receiving one of two interventions: (1) OVM or (2) sham OVM (SOVM). The participants in each group will receive six sessions (one per week for six weeks) (Table 1). Given

the nature of the study, it is not possible to blind the therapist, but the assessor and patients will be blinded to the treatment conditions. For ethical reasons, the patients in both groups will receive an information booklet called The Back Book in Portuguese [30] on the first day of treatment.

Group 1: osteopathic visceral manipulation

This group will receive OVM (15 min per session, one session per week for six weeks). The OVM techniques that will be used are described by Ricard [31] and will be performed by a single osteopath with more than ten years of experience. In the first part of each consultation, all patients will be submitted to a direct visceral evaluation [12]. Each treatment will be individualized for each patient using specific visceral manipulation techniques [11, 16] involving light or deep manual fascial releases as well as specific small and large intestine mobilizations in the abdomen, as appropriate [31].

Group 2: sham technique

This group will receive SOVM at the same time as Group 1 (15 min per session, one session per week for six weeks), which will involve just light touches over the different parts of the abdomen, without any deep mobilization or movement. The osteopath will apply her hands over the same points with the same duration as in OVM to give the patient the perception of being treated [11, 12, 13, 15].

Outcome measures

A blinded assessor will record outcome measures.

The primary outcomes will be LBP intensity (NPRS) and the Oswestry Disability Index (ODI) after the six weeks of treatment and three months after randomization, because pain is the most common reason patients seek private physical therapy clinics for the treatment of LBP. From a patient's perspective, it is also the outcome that most determines whether treatment has been successful [32].

The secondary outcomes will be the EMG signals during the FRP and fingertip-to-floor test (FFT) after the first treatment session, after the six weeks of treatment and three months after randomization and the FABQ after the six weeks of treatment and three months after randomization.

Participants' timeline

A brief Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) flow diagram is provided in Fig. 1, and a populated SPIRIT checklist is provided in Additional file 1.

	STUDY PERIOD							
	Enrolment	Allocation*	Post-allocation (treatment)					Follow-up
TIMEPOINT	0	1 week	2 week	3 weeks	4 weeks	5 weeks	6 weeks	3 months
ENROLMENT:								
Eligibility screen	X							
Informed consent	X							
Clinical evaluation / Anamnesis	X							
Inclusion / exclusion criteria	X							
Allocation		X						
INTERVENTIONS:								
Received OVM		X	X	X	X	X	X	
Received sham OVM		X	X	X	X	X	X	
ASSESSMENTS:								
Demographic data	X							
Back pain characteristics	X						X	X
Blinding		X	X	X	X	X	X	X
ODI	X						X	X
NPRS	X	X	X	X	X	X	X	X
Fingertip-to-floor	X	X	X	X	X	X	X	X
EMG signal	X	X	X	X	X	X	X	X
FABQ	X						X	X

Fig. 1
Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) figure for patient participations. ODI Oswestry Index Disability, NPRS Numeric Pain Rating Scale, EMG electromyographic, FABQ Fear-Avoidance Beliefs Questionnaire

Table 1
Items included in the Template for Intervention Description and Replication (TIDieR) checklist: information to include when describing an intervention. Full version of checklist provides space for authors and reviewers to give location of the information

Item no.	Item
Brief name	
1	OVM
Why	
2	Visceral osteopathy is described as a manual treatment performed directly on the viscera with the goal to normalize the mobility dysfunction of the organ and try to eliminate fascial restrictions and relax the visceral spasms.
What	
3	As previously described, the treatment with OVM is manual therapy, because of this it is performed only with the hands.
4	Manual techniques will be performed in the small and large intestine of the volunteers. At the beginning of each session, individuals will be assessed and points of spasms of the visceral musculature of the small and large intestine or fascial restriction will be located. All the techniques are described in the visceral osteopathy book [31].
Who provided	
5	The physiotherapist who will perform the treatment is graduated in physiotherapy for 13 years and she has > 10 years of experience in this type of treatment. She is an osteopath certified by Madrid's Osteopathy School (Escuela de Osteopatía de Madrid).
How	
6	Six individual weekly sessions of 15 min each will be carried out.
Where	
7	The sessions will be carried out in a private clinic in the city of Rondonópolis/MT.
When and how long	
8	The participants will receive six individual weekly sessions. The duration will be 15 min for each session.
Tailoring	
9	At the beginning of each session, the volunteers will be evaluated according to visceral spasms in the large and small intestine and fascial restriction for manual treatment according to the need of each patient. After the evaluation, the patients will be treated with techniques of visceral osteopathy in the large and small intestine to normalize the visceral musculature spasms.

Item no.	Item
Modifications	
10[a]	–
How well	
11	Osteopaths are trained to identify visceral spams and/or fascial restriction when they do osteopathy's formation. We try to propose a treatment respecting the individuality of the patients and seeking to reproduce better the clinical practice. As previously proposed by Panagoupols et al. [11] and Tamer et al. [16]).
12[a]	–

[a]If a checklist is completed for a protocol, these items are not relevant to protocol and cannot be described until the study is complete

Sample size calculation

The sample size was calculated using G Power 3.1.9.2 software. This calculation was based on the detection of a 10-point difference on the ODI and 2.5-point difference on the NPRS, which have been identified as the minimum clinically important differences [33]. A sample size of 32 participants per group would provide a 90% power to detect a clinically important difference between groups, assuming a common standard deviation of 12 on the ODI [34] and 3.0 on the NPRS and a two-sided hypothesis with an alpha level of 0.5. The sample will be increased by 20% to compensate for possible dropouts, leading to 38 individuals in each group (overall sample = 76 participants).

Recruitment

The patients will be interviewed by the blinded assessor, who will determine eligibility. Eligible patients will receive clarifications regarding the objectives of the study and will be asked to sign a statement of informed consent. Sociodemographic data and medical history will then be recorded. The assessor will collect the data related to the study outcomes at baseline, before and after a single treatment session, after the completion of the six weeks of treatment, and three months after randomization. All data will be coded and entered into Excel files (Microsoft Corporation).

Randomization

Patients who meet the eligibility criteria will be randomly allocated to their respective intervention groups.

Allocation concealment

The individuals will be randomly allocated to the two groups. To minimize the risk of imbalance in the size of the groups, a randomization list will be generated using two blocks: number 1 for the manipulation group and number 2 for the placebo-controlled group. The allocation sequence will be stipulated in sequentially numbered, opaque, sealed envelopes. Following the baseline evaluation, each participant will be allocated to one of the groups by opening an envelope. This process will be performed by a member of the research team who is not involved in the recruitment process or other aspects of the study.

Blinding

The design study of the trial does not allow blinding of the therapist. All the pre- and post-treatment assessments and the follow-up assessment will be done by a person blinded to group allocation and treatment. The statistician performing the statistical analyses will also be blinded to group allocation and treatment.

Evaluation and follow-up

The evaluation process will be conducted by a physiotherapist with experience in the evaluation procedures and blinded to the allocation of the participants to the different groups. Evaluations will be conducted in the following manner:

- Pre-treatment evaluation
- Evaluation immediately following a single intervention session
- Post-treatment evaluation
- Evaluation three months after randomization

Measurements

The scales to be administered are the NPRS, ODI, EMG signal (Biering-Sorensen test and Flexion-relaxation phenomenon), FFT, and Fear-Avoidance Beliefs Questionnaire (FABQ).

Numeric Pain Rating Scale

The NPRS will be used to determine the level of pain intensity perceived by the patient using an 11-point scale, on which 0 represents the absence of pain and 10 represents the worst pain imaginable [35]. The participants will be instructed to report their sensation of pain intensity at the moment of the evaluation to compare with the immediate effect of treatment and to report average pain intensity based on the previous seven days for comparisons at the end of the six-week treatment and three-month follow-up.

Oswestry Disability Index

The ODI is the most commonly used outcome measure for LBP. It is a self-administered questionnaire and each section is scored on a scale from 0 (no disability) to 5 (maximum disability). The index is calculated by dividing the sum of the item scores by the maximum possible score, which is then multiplied by 100 and expressed as a percentage. Thus, for every question not answered, the denominator is reduced by 5. If a patient marks more than one statement on an item, the higher scoring statement is recorded as a true indication of disability. The questionnaire takes 3.5–5 min to complete and approximately 1 min to score [36].

Electromyographic analysis

Biering-Sorensen test

Before the FRP, all individuals will perform the Sorensen endurance test [37]. The prone position will be adopted with the trunk placed beyond the edge of the table, with the anterior superior iliac spine aligned with the edge of the table and the lower limbs fixed to the table. On this test, the patient maintains the horizontal position with the upper limbs crossed and in contact with the chest for 10 s, three times, with a 10-min rest after the third time [19, 21]. The maximum 1-s root mean square (RMS) activity recorded during the Sorenson test will be defined as the maximal voluntary contraction (MVC) value and will be used as a reference for other electromyographic data.

Flexion-relaxation phenomenon

The EMG signal will be collected during this movement. The flexion/extension trunk movement will be started in the upright position. The participant will be instructed to move in response to voice command, keeping the

knees straight but not locked, and the arms hanging freely, while slowly flexing forward to full flexion over a 3-s period, pausing for 3 s at full trunk flexion and then returning to the upright starting position during the 3 s of the trunk extension period. This protocol is typical of those used in studies on the FRP [17, 18, 21, 27].

The movement will be performed three times. Data from the third replication will be used in the analysis. Before the first reading, the patients will practice three times to become familiar with the movement [20, 21].

Two different forms of a flexion-relaxation ratio (FRR) will be used to quantify the degree to which the FRP is present [17, 18]. One will be calculated by dividing the maximum RMS of EMG activity level during flexion (while bending forward) by the lowest mean EMG activity as measured over a 1- interval during the fully flexed phase. Another FRR will be similarly calculated by dividing the maximum RMS EMG activity level during extension (while returning to the upright position) by the same minimum. The beginning and end of the fully flexed phase for each cycle will be determined from the plot of the motion data.

Electromyographic signal

Electromyography is the most widely used assessment tool for the study of muscle activation during the FRP [17, 18]. A four-channel conditioning module (BTS FREEEMG 1000®) will be used with an A/D converter with 16-bit resolution, a common rejection mode ratio > 100 dB and 20–450 Hz bandpass filter. The EMG signals will be amplified with a 2000-fold gain using a 1-kHz sampling frequency and wireless transmission. The signals will be captured with self-adhesive, disposable, Ag/AgCl surface electrodes measuring 1 cm in diameter (Medi-Trace 200 Kendall Healthcare, Tyco, Canada). After cleaning the skin of the sites with 70% alcohol, the electrodes will be positioned at a distance of 2 cm center to center on the paraspinal muscles at T12 and L1 on each side with approximately 1 cm vertical distance between the edges of the electrodes in semi-flexed trunk position [21, 27]. The electrodes will not be removed during treatment, but the outline of each electrode will be made with a skin marking pen so that they can be placed in the same location for subsequent measurements if they become detached during treatment.

Fingertip-to-floor test

The FFT will be performed during the third cycle of the FRP with full trunk flexion (static phase). The third finger of the dominant hand will be used [38]. The participants will stand on a platform measuring 30 cm in height to avoid touching the floor, which would make the measurement unviable.

Fear-Avoidance Beliefs Questionnaire

The FABQ is a 16-item instrument used to determine a patient's beliefs regarding the effects of physical activity and work on musculoskeletal pain. The responses for each item are scored on a seven-point scale (0 = completely disagree to 6 = completely agree). The original factor analysis revealed two subscales: a physical activity subscale with five items (maximum score = 24) and the work subscale with 11 items (maximum score = 42). The total is in the range of 0–96 points, with a higher score indicating more strongly held fear-avoidance beliefs. The FABQ takes about 10 min to complete [39].

Statistical analysis

Statistical analysis will be performed using intention-to-treat analysis. If data losses occur during the study, the last observation will be carried forward to adjust the missing data in follow-up evaluations. The Shapiro–Wilk test will be used to determine the normality of the data. Anthropometric differences between groups will be determined using the independent t-test for data will normal distribution and the Mann–Whiney test for data with non-normal distribution. Repeated-measures analysis of variance (ANOVA) followed by the Bonferroni post hoc test will be used to determine the effects of treatment with regard to the NPRS, RMDQ, FFT, FABQ,

and EMG considering the following interactions: group (OVM and SOVM) vs evaluation (pre-interventions, after one session, after six weeks, and three months after randomization) vs movement (flexion extension). If the data exhibit non-normal distribution, Friedman's ANOVA will be used with Dunn's post hoc test. A p value < 0.05 will be considered indicative of statistical significance. The data will be organized and tabulated using the Statistical Package for the Social Sciences (SPSS, v.19.0).

Adverse events and safety

Adverse events (AEs) are recorded as part of the data collection for each session and will be reported to the clinical authorities and to the ethics committee. Participants suffering AEs will be referred for appropriate treatment.

Compliance and blinding assessment

To assess patients' blinding to treatment allocation, patients are asked post treatment (six weeks after the start of treatment) to report which study treatment they think that they received (OVM/SOVM). The effect of their reports on outcome will be examined in explorative analysis.

Discussion

This paper presents a detailed description of a prospective, placebo-controlled, assessor-blinded, clinical RCT designed to demonstrate the effect of a six-week OVM program on the FRP in individuals with non-specific chronic LBP and functional constipation. It will also allow us to investigate neurophysiologic and biomechanical processes that may contribute to the therapeutic effects of OVM. Analyzing FRP measured in patients with LBP submitted to OVM may help clarify the contributions of passive and active structures during and following OVM, thereby providing evidence for suspected therapeutic mechanisms. The results will be published and the evidence found may contribute to the use of visceral manipulation for this population.

The results and practical relevance of our study will be of importance not only for researchers and policy makers but also for patients suffering from non-specific chronic LBP and functional intestinal constipation.

Given the nature of the study, the limitation of the study is that the therapist will not be blinded. Nevertheless, the design also has important strengths: reproducibility; and the blinding of the assessor and participant. The outcome will provide evidence-based conclusions regarding the effectiveness of this treatment for the management of patients with non-specific chronic LBP and functional constipation.

Trial status

Participants will be recruited to start in January 2018. Data collection will be finished in May 2018 and study completion is expected to be July 2018.

Abbreviations

ANOVA:
Analysis of variance

CAPES:
Coordenação de Aperfeiçoamento de Pessoa de Nível Superior

CONSORT:
Consolidated Standards of Reporting Trials

EMG:
Electromyographic

FAPEMAT:
Fundação de Amparo á Pesquisa do Estado de Mato Grosso
FFT:
Fingertip-to-floor test

FRP:
Flexion-relaxation phenomenon
FRR:
Flexion-relaxation ratio

LBP:
Low back pain
MVC:
Maximal voluntary contraction
NPRS:
Numeric Pain Rating Scale

ODI:
Oswestry Disability Index
OVM:
Osteopathic visceral manipulation

RMS:
Root mean square
SENIAM:
Surface electromyography for non-invasive assessment of muscles
SOVM:
Sham osteopathic visceral manipulation
SPSS:
Statistical Package for the Social Sciences

Declarations

Acknowledgments

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Availability of data and materials

Not applicable.

Authors' contributions

CRB contributed to the protocol development and provided clinical expertise. FP is responsible for designing statistical procedures and drafting this part of the protocol and manuscript. FCL is responsible for designing statistical procedures and drafting this part of the protocol and manuscript. PRGL contributed to the protocol development and provided clinical expertise. JCFC contributed to the protocol development, provided clinical expertise, and drafted part of the manuscript. WVBF is the principal investigator and has contributed to the concept and study design, provided clinical expertise and manuscript development. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The proposed study will follow the guidelines for research involving human subjects established by the National Health Board of the Brazilian Health Ministry in October 1996. The study will be conducted at physical therapy clinics in the city of Rondonópolis, state of Mato Grosso, Brazil and received approval from the Human Research Ethics Committee of the Nove de Julho Educational Association (certificate no. 2.348.912/2017). The participants will have access to all information and will be allowed to withdraw from the study at any time with no negative repercussions. The identification of each individual will remain concealed based on the ethical principles of confidentiality and privacy.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Additional files

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

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	___1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	___3_____
	2b	All items from the World Health Organization Trial Registration Data Set	___3_____
Protocol version	3	Date and version identifier	___3_____
Funding	4	Sources and types of financial, material, and other support	___19_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_1, 19, 20__
	5b	Name and contact information for the trial sponsor	__19_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	__19_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	__11_____

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	__3,4,5____
	6b	Explanation for choice of comparators	__4,5_____
Objectives	7	Specific objectives or hypotheses	____5_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	____6_____

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	___6_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	__6,7_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	__7,8_____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	___16_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	___6_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	__6,7_____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	___8,9_____

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	_9,SPIRIT figure_
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	__9_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	___10_____

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	___10_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	___10_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	___11_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	____11____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	___10_____

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11,12,13,14, 15

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	___15_____
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	__10,15,16_
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	__15,16____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_15,16_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	__15, 16___

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	___19_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	___16_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	__18_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	__19_____

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	____18____

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	___3_____
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	____10____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	___NA_____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	___10, 16__
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	___19 ____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	___11_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	___16_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	__17_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	__NA_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	__17_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	__18_____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	__NA_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

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