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Vertebroplasty in multiple myeloma patients with vertebral compression fractures: Protocol for a single-blind randomized controlled trial.

Line Adsbøll Wickstrøm[1], MD, Leah Y. Carreon, MD, MSc[1,2],
Thomas Lund, MD, PhD[3], Niels Abildgaard, MD, DMSc[3], Marianne Dyrby Lorenzen[1], RN,MCN,
Mikkel Ø. Andersen, MD[1,2]

Author affiliations:

1. Spine Surgery & Research, Spinecenter of Southern Denmark, Lillebaelt HospitalMiddelfart

2. Department of Regional Health Research, Faculty of Health Services, University of Southern Denmark, Odense, Denmark

3. Department of Haematology, Odense University Hospital, Odense, Denmark

Corresponding author:

Line Adsbøll Wickstrøm, line.adsboll.wickstrom@rsyd.dk

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Abstract:

Introduction:

Multiple myeloma is a plasma cell cancer where about 1/3 of the patients present with pathological fractures at the time of diagnosis. Despite treatment, the majority of the patients will develop additional fractures during the course of the disease. Vertebral fractures are very painful and affect patients' daily function. Because survival and prognosis has improved significantly over the last two decades for multiple myeloma (MM) patients, there is an increased need to focus on optimal fracture treatment. Traditionally, fracture pain is treated conservatively with opioids, bisphosphonates, bracing, and radiation therapy. Vertebral augmentation has been used the last three decades as a minimally invasive treatment option for vertebral compression fractures, but the evidence base for the efficacy is weak.

We describe a randomized controlled trial to assess the impact of vertebroplasty on clinical outcome in the treatment of MM patients with painful vertebral fractures.

Methods:

One hundred multiple myeloma patients with painful vertebral fractures will be randomized in a prospective, single blinded, multicenter, clinical trial where patients are randomized to either usual care or usual care supplemented with vertebroplasty with a possibility of crossover 4 weeks after randomization. The primary outcome will be change in Oswestry Disability Index assessed at follow up at 4, 8, 26 and 52 weeks.

Analysis:

Primary and secondary outcomes are assessed at baseline and at 4, 8, 26 and 52 weeks. Categorical data will be presented by means of frequencies and related percentages; continuous data will be displayed by means of descriptive statistics. Repeated measures ANCOVA with baseline ODI, VAS pain, EQ-5D-3L, and number of levels involved will be performed.

Ethics and dissemination:

The study has been evaluated by the Regional Committees on Health Research for Southern Denmark (S-20200075) and notified and approved by the Region of Southern Denmark and listed in the internal record, journal no. 20/22355. All participants provide consent. The protocol will follow the SPIRIT (Standard Protocol Items for Randomized Trials) statement. The Danish Myeloma Patient Organization supports the study. Findings will be disseminated in peer-reviewed publications and presented at national and international conferences. Trial registration number NCT04533217.

Strengths and limitations of this study:

Strengths

- Ramdomized controlled trial
- Nationwide study (participation of all hematologic departments in Denmark

Limitations

- Single-blinded randomization

Introduction:

Multiple myeloma is a plasma cell cancer in the bone marrow associated with activated osteoclastic bone degradation, lack of bone formation, and pathological fractures with protracted healing due to inhibited osteoblast function (1, 2). These biological changes are induced by the expansion of proliferating malignant plasma cells in the bone marrow (2).

The incidence is about 7 per 100,000 in Denmark, equivalent to approximately about 400 new cases a year (3). At the time of diagnosis pathological fractures are present in about 1/3 of the patients and a greater proportion develop fractures during the course of the disease (3, 4). The annual risk of spontaneous spinal fractures is 15-24 % despite bisphosphonate prophylaxis (3).

Although multiple myeloma is incurable, survival and prognosis has improved significantly over the last two decades (5). This justifies and necessitates increased focus on optimal fracture treatment to ensure good physical function and quality of life for the patients' remaining lifetime. Vertebral fractures are very painful and affect patients' daily function (2, 4, 6). Traditionally, the fracture pain is treated conservatively with opioids, bisphosphonates, bracing, and radiation therapy (3).

Vertebroplasty was first reported in the late 80s for the treatment of vertebral hemangiomas and osteolytic vertebral tumors (7). Under fluoroscopy, a Jamshidi needle is inserted through the pedicles (8) into the vertebral body. Polymethylmethacrylate is injected into the vertebral body, still under imaging guidance, to minimize extravasation into the spinal canal. Vertebral augmentation, including percutaneous vertebroplasty (PVP) and kyphoplasty (KP), has been used as a minimally invasive treatment option for vertebral compression fractures (VCFs) (4, 9, 10).

The procedure is considered to be well suited for treatment of patients with malignant spine disease as it can be done under local anaesthesia, provides rapid pain relief (11, 12), and prevents prolonged immobilization. PVP and KP provide stability within the fractured vertebral body by preventing microscopic movement and macroscopic collapse. It has also been suggested that polymethylmethacrylate (PMMA) bone cement induces exothermic reactions that are toxic to nerve endings and therefore provide pain relief (13).

Two randomized trials and a later review was published in 2009 (14, 15) and 2018 (16), respectively, regarding vertebral augmentation. The two trials were done in different patient populations, namely patients with benign osteoporosis. The disappointing outcome of these two trials has unfortunately led to uncertainties regarding the effect in other indications, such as metastatic disease.

In 2019, a systematic review on vertebral augmentation of cancer related painful vertebral lesions was published (12). This review included not only randomized studies, but also other publications involving vertebral augmentation techniques. In all 87 studies were included in the study and meta-analysis was performed. The review demonstrated clinically relevant improvement in pain and health related quality of life.

A recent Danish national clinical guideline (17, 18) on painful vertebral compression fractures, caused by cancer including multiple myeloma, recommends percutaneous vertebroplasty as pain management. The evidence is mainly based on two randomized studies: The CAFE study by Berenson et al. (19) including 49 patients suffering from multiple myeloma randomized between kyphoplasty and conservative treatment and the study by Audat et al.(20) randomizing 27 patients to either conventional therapy or conventional therapy adding vertebroplasty or kyphoplasty. The recommendations in the Danish guideline are weak

due to risk of bias, including lack of blinding in randomized studies. In addition, the CAFE study was further downgraded for indirectness as the study contains a population consisting predominantly of patients with primary cancer other than multiple myeloma.

Rationale for this study

Evidence-based guidelines for supplementing chemotherapy with vertebral augmentation when treating multiple myeloma patients with pathological fractures are lacking. The overall evidence from the two randomized controlled trials comparing supplementary vertebral augmentation to usual care is of low quality (17, 18) and requires more robust investigations regarding the role of vertebroplasty in the treatment algorithm of multiple myeloma with spinal involvement.

For that reason, we decided to perform a single blinded, randomized, controlled trial comparing usual care versus usual care supplemented with vertebroplasty in treating multiple myeloma patients with pathological fractures.

Methods and analysis:

Purpose

To examine the efficacy of PVP in multiple myeloma patients with vertebral compression fracture, based on improvement in patient reported outcome

Study design and patient involvement

The initial idea behind this project was created by a patient appointed by the Danish Cancer Society to participate in the working group behind the National Clinical Guideline on percutaneous vertebroplasty for the palliative treatment of malignant vertebral compression fractures caused by multiple myeloma (17, 18). She urged the group members to set up a study to provide high-quality evidence needed to recommend the treatment.

The study design is a randomized, prospective, single blinded, multicentre, clinical trial where patients are randomized to either usual care or usual care supplemented with vertebroplasty with a possibility of crossover 4 weeks after randomization.

The study design has been developed in collaboration with the Danish Myeloma Patients' Association "Dansk Myelomatose Forening" and designed in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines (21).

The trial design is illustrated in Figure 1 and trial timeline in Figure 2.

Trial sites

The trial is a multi-centre trial with the participation of all Danish haematological departments. The departments are as follows:

- Department of Haematology, Aalborg University Hospital
- Department of Haematology, Aarhus University Hospital
- Department of Haematology, Holstebro Regional Hospital
- Department of Haematology, University Hospital of Southern Denmark, Esbjerg

- Department of Haematology, University Hospital of Southern Denmark, Vejle
- Department of Haematology, Zealand University Hospital, Roskilde
- Department of Haematology, Herlev Hospital
- Department of Haematology, Rigshospitalet, Copenhagen
- Department of Haematology, Odense University Hospital

Participating spine surgical units are as follows:

- Department of Orthopaedic Surgery, Rigshospitalet
- Spine Center of Southern Denmark, Lillebaelt Hospital, Middelfart
- Department of Orthopaedic Surgery, Aarhus University Hospital

Study population

Study subjects will be recruited from patients diagnosed with multiple myeloma assessed and found eligible for vertebroplasty due to painful vertebral compression fractures. Possible candidates will be identified at the departments of haematology where the patients are treated for their disease.

Inclusion criteria:

- Patients diagnosed with symptomatic multiple myeloma and spinal compression fractures
- Fractures verified on MRI- or CT-scan between and including Th6 and L5
- Fracture involves 4 vertebral body levels or less
- PVP can be done in one session
- Possible indication for vertebroplasty
- Back pain score measured on a visual analogue scale (VAS) ≥ 5
- Age ≥ 18 years
- Able to understand and read Danish
- Written informed consent
- Relevant pain started ≤ 3 months prior to inclusion

Exclusion criteria:

- Contra-indications for spine surgery
- Platelets < 30 mia/l
- Bedridden
- Presence of neurologic deficit
- Psychological or psychiatric disorder that is expected to interfere with compliance

Randomization:

Prior to randomization, the patients will be divided into two groups, stratifying between patients with known multiple myeloma with a newly diagnosed spinal fracture and relevant pain ≤ 3 months prior to inclusion and patients with newly diagnosed multiple myeloma with relevant pain associated to a spine fracture initiating ≤ 3 months prior to the diagnosis.

Furthermore, to ensure balanced control and intervention groups the included patients at randomization will be stratified according to 1) planned PVP of 1 vs. 2-4 levels, and 2) former vertebral fractures that are not planned treated with PVP.

The patients in each subgroup will be randomized to one of two parallel treatment arms allocated in a 1:1 ratio. Sealed numbered envelopes containing electronically randomized group allocations will be prepared prior to trial commencement. Following informed consent, a sealed pre-randomized envelope will be allocated by the study nurse and the patient label affixed to the envelope.

Control Treatment

The patients will receive the treating departments' standard care.

Investigational treatment:

The investigational treatment arm will be the group receiving supplementary vertebroplasty of the vertebral compression fractures.

Outcomes

Primary outcome:

- Back-specific Functional Status using Oswestry Disability Index (ODI) at time of randomization and 4-weeks post-randomization. The ODI assesses pain-related physical functioning in spinal disorders. (22). The ODI contains 10 questions about how back pain affects the ability to manage everyday life. These are summarized in a score ranging from 0 to 100. Higher scores reflect worse pain and disability.

Secondary outcomes:

- Self-reported average pain intensity (VAS) during the preceding 24 hours at enrolment, and weekly in 12 weeks after enrolment. The rating scale from 0 to 10, with higher scores indicating more severe pain.
- Health Related Quality of Life (HRQL) on the EuroQol 5-dimension 3-level (EQ-5D-3L) (23). EQ-5D-3L is a widely used generic measure of HRQL. It evaluates five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression, each with three levels of severity. The resulting health is converted into a single summary index with a total score ranging from –0.6 to 1, where 1 corresponds to perfect health.
- HRQL according to the FACT-G, EORTC QLQ C30 and MY20 questionnaires.
- Long-term stability of the treated vertebral bone (e.g., fracture, vertebral body height, or malalignment) as measures by long-standing radiographs.
- Questionnaire about general health services, including questions about e.g. sick leave and home care.

Data collection:

After informed consent is obtained from the patient, the hematologist will fill out screening forms regarding disease stage, lines of treatment, current disease status, bisphosphonate status, and pain relief treatment. The patient will complete surveys including the ODI, VAS pain score and QoL. Time points for data collection is presented in Table 1.

Sample size

The sample size calculations for this study is a challenge, as there are very few published papers reporting outcomes following vertebroplasty on vertebral fractures due to multiple myeloma. The sample size calculations are thus based on results from treating osteoporotic vertebral fractures with vertebroplasty. To obtain a minimal clinically relevant improvement of at least 15 points on the Oswestry Disability Index, we need to enrol 44 patients in each group. To account for approximately 10 % dropout we aim to enroll 100 patients.

$N = (Z(crit) + Z(pwr))x\ s^2 * 2 / MIREDIF^2)$,

with a mean minimum difference between groups of 15, SD=25, two tailed p=0.05, assuming a normal distribution with Z (crit)=1.96, Z (pwr)=0.80

Analyses:

Baseline characteristics:

The baseline characteristics of patients and operative details will be recorded.

Statistical analysis:

Data will be analyzed according to their type using STATA, i.e.; categorical data will be presented by means of frequencies and related percentages; continuous data will be displayed by means of descriptive statistics (mean, standard deviation, number of observations, minimum, median, maximum).

The primary outcome measure will be improvement in ODI scores at 4 weeks after initiation of treatment. Repeated measures ANCOVA with baseline ODI, VAS pain, EQ-5D-3L, and number of levels involved will be performed.

Ethics and dissemination:

The study will be performed according to the Declaration of Helsinki and the Danish Code of Conduct for Research Integrity (24). The study has been evaluated by the Regional Committees on Health Research for Southern Denmark (S-20200075), and has been notified to and approved by the Region of Southern Denmark and listed in the internal record, journal no. 20/22355. , and permission to extract data from hospital records will be obtained from the patients. Consent to use patient-reported information from the DaneSpine database is obtained electronically prior to patients completing the questionnaires. Patients who do not consent will not be included.

Findings will be disseminated in peer-reviewed publications and presented at national and international conferences following guidance from the SPIRIT guidelines.

Discussion:

This article presents a protocol for a single blinded randomized controlled trial comparing usual care versus usual care supplemented with vertebroplasty in treating multiple myeloma patients with painful vertebral fractures. Further prospectively registered data on health, social variables and patient-reported outcomes are collected.

As the median survival is significantly better for MM patients than for patients with spinal metastases associated with solid cancers it justifies and necessitates increased focus on optimal fracture treatment in MM patients specifically. An increasing number of MM patients experience more than 5 years, even more

than 10 years survival, which highlights the importance of ensuring good physical function and quality of life for the patients.

The outcome of the proposed project will impact future national and international guidelines on the treatment regimen for patients with multiple myeloma and vertebral fractures.

The main strength of this study is the randomized treatment assignments, reducing the risk of selection bias.

Author contributorship statement and conflict of interest:

- Line Adsbøll Wickstrøm: PhD student, investigator
- Leah Y. Carreon: Co-supervisor
- Thomas Lund: Consultant, mediation of contact to the Danish Myeloma Patients' Association "Dansk Myelomatose Forening"
- Niels Abildgaard: Co-supervisor, mediation of contact to the Danish hematologic departments
- Marianne Dyrby Lorenzen: Administration
- Mikkel Ø. Andersen: Principal supervisor

All authors have participated in the design and organization of the study. Authors have no affiliation apart from stated, and have no conflicts of interests.

Funding:

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- Faculty of Health Sciences, University of Southern Denmark
- Research means, Region of Southern Denmark or Hospital Lillebaelt Research Committee
- External funding

No funding has yet been collected.

Datasharing:

When the project is terminated, data from the project database will be archived at the Danish National Archives, and the research group will save an anonymized version of patient information from the database. After the project results are published, interested researchers will have two options for re-use of the data: upon receiving required permits they may apply for data extracts from DaneSpine and from the Danish National Archives – or they may receive anonymized raw data from DaneSpine and the project data base from us. This way, data will be Findable, Accessible, Interoperable and Reusable.

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Tabel 1 Datacollection - timeline

Clinical tools	At incl.	1 week post-incl.	2 w	3 w	4 w	5 w	6 w	7 w	8 w	9 w	10 w	11 w	12 w	26 w	52 w
ODI	x				x				x					x	x
VAS leg and back	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
EQ-5D	x				x				x					x	x
FACT-G	x												x		x
EORTC QLQ-C30	x												x		x
EORTC QLQ-MY20	x												x		x
X-ray	x												x		x
MRI	x														

Biopsy	x														

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

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		Reporting Item	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	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	8
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 8

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	n/a
Roles and responsibilities: sponsor and funder	#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	n/a
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	n/a
Objectives	#7	Specific objectives or hypotheses	n/a
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, non-inferiority, exploratory)	4
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	4-5

		collected. Reference to where list of study sites can be obtained	
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)	5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-6
Interventions: modifications	#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)	5-6
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
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	6
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)	12, 14
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	6-7

Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	n/a
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	5-6
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	5-6
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5-6
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5-6
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	5-6
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements,	13

		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	
Data collection plan: retention	#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	13
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	13
Statistics: outcomes	#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	7
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	7
Statistics: analysis population and missing data	#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)	7
Methods: Monitoring			
Data monitoring: formal committee	#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	8
Data monitoring: interim analysis	#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	n/a

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	n/a
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	7
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)	n/a
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	7
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	8
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	n/a
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	n/a

		participation	
Dissemination policy: trial results	#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	7
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

Vertebroplasty in multiple myeloma patients with vertebral compression fractures: Protocol for a single-blind randomized controlled trial.

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Vertebroplasty in multiple myeloma patients with vertebral compression fractures: Protocol for a single-blind randomized controlled trial.

Line Adsbøll Wickstrøm[1], MD, Leah Y. Carreon, MD, MSc[1,2],
Thomas Lund, MD, PhD[3], Niels Abildgaard, MD, DMSc[3], Marianne Dyrby Lorenzen[1], RN, MCN,
Mikkel Ø. Andersen, MD[1,2]

Author affiliations:

1. Spine Surgery & Research, Spinecenter of Southern Denmark, Lillebaelt HospitalMiddelfart

2. Department of Regional Health Research, Faculty of Health Services, University of Southern Denmark, Odense, Denmark

3. Department of Haematology, Odense University Hospital, Odense, Denmark

Corresponding author:

Line Adsbøll Wickstrøm, line.adsboll.wickstrom@rsyd.dk

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Abstract:

Introduction:

Multiple myeloma is a plasma cell cancer where about 1/3 of the patients present with pathological fractures at the time of diagnosis. Despite treatment, the majority of the patients will develop additional fractures.
Because survival and prognosis has improved significantly over the last two decades for multiple myeloma (MM) patients, there is an increased need to focus on optimal fracture treatment. Traditionally, fracture pain is treated conservatively with opioids, bisphosphonates, bracing, and radiation therapy. Vertebral augmentation has been used the last three decades as a minimally invasive treatment option for vertebral compression fractures, but the evidence base for the efficacy is weak.

We describe a trial assessing the impact of vertebroplasty on clinical outcome in the treatment of MM patients with painful vertebral fractures.

Methods:

100 MM patients with painful vertebral fractures will be randomized in a prospective, single blinded, multicenter, clinical trial where patients are randomized to either usual care or usual care supplemented with vertebroplasty with a possibility of crossover 4 weeks after randomization. The primary outcome will be change in Oswestry Disability Index at 4 weeks.

Analysis:

Primary and secondary outcomes are assessed at baseline and at 4, 8, 26 and 52 weeks. Categorical data will be presented by means of frequencies and related percentages; continuous data will be displayed by means of descriptive statistics.

Ethics and dissemination:

The study has been evaluated by the Regional Committees on Health Research for Southern Denmark (S-20200075) and notified and approved by the Region of Southern Denmark and listed in the internal record, journal no. 20/22355. All participants provide consent. The protocol will follow the SPIRIT (Standard Protocol Items for Randomized Trials) statement. The Danish Myeloma Patient Organization supports the study. Findings will be disseminated in peer-reviewed publications and presented at national and international conferences. Trial registration number NCT04533217.

Strengths and limitations of this study:

Strengths

- Ramdomized controlled trial
- Nationwide study (participation of all hematologic departments in Denmark

Limitations

- Single-blinded randomization

Introduction:

Multiple myeloma is a plasma cell cancer in the bone marrow associated with activated osteoclastic bone degradation, lack of bone formation, and pathological fractures with protracted healing due to inhibited osteoblast function (1, 2). These biological changes are induced by the expansion of proliferating malignant plasma cells in the bone marrow (2).

The incidence is about 7 per 100,000 in Denmark, equivalent to approximately about 400 new cases a year (3). At the time of diagnosis pathological fractures are present in about 1/3 of the patients and a greater proportion develop fractures during the course of the disease (3, 4). The annual risk of spontaneous spinal fractures is 15-24 % despite bisphosphonate prophylaxis (3).

Although multiple myeloma is incurable, survival and prognosis has improved significantly over the last two decades (5). This justifies and necessitates increased focus on optimal fracture treatment to ensure good physical function and quality of life for the patients' remaining lifetime. Vertebral fractures are very painful and affect patients' daily function (2, 4, 6). Traditionally, the fracture pain is treated conservatively with opioids, bisphosphonates, bracing, and radiation therapy (3).

Vertebroplasty was first reported in the late 80s for the treatment of vertebral hemangiomas and osteolytic vertebral tumors (7). Under fluoroscopy, a Jamshidi needle is inserted through the pedicles (8) into the vertebral body. Polymethylmethacrylate is injected into the vertebral body, still under imaging guidance, to minimize extravasation into the spinal canal. Vertebral augmentation, including percutaneous vertebroplasty (PVP) and kyphoplasty (KP), has been used as a minimally invasive treatment option for vertebral compression fractures (VCFs) (4, 9, 10).

The procedure is considered to be well suited for treatment of patients with malignant spine disease as it can be done under local anaesthesia, provides rapid pain relief (11, 12), and prevents prolonged immobilization. PVP and KP provide stability within the fractured vertebral body by preventing microscopic movement and macroscopic collapse. It has also been suggested that polymethylmethacrylate (PMMA) bone cement induces exothermic reactions that are toxic to nerve endings and therefore provide pain relief (13).

Two randomized trials and a later review was published in 2009 (14, 15) and 2018 (16), respectively, regarding vertebral augmentation. The two trials were done in different patient populations, namely patients with benign osteoporosis. The disappointing outcome of these two trials has unfortunately led to uncertainties regarding the effect in other indications, such as metastatic disease.

In 2019, a systematic review on vertebral augmentation of cancer related painful vertebral lesions was published (12). This review included not only randomized studies, but also other publications involving vertebral augmentation techniques. In all 87 studies were included in the study and meta-analysis was performed. The review demonstrated clinically relevant improvement in pain and health related quality of life.

A recent Danish national clinical guideline (17, 18) on painful vertebral compression fractures, caused by cancer including multiple myeloma, recommends percutaneous vertebroplasty as pain management. The evidence is mainly based on two randomized studies: The CAFE study by Berenson et al. (19) including 49 patients suffering from multiple myeloma randomized between kyphoplasty and conservative treatment and the study by Audat et al. (20) randomizing 27 patients to either conventional therapy or conventional therapy adding vertebroplasty or kyphoplasty. The recommendations in the Danish guideline are weak due to risk of bias, including lack of blinding in randomized studies. In addition, the CAFE study was further

downgraded for indirectness as the study contains a population consisting predominantly of patients with primary cancer other than multiple myeloma.

Rationale for this study

Evidence-based guidelines for supplementing chemotherapy with vertebral augmentation when treating multiple myeloma patients with pathological fractures are lacking. The overall evidence from the two randomized controlled trials comparing supplementary vertebral augmentation to usual care is of low quality (17, 18) and requires more robust investigations regarding the role of vertebroplasty in the treatment algorithm of multiple myeloma with spinal involvement.

For that reason, we decided to perform a single blinded, randomized, controlled trial comparing usual care versus usual care supplemented with vertebroplasty in treating multiple myeloma patients with pathological fractures.

Methods and analysis:

Purpose

To examine the efficacy of PVP in multiple myeloma patients with vertebral compression fracture, based on improvement in patient reported outcome

Patient and public involvement

The initial idea behind this project was created by a patient appointed by the Danish Cancer Society to participate in the working group behind the National Clinical Guideline on percutaneous vertebroplasty for the palliative treatment of malignant vertebral compression fractures caused by multiple myeloma (17, 18). She urged the group members to set up a study to provide high-quality evidence needed to recommend the treatment.
The study design has been developed in collaboration with the Danish Myeloma Patients' Association "Dansk Myelomatose Forening".

Study design

The study design is a randomized, prospective, single blinded, multicentre, clinical trial where patients are randomized to either usual care or usual care supplemented with vertebroplasty with a possibility of crossover 4 weeks after randomization. It is designed in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines (21).

The trial design is illustrated in Figure 1 and trial timeline in Figure 2.

Trial sites

The trial is a multi-centre trial with the participation of all Danish haematological departments. The departments are as follows:

- Department of Haematology, Aalborg University Hospital
- Department of Haematology, Aarhus University Hospital
- Department of Haematology, Holstebro Regional Hospital
- Department of Haematology, University Hospital of Southern Denmark, Esbjerg

- Department of Haematology, University Hospital of Southern Denmark, Vejle
- Department of Haematology, Zealand University Hospital, Roskilde
- Department of Haematology, Herlev Hospital
- Department of Haematology, Rigshospitalet, Copenhagen
- Department of Haematology, Odense University Hospital

Participating spine surgical units are as follows:

- Department of Orthopaedic Surgery, Rigshospitalet
- Spine Center of Southern Denmark, Lillebaelt Hospital, Middelfart
- Department of Orthopaedic Surgery, Aarhus University Hospital

Study population

Study subjects will be recruited from patients diagnosed with multiple myeloma assessed and found eligible for vertebroplasty due to painful vertebral compression fractures. Possible candidates will be identified at the departments of haematology where the patients are treated for their disease.

Inclusion criteria:

- Patients diagnosed with symptomatic multiple myeloma and spinal compression fractures
- Fractures verified on MRI- or CT-scan (OF-type 1-4) between and including Th6 and L5
- Fracture involves 4 vertebral body levels or less
- PVP can be done in one session
- Possible indication for vertebroplasty
- Back pain score measured on a visual analogue scale (VAS) ≥ 5
- Age ≥ 18 years
- Able to understand and read Danish
- Written informed consent
- Relevant pain started ≤ 3 months prior to inclusion

Exclusion criteria:

- Contra-indications for spine surgery:
  - Platelets < 30 mia/l
  - OF-type 5 and Pincer-type
- Bedridden
- Presence of neurologic deficit
- Psychological or psychiatric disorder that is expected to interfere with compliance

Randomization:

Prior to randomization, the patients will be divided into two groups, stratifying between patients with known multiple myeloma with a newly diagnosed spinal fracture and relevant pain ≤ 3 months prior to inclusion and patients with newly diagnosed multiple myeloma with relevant pain associated to a spine fracture initiating ≤ 3 months prior to the diagnosis.

Furthermore, to ensure balanced control and intervention groups the included patients at randomization will be stratified according to 1) planned PVP of 1 vs. 2-4 levels, and 2) former vertebral fractures that are not planned treated with PVP.

The patients in each subgroup will be randomized to one of two parallel treatment arms allocated in a 1:1 ratio. Sealed numbered envelopes containing electronically randomized group allocations will be prepared prior to trial commencement. Following informed consent, a sealed pre-randomized envelope will be allocated by the study nurse and the patient label affixed to the envelope.

Control Treatment

The patients will receive the treating departments' standard care, following the Danish National Guidelines (22).

Investigational treatment:

The investigational treatment arm will be the group receiving supplementary vertebroplasty of the vertebral compression fractures.

Outcomes

Primary outcome:

- Back-specific Functional Status using Oswestry Disability Index (ODI) at time of randomization and 4-weeks post-randomization. The ODI assesses pain-related physical functioning in spinal disorders. (23). The ODI contains 10 questions about how back pain affects the ability to manage everyday life. These are summarized in a score ranging from 0 to 100. Higher scores reflect worse pain and disability.

Secondary outcomes:

- Self-reported average pain intensity (VAS) during the preceding 24 hours at enrolment, and weekly in 12 weeks after enrolment. The rating scale from 0 to 10, with higher scores indicating more severe pain.
- Health Related Quality of Life (HRQL) on the EuroQol 5-dimension 3-level (EQ-5D-3L) (24). EQ-5D-3L is a widely used generic measure of HRQL. It evaluates five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression, each with three levels of severity. The resulting health is converted into a single summary index with a total score ranging from –0.6 to 1, where 1 corresponds to perfect health.
- HRQL according to the FACT-G, EORTC QLQ C30 and MY20 questionnaires.
- Long-term stability of the treated vertebral bone (e.g., fracture, including re-fracture, vertebral body height, or malalignment) as measures by long-standing radiographs.
- Questionnaire about general health services, including questions about e.g. sick leave and home care.

Data collection:

After informed consent is obtained from the patient, the hematologist will fill out screening forms regarding disease stage, lines of treatment, current disease status, bisphosphonate status, and pain relief

treatment. The patient will complete surveys including the ODI, VAS pain score and QoL. Time points for data collection is presented in Table 1.

Sample size

The sample size calculations for this study is a challenge, as there are very few published papers reporting outcomes following vertebroplasty on vertebral fractures due to multiple myeloma. The sample size calculations are thus based on results from treating osteoporotic vertebral fractures with vertebroplasty. To obtain a minimal clinically relevant improvement of at least 15 points on the Oswestry Disability Index, we need to enrol 44 patients in each group. To account for approximately 10 % dropout we aim to enroll 100 patients.

$N = (Z(crit) + Z(pwr))x\ s^2 * 2 / MIREDIF^2)$,

with a mean minimum difference between groups of 15, SD=25, two tailed p=0.05, assuming a normal distribution with Z (crit)=1.96, Z (pwr)=0.80

Analyses:

Baseline characteristics:

The baseline characteristics of patients and operative details including complications will be recorded.

Statistical analysis:

Data will be analyzed according to their type using STATA, i.e.; categorical data will be presented by means of frequencies and related percentages; continuous data will be displayed by means of descriptive statistics (mean, standard deviation, number of observations, minimum, median, maximum).

The primary outcome measure will be improvement in ODI scores at 4 weeks after initiation of treatment. Repeated measures ANCOVA with baseline ODI, VAS pain, EQ-5D-3L, and number of levels involved will be performed.

Ethics and dissemination:

The study will be performed according to the Declaration of Helsinki and the Danish Code of Conduct for Research Integrity (25). The study has been evaluated by the Regional Committees on Health Research for Southern Denmark (S-20200075) and has been notified to and approved by the Region of Southern Denmark and listed in the internal record, journal no. 20/22355, and permission to extract data from hospital records will be obtained from the patients. Consent to use patient-reported information from the DaneSpine database is obtained electronically prior to patients completing the questionnaires. Patients who do not consent will not be included.

Findings will be disseminated in peer-reviewed publications and presented at national and international conferences following guidance from the SPIRIT guidelines.

Discussion:

This article presents a protocol for a single blinded randomized controlled trial comparing usual care versus usual care supplemented with vertebroplasty in treating multiple myeloma patients with painful vertebral

fractures. Further prospectively registered data on health, social variables and patient-reported outcomes are collected.

As the median survival is significantly better for MM patients than for patients with spinal metastases associated with solid cancers it justifies and necessitates increased focus on optimal fracture treatment in MM patients specifically. An increasing number of MM patients experience more than 5 years, even more than 10 years survival, which highlights the importance of ensuring good physical function and quality of life for the patients.

The outcome of the proposed project will impact future national and international guidelines on the treatment regimen for patients with multiple myeloma and vertebral fractures.

The main strength of this study is the randomized treatment assignments, reducing the risk of selection bias.

Author contributorship statement and conflict of interest:

- Line Adsbøll Wickstrøm: PhD student, investigator
- Leah Y. Carreon: Co-supervisor
- Thomas Lund: Consultant, mediation of contact to the Danish Myeloma Patients' Association "Dansk Myelomatose Forening"
- Niels Abildgaard: Co-supervisor, mediation of contact to the Danish hematologic departments
- Marianne Dyrby Lorenzen: Administration
- Mikkel Ø. Andersen: Principal supervisor

All authors have participated in the design and organization of the study. Authors have no affiliation apart from stated, and have no conflicts of interests.

Funding:

Expences, including salary, tuition fees and miscellaneous is applied for from the following:

- Faculty of Health Sciences, University of Southern Denmark
- Research means, Region of Southern Denmark or Hospital Lillebaelt Research Committee
- External funding

No funding has yet been collected.

Datasharing:

When the project is terminated, data from the project database will be archived at the Danish National Archives, and the research group will save an anonymized version of patient information

from the database. After the project results are published, interested researchers will have two options for re-use of the data: upon receiving required permits they may apply for data extracts from DaneSpine and from the Danish National Archives – or they may receive anonymized raw data from DaneSpine and the project data base from us. This way, data will be Findable, Accessible, Interoperable and Reusable.

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Tabel 1 Datacollection - timeline

Clinical tools	At incl.	1 week post-incl.	2 w	3 w	4 w	5 w	6 w	7 w	8 w	9 w	10 w	11 w	12 w	26 w	52 w
ODI	x				x				x					x	x
VAS leg and back	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
EQ-5D	x				x				x					x	x
FACT-G	x												x		x
EORTC QLQ-C30	x												x		x
EORTC QLQ-MY20	x												x		x

X-ray	x											x		x
MRI	x													
Biopsy	x													

First thank you for the opportunity to revise our manuscript and secondly to the reviewers for their time and good suggestions to improve the paper and trial.

Reviewer: 1

Dr. Andrés Romero, National Cancer Institute Mexico City

Comments to the Author:

First, excellent paper. I would recommend following complications like the risk of new fractures (already described for myeloma patients) and explain the usual care your patients are receiving (especially radiotherapy) because of the crossover

It is our intention to record any complications such as re-fractures and complications related to the surgical procedure. This has been clarified in the paper.

The usual care is following the Danish national guidelines. Reference has been added to the paper. This reference includes recommendations concerning radiotherapy.

Reviewer: 2

Dr. Reade De Leacy, Icahn School of Medicine at Mount Sinai

Comments to the Author:

I have some concerns regarding the enrollment numbers calculated. The authors admit that they had difficulty identifying an appropriate number of enrollments and have based the calculation derived osteoporotic compression fracture literature which is a clearly different disease process and may influence outcomes. This seems like a concerning assumption upon which to based an important study. Both of the 2009 papers were dramatically underpowered to show a treatment effect with their enrollment targets and amongst other issues led to both of these papers also being downgraded to Level 2 evidence. I hope that this has been taken into account when planning this important study.

The power calculation has been a major concern, as it would be a disaster to conduct a nationwide RCT supported by the Danish National Health Board and end up with inconclusive results.

We agree with the reviewer regarding the two 2009 papers. In these papers, there were many issues concerning the inclusion of patients such as enrolling patients with fractures up to 12 months' duration, including patients without MRI and VAS-scores as low as three.

The power calculation in the present study is based on results in a mixed osteoporotic and malignant population published in the annual reports from DaneSpine, the Danish National Spine database (http://drks.ortopaedi.dk/wp-content/uploads/2020/06/%C3%85rsrapport-DRKS-2019-version-3.0-1.pdf) and results likewise based on DaneSpine regarding results treating mixed malignant patients (Dan Med J 2018;65(10):A5509). We firmly believe the present study is adequately powered.

There is no description of the inclusion criteria for the type of compression fracture in terms of AO, Gennant or Magerl classification or the degree of height loss of the target vertebral body tolerated at presentation. Furthermore including patient with chronic compression fractures out to 3 months adds heterogeneity to the patient population which we have seen in prior augmentation trials and further concerns me regarding powering for the primary outcome. Are patients to be excluded with baseline LBP or spondylosis or a history of prior back surgery ???

When classifying the fractures in the present study we use the osteoporotic fracture classification (OF classification), this has been clarified in the paper.

We understand the reviewer's concerns about including patients with chronic compression fractures out to 3 months is relevant. However, this is more relevant when treating osteoporotic fractures as one expects spontaneous healing in contrast to malignant lesions. By only including patients diagnosed with symptomatic multiple myeloma and a back pain score measured on a visual analogue scale (VAS) ≥ 5 we believe the cohort in the present study is homogenous.

Previous spine surgery is not a contra indication for inclusion and as stated in the inclusion criteria relevant pain started ≤ 3 months prior to inclusion excludes severe preexisting spine pathology.

This is an important question and could be a valuable trial. More clarity on its design and refining the inclusion and exclusion criteria to identify a more mechanically homogenous patient population upon which to test this important hypothesis is needed.

The inclusion and exclusion criteria have been clarified.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

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Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	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	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	8
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 8

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	n/a
Roles and responsibilities: sponsor and funder	#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	n/a
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	n/a
Objectives	#7	Specific objectives or hypotheses	n/a
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, non-inferiority, exploratory)	4
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	4-5

		collected. Reference to where list of study sites can be obtained	
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)	5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-6
Interventions: modifications	#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)	5-6
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
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	6
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)	12, 14
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	6-7

Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	n/a
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	5-6
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	5-6
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5-6
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5-6
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	5-6
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements,	13

		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	
Data collection plan: retention	#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	13
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	13
Statistics: outcomes	#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	7
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	7
Statistics: analysis population and missing data	#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)	7
Methods: Monitoring			
Data monitoring: formal committee	#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	8
Data monitoring: interim analysis	#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	n/a

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	n/a
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	7
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)	n/a
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	7
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	8
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	n/a
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	n/a

		participation	
Dissemination policy: trial results	#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	7
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a