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

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4 Vertebroplasty in multiple myeloma patients with vertebral compression fractures:
5 Protocol for a single-blind randomized controlled trial.
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10 Line Adsbøll Wickstrøm¹, MD, Leah Y. Carreon, MD, MSc^{1,2},
11 Thomas Lund, MD, PhD³, Niels Abildgaard, MD, DMSc³, Marianne Dyrby Lorenzen¹, RN,MCN,
12 Mikkel Ø. Andersen, MD^{1,2}
13
14
15
16
17

18 Author affiliations:
19

- 20
21 1. Spine Surgery & Research, Spinecenter of Southern Denmark, Lillebaelt HospitalMiddelfart
22
23 2. Department of Regional Health Research, Faculty of Health Services, University of Southern
24 Denmark, Odense, Denmark
25
26 3. Department of Haematology, Odense University Hospital, Odense, Denmark
27
28
29
30
31

32 Corresponding author:
33

34 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*

- Randomized 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

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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.

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

11 *Control Treatment*

12
13 The patients will receive the treating departments' standard care.

15 *Investigational treatment:*

16
17 The investigational treatment arm will be the group receiving supplementary vertebroplasty of the
18 vertebral compression fractures.

20 *Outcomes*

22 *Primary outcome:*

- 23
24 • Back-specific Functional Status using Oswestry Disability Index (ODI) at time of randomization and
25 4-weeks post-randomization. The ODI assesses pain-related physical functioning in spinal disorders.
26 (22). The ODI contains 10 questions about how back pain affects the ability to manage everyday
27 life. These are summarized in a score ranging from 0 to 100. Higher scores reflect worse pain and
28 disability.

31 *Secondary outcomes:*

- 32
33 • Self-reported average pain intensity (VAS) during the preceding 24 hours at enrolment, and weekly
34 in 12 weeks after enrolment. The rating scale from 0 to 10, with higher scores indicating more
35 severe pain.
- 36
37 • Health Related Quality of Life (HRQL) on the EuroQol 5-dimension 3-level (EQ-5D-3L) (23). EQ-5D-3L
38 is a widely used generic measure of HRQL. It evaluates five dimensions: mobility, self-care, usual
39 activities, pain/discomfort and anxiety/depression, each with three levels of severity. The resulting
40 health is converted into a single summary index with a total score ranging from -0.6 to 1, where 1
41 corresponds to perfect health.
- 42
43 • HRQL according to the FACT-G, EORTC QLQ C30 and MY20 questionnaires.
- 44
45 • Long-term stability of the treated vertebral bone (e.g., fracture, vertebral body height, or
46 malalignment) as measures by long-standing radiographs.
- 47
48 • Questionnaire about general health services, including questions about e.g. sick leave and home
49 care.

50 *Data collection:*

51
52 After informed consent is obtained from the patient, the hematologist will fill out screening forms
53 regarding disease stage, lines of treatment, current disease status, bisphosphonate status, and pain relief
54 treatment. The patient will complete surveys including the ODI, VAS pain score and QoL. Time points for
55 data collection is presented in Table 1.

57 *Sample size*

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

$$11 \quad N = (Z(\text{crit}) + Z(\text{pwr}))^2 \times s^2 / \text{MIREDF}^2,$$

12
13 with a mean minimum difference between groups of 15, SD=25, two tailed p=0.05, assuming a normal
14 distribution with Z (crit)=1.96, Z (pwr)=0.80
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16 *Analyses:*

17 *Baseline characteristics:*

18 The baseline characteristics of patients and operative details will be recorded.
19

20 *Statistical analysis:*

21 Data will be analyzed according to their type using STATA, i.e.; categorical data will be presented by means
22 of frequencies and related percentages; continuous data will be displayed by means of descriptive statistics
23 (mean, standard deviation, number of observations, minimum, median, maximum).
24

25 The primary outcome measure will be improvement in ODI scores at 4 weeks after initiation of treatment.
26 Repeated measures ANCOVA with baseline ODI, VAS pain, EQ-5D-3L, and number of levels involved will be
27 performed.
28

29 *Ethics and dissemination:*

30 The study will be performed according to the Declaration of Helsinki and the Danish Code of Conduct for
31 Research Integrity (24). The study has been evaluated by the Regional Committees on Health Research for
32 Southern Denmark (S-20200075), and has been notified to and approved by the Region of Southern
33 Denmark and listed in the internal record, journal no. 20/22355. , and permission to extract data from
34 hospital records will be obtained from the patients. Consent to use patient-reported information from the
35 DaneSpine database is obtained electronically prior to patients completing the questionnaires. Patients
36 who do not consent will not be included.
37

38 Findings will be disseminated in peer-reviewed publications and presented at national and international
39 conferences following guidance from the SPIRIT guidelines.
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44 **Discussion:**

45 This article presents a protocol for a single blinded randomized controlled trial comparing usual care versus
46 usual care supplemented with vertebroplasty in treating multiple myeloma patients with painful vertebral
47 fractures. Further prospectively registered data on health, social variables and patient-reported outcomes
48 are collected.
49

50 As the median survival is significantly better for MM patients than for patients with spinal metastases
51 associated with solid cancers it justifies and necessitates increased focus on optimal fracture treatment in
52 MM patients specifically. An increasing number of MM patients experience more than 5 years, even more
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4 than 10 years survival, which highlights the importance of ensuring good physical function and quality of
5 life for the patients.
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7 The outcome of the proposed project will impact future national and international guidelines on the
8 treatment regimen for patients with multiple myeloma and vertebral fractures.
9

10 The main strength of this study is the randomized treatment assignments, reducing the risk of selection
11 bias.
12
13

14 15 **Author contributorship statement and conflict of interest:**

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

24
25
26 All authors have participated in the design and organization of the study. Authors have no affiliation
27 apart from stated, and have no conflicts of interests.
28
29

30 31 **Funding:**

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

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

36
37 No funding has yet been collected.
38
39

40 41 **Datasharing:**

42
43 When the project is terminated, data from the project database will be archived at the Danish
44 National Archives, and the research group will save an anonymized version of patient information
45 from the database. After the project results are published, interested researchers will have two
46 options for re-use of the data: upon receiving required permits they may apply for data extracts
47 from DaneSpine and from the Danish National Archives – or they may receive anonymized raw
48 data from DaneSpine and the project data base from us. This way, data will
49 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														

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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		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

1	Roles and	#5b	Name and contact information for the trial sponsor	n/a
2	responsibilities:			
3	sponsor contact			
4	information			
5				
6				
7				
8	Roles and	#5c	Role of study sponsor and funders, if any, in study design;	n/a
9	responsibilities:		collection, management, analysis, and interpretation of	
10	sponsor and funder		data; writing of the report; and the decision to submit the	
11			report for publication, including whether they will have	
12			ultimate authority over any of these activities	
13				
14				
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16				
17	Roles and	#5d	Composition, roles, and responsibilities of the coordinating	n/a
18	responsibilities:		centre, steering committee, endpoint adjudication	
19	committees		committee, data management team, and other individuals	
20			or groups overseeing the trial, if applicable (see Item 21a	
21			for data monitoring committee)	
22				
23				
24				
25	Introduction			
26				
27				
28	Background and	#6a	Description of research question and justification for	3-4
29	rationale		undertaking the trial, including summary of relevant	
30			studies (published and unpublished) examining benefits	
31			and harms for each intervention	
32				
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34				
35	Background and	#6b	Explanation for choice of comparators	n/a
36	rationale: choice of			
37	comparators			
38				
39				
40	Objectives	#7	Specific objectives or hypotheses	n/a
41				
42				
43	Trial design	#8	Description of trial design including type of trial (eg,	4
44			parallel group, crossover, factorial, single group),	
45			allocation ratio, and framework (eg, superiority,	
46			equivalence, non-inferiority, exploratory)	
47				
48				
49				
50	Methods:			
51	Participants,			
52	interventions, and			
53	outcomes			
54				
55				
56				
57	Study setting	#9	Description of study settings (eg, community clinic,	4-5
58			academic hospital) and list of countries where data will be	
59				
60				

1		collected. Reference to where list of study sites can be	
2		obtained	
3			
4	Eligibility criteria	#10 Inclusion and exclusion criteria for participants. If	5
5		applicable, eligibility criteria for study centres and	
6		individuals who will perform the interventions (eg,	
7		surgeons, psychotherapists)	
8			
9			
10			
11	Interventions:	#11a Interventions for each group with sufficient detail to allow	5-6
12	description	replication, including how and when they will be	
13		administered	
14			
15			
16			
17	Interventions:	#11b Criteria for discontinuing or modifying allocated	5-6
18	modifications	interventions for a given trial participant (eg, drug dose	
19		change in response to harms, participant request, or	
20		improving / worsening disease)	
21			
22			
23			
24	Interventions:	#11c Strategies to improve adherence to intervention protocols,	n/a
25	adherence	and any procedures for monitoring adherence (eg, drug	
26		tablet return; laboratory tests)	
27			
28			
29	Interventions:	#11d Relevant concomitant care and interventions that are	n/a
30	concomitant care	permitted or prohibited during the trial	
31			
32			
33	Outcomes	#12 Primary, secondary, and other outcomes, including the	6
34		specific measurement variable (eg, systolic blood	
35		pressure), analysis metric (eg, change from baseline, final	
36		value, time to event), method of aggregation (eg, median,	
37		proportion), and time point for each outcome. Explanation	
38		of the clinical relevance of chosen efficacy and harm	
39		outcomes is strongly recommended	
40			
41			
42			
43			
44			
45	Participant timeline	#13 Time schedule of enrolment, interventions (including any	12, 14
46		run-ins and washouts), assessments, and visits for	
47		participants. A schematic diagram is highly recommended	
48		(see Figure)	
49			
50			
51			
52	Sample size	#14 Estimated number of participants needed to achieve study	6-7
53		objectives and how it was determined, including clinical	
54		and statistical assumptions supporting any sample size	
55		calculations	
56			
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1	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	n/a
2				
3				
4				
5	Methods:			
6	Assignment of			
7	interventions (for			
8	controlled trials)			
9				
10				
11				
12	Allocation: sequence	#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
13	generation			
14				
15				
16				
17				
18				
19				
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21				
22				
23				
24	Allocation	#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
25	concealment			
26	mechanism			
27				
28				
29				
30				
31	Allocation:	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5-6
32	implementation			
33				
34				
35				
36	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5-6
37				
38				
39				
40				
41				
42	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	5-6
43	emergency unblinding			
44				
45				
46				
47	Methods: Data			
48	collection,			
49	management, and			
50	analysis			
51				
52				
53				
54	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
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1		training of assessors) and a description of study	
2		instruments (eg, questionnaires, laboratory tests) along	
3		with their reliability and validity, if known. Reference to	
4		where data collection forms can be found, if not in the	
5		protocol	
6			
7			
8			
9	Data collection plan:	#18b Plans to promote participant retention and complete	13
10	retention	follow-up, including list of any outcome data to be	
11		collected for participants who discontinue or deviate from	
12		intervention protocols	
13			
14			
15			
16	Data management	#19 Plans for data entry, coding, security, and storage,	13
17		including any related processes to promote data quality	
18		(eg, double data entry; range checks for data values).	
19		Reference to where details of data management	
20		procedures can be found, if not in the protocol	
21			
22			
23			
24	Statistics: outcomes	#20a Statistical methods for analysing primary and secondary	7
25		outcomes. Reference to where other details of the	
26		statistical analysis plan can be found, if not in the protocol	
27			
28			
29			
30	Statistics: additional	#20b Methods for any additional analyses (eg, subgroup and	7
31	analyses	adjusted analyses)	
32			
33			
34	Statistics: analysis	#20c Definition of analysis population relating to protocol non-	7
35	population and	adherence (eg, as randomised analysis), and any	
36	missing data	statistical methods to handle missing data (eg, multiple	
37		imputation)	
38			
39			
40			
41	Methods: Monitoring		
42			
43	Data monitoring:	#21a Composition of data monitoring committee (DMC);	8
44	formal committee	summary of its role and reporting structure; statement of	
45		whether it is independent from the sponsor and competing	
46		interests; and reference to where further details about its	
47		charter can be found, if not in the protocol. Alternatively,	
48		an explanation of why a DMC is not needed	
49			
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54	Data monitoring:	#21b Description of any interim analyses and stopping	n/a
55	interim analysis	guidelines, including who will have access to these interim	
56		results and make the final decision to terminate the trial	
57			
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1	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
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8	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
9				
10				
11				
12				
13	Ethics and			
14	dissemination			
15				
16				
17	Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	7
18				
19				
20				
21	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
22				
23				
24				
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27				
28	Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
29				
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32				
33				
34	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
35				
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39	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
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46	Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	8
47				
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50	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
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56	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
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		participation	
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3	Dissemination policy:	#31a Plans for investigators and sponsor to communicate trial	7
4	trial results	results to participants, healthcare professionals, the public,	
5		and other relevant groups (eg, via publication, reporting in	
6		results databases, or other data sharing arrangements),	
7		including any publication restrictions	
8			
9			
10			
11	Dissemination policy:	#31b Authorship eligibility guidelines and any intended use of	n/a
12	authorship	professional writers	
13			
14			
15	Dissemination policy:	#31c Plans, if any, for granting public access to the full protocol,	n/a
16	reproducible research	participant-level dataset, and statistical code	
17			
18			
19	Appendices		
20			
21	Informed consent	#32 Model consent form and other related documentation	n/a
22	materials	given to participants and authorised surrogates	
23			
24			
25	Biological specimens	#33 Plans for collection, laboratory evaluation, and storage of	n/a
26		biological specimens for genetic or molecular analysis in	
27		the current trial and for future use in ancillary studies, if	
28		applicable	
29			
30			
31			

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 35 [Penelope.ai](#)
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Vertebroplasty in multiple myeloma patients with vertebral compression fractures: Protocol for a single-blind randomized controlled trial.

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Manuscript ID	bmjopen-2020-045854.R1
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Primary Subject Heading:	Surgery
Secondary Subject Heading:	Oncology, Haematology (incl blood transfusion)
Keywords:	Spine < ORTHOPAEDIC & TRAUMA SURGERY, Myeloma < HAEMATOLOGY, ONCOLOGY

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4 Vertebroplasty in multiple myeloma patients with vertebral compression fractures:
5 Protocol for a single-blind randomized controlled trial.
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10 Line Adsbøll Wickstrøm¹, MD, Leah Y. Carreon, MD, MSc^{1,2},
11 Thomas Lund, MD, PhD³, Niels Abildgaard, MD, DMSc³, Marianne Dyrby Lorenzen¹, RN, MCN,
12 Mikkel Ø. Andersen, MD^{1,2}
13
14
15
16
17
18

19 Author affiliations:

- 20
21 1. Spine Surgery & Research, Spinecenter of Southern Denmark, Lillebaelt HospitalMiddelfart
22
23 2. Department of Regional Health Research, Faculty of Health Services, University of Southern
24 Denmark, Odense, Denmark
25
26 3. Department of Haematology, Odense University Hospital, Odense, Denmark
27
28
29
30
31

32 Corresponding author:

33
34 Line Adsbøll Wickstrøm, line.adsboll.wickstrom@rsyd.dk
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Version 1.2 – 11.03.2021

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*

- Randomized 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

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4 downgraded for indirectness as the study contains a population consisting predominantly of patients with
5 primary cancer other than multiple myeloma.
6
7

8 *Rationale for this study*

9
10 Evidence-based guidelines for supplementing chemotherapy with vertebral augmentation when treating
11 multiple myeloma patients with pathological fractures are lacking. The overall evidence from the two
12 randomized controlled trials comparing supplementary vertebral augmentation to usual care is of low
13 quality (17, 18) and requires more robust investigations regarding the role of vertebroplasty in the
14 treatment algorithm of multiple myeloma with spinal involvement.
15
16

17 For that reason, we decided to perform a single blinded, randomized, controlled trial comparing usual care
18 versus usual care supplemented with vertebroplasty in treating multiple myeloma patients with
19 pathological fractures.
20
21
22

23 **Methods and analysis:**

24 *Purpose*

25
26 To examine the efficacy of PVP in multiple myeloma patients with vertebral compression fracture, based on
27 improvement in patient reported outcome
28
29

30 *Patient and public involvement*

31
32 The initial idea behind this project was created by a patient appointed by the Danish Cancer Society to
33 participate in the working group behind the National Clinical Guideline on percutaneous vertebroplasty for
34 the palliative treatment of malignant vertebral compression fractures caused by multiple myeloma (17, 18).
35 She urged the group members to set up a study to provide high-quality evidence needed to recommend
36 the treatment.
37

38 The study design has been developed in collaboration with the Danish Myeloma Patients' Association
39 "Dansk Myelomatose Forening".
40

41 *Study design*

42
43 The study design is a randomized, prospective, single blinded, multicentre, clinical trial where patients are
44 randomized to either usual care or usual care supplemented with vertebroplasty with a possibility of
45 crossover 4 weeks after randomization. It is designed in accordance with the SPIRIT (Standard Protocol
46 Items: Recommendations for Interventional Trials) guidelines (21).
47

48 The trial design is illustrated in Figure 1 and trial timeline in Figure 2.
49

50 *Trial sites*

51
52 The trial is a multi-centre trial with the participation of all Danish haematological departments. The
53 departments are as follows:
54

- 55 - Department of Haematology, Aalborg University Hospital
- 56 - Department of Haematology, Aarhus University Hospital
- 57 - Department of Haematology, Holstebro Regional Hospital
- 58 - Department of Haematology, University Hospital of Southern Denmark, Esbjerg
- 59
- 60

- 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:
 - o Platelets < 30 mia/l
 - o 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.

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4 Furthermore, to ensure balanced control and intervention groups the included patients at randomization
5 will be stratified according to 1) planned PVP of 1 vs. 2-4 levels, and 2) former vertebral fractures that are
6 not planned treated with PVP.
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9

10 The patients in each subgroup will be randomized to one of two parallel treatment arms allocated in a 1:1
11 ratio. Sealed numbered envelopes containing electronically randomized group allocations will be prepared
12 prior to trial commencement. Following informed consent, a sealed pre-randomized envelope will be
13 allocated by the study nurse and the patient label affixed to the envelope.
14
15

16 *Control Treatment*

17 The patients will receive the treating departments' standard care, following the Danish National Guidelines
18 (22).
19

20 *Investigational treatment:*

21 The investigational treatment arm will be the group receiving supplementary vertebroplasty of the
22 vertebral compression fractures.
23
24
25

26 *Outcomes*

27 Primary outcome:

- 28 • Back-specific Functional Status using Oswestry Disability Index (ODI) at time of randomization and
29 4-weeks post-randomization. The ODI assesses pain-related physical functioning in spinal disorders.
30 (23). The ODI contains 10 questions about how back pain affects the ability to manage everyday
31 life. These are summarized in a score ranging from 0 to 100. Higher scores reflect worse pain and
32 disability.
33
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35

36
37 *Secondary outcomes:*

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

56 After informed consent is obtained from the patient, the hematologist will fill out screening forms
57 regarding disease stage, lines of treatment, current disease status, bisphosphonate status, and pain relief
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4 treatment. The patient will complete surveys including the ODI, VAS pain score and QoL. Time points for
5 data collection is presented in Table 1.
6

7 *Sample size*

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

$$16 N = (Z(\text{crit}) + Z(\text{pwr})) \times s^2 \times 2 / \text{MIREDF}^2,$$

17
18 with a mean minimum difference between groups of 15, SD=25, two tailed p=0.05, assuming a normal
19 distribution with Z (crit)=1.96, Z (pwr)=0.80
20

21 *Analyses:*

22 *Baseline characteristics:*

23
24 The baseline characteristics of patients and operative details including complications will be recorded.
25

26 *Statistical analysis:*

27
28 Data will be analyzed according to their type using STATA, i.e.; categorical data will be presented by means
29 of frequencies and related percentages; continuous data will be displayed by means of descriptive statistics
30 (mean, standard deviation, number of observations, minimum, median, maximum).
31

32
33 The primary outcome measure will be improvement in ODI scores at 4 weeks after initiation of treatment.
34 Repeated measures ANCOVA with baseline ODI, VAS pain, EQ-5D-3L, and number of levels involved will be
35 performed.
36

37 *Ethics and dissemination:*

38
39 The study will be performed according to the Declaration of Helsinki and the Danish Code of Conduct for
40 Research Integrity (25). The study has been evaluated by the Regional Committees on Health Research for
41 Southern Denmark (S-20200075) and has been notified to and approved by the Region of Southern
42 Denmark and listed in the internal record, journal no. 20/22355, and permission to extract data from
43 hospital records will be obtained from the patients. Consent to use patient-reported information from the
44 DaneSpine database is obtained electronically prior to patients completing the questionnaires. Patients
45 who do not consent will not be included.
46

47
48 Findings will be disseminated in peer-reviewed publications and presented at national and international
49 conferences following guidance from the SPIRIT guidelines.
50

51 **Discussion:**

52
53 This article presents a protocol for a single blinded randomized controlled trial comparing usual care versus
54 usual care supplemented with vertebroplasty in treating multiple myeloma patients with painful vertebral
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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.

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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

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4 from the database. After the project results are published, interested researchers will have two
5 options for re-use of the data: upon receiving required permits they may apply for data extracts
6 from DaneSpine and from the Danish National Archives – or they may receive anonymized raw
7 data from DaneSpine and the project data base from us. This way, data will
8 be Findable, Accessible, Interoperable and Reusable.
9
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11 12 13 **References**

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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

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2
3
4 First thank you for the opportunity to revise our manuscript and secondly to the reviewers for their
5 time and good suggestions to improve the paper and trial.
6

7 *Reviewer: 1*

8
9 *Dr. Andrés Romero, National Cancer Institute Mexico City*

10
11 *Comments to the Author:*

12
13 *First, excellent paper. I would recommend following complications like the risk of new fractures (already*
14 *described for myeloma patients) and explain the usual care your patients are receiving (especially*
15 *radiotherapy) because of the crossover*

16
17 It is our intention to record any complications such as re-fractures and complications related to the
18 surgical procedure. This has been clarified in the paper.

19
20 The usual care is following the Danish national guidelines. Reference has been added to the paper.
21 This reference includes recommendations concerning radiotherapy.

22
23 *Reviewer: 2*

24
25 *Dr. Reade De Leacy, Icahn School of Medicine at Mount Sinai*

26
27 *Comments to the Author:*

28
29 *I have some concerns regarding the enrollment numbers calculated. The authors admit that they had*
30 *difficulty identifying an appropriate number of enrollments and have based the calculation derived*
31 *osteoporotic compression fracture literature which is a clearly different disease process and may influence*
32 *outcomes. This seems like a concerning assumption upon which to based an important study. Both of the*
33 *2009 papers were dramatically underpowered to show a treatment effect with their enrollment targets and*
34 *amongst other issues led to both of these papers also being downgraded to Level 2 evidence. I hope that this*
35 *has been taken into account when planning this important study.*

36
37 The power calculation has been a major concern, as it would be a disaster to conduct a nationwide
38 RCT supported by the Danish National Health Board and end up with inconclusive results.

39
40 We agree with the reviewer regarding the two 2009 papers. In these papers, there were many issues
41 concerning the inclusion of patients such as enrolling patients with fractures up to 12 months'
42 duration, including patients without MRI and VAS-scores as low as three.

43
44 The power calculation in the present study is based on results in a mixed osteoporotic and malignant
45 population published in the annual reports from DaneSpine, the Danish National Spine database
46 (<http://drks.ortopaedi.dk/wp-content/uploads/2020/06/%C3%85rsrapport-DRKS-2019-version-3.0-1.pdf>)
47 and results likewise based on DaneSpine regarding results treating mixed malignant patients
48 (Dan Med J 2018;65(10):A5509). We firmly believe the present study is adequately powered.

49
50
51 *There is no description of the inclusion criteria for the type of compression fracture in terms of AO, Gennant*
52 *or Magerl classification or the degree of height loss of the target vertebral body tolerated at presentation.*
53 *Furthermore including patient with chronic compression fractures out to 3 months adds heterogeneity to the*
54 *patient population which we have seen in prior augmentation trials and further concerns me regarding*
55 *powering for the primary outcome. Are patients to be excluded with baseline LBP or spondylosis or a history*
56 *of prior back surgery ???*
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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.

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.

Upload your completed checklist as an extra file when you submit to a journal.

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

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. *BMJ*. 2013;346:e7586

		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

1	Roles and	#5b	Name and contact information for the trial sponsor	n/a
2	responsibilities:			
3	sponsor contact			
4	information			
5				
6				
7				
8	Roles and	#5c	Role of study sponsor and funders, if any, in study design;	n/a
9	responsibilities:		collection, management, analysis, and interpretation of	
10	sponsor and funder		data; writing of the report; and the decision to submit the	
11			report for publication, including whether they will have	
12			ultimate authority over any of these activities	
13				
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16				
17	Roles and	#5d	Composition, roles, and responsibilities of the coordinating	n/a
18	responsibilities:		centre, steering committee, endpoint adjudication	
19	committees		committee, data management team, and other individuals	
20			or groups overseeing the trial, if applicable (see Item 21a	
21			for data monitoring committee)	
22				
23				
24				
25	Introduction			
26				
27				
28	Background and	#6a	Description of research question and justification for	3-4
29	rationale		undertaking the trial, including summary of relevant	
30			studies (published and unpublished) examining benefits	
31			and harms for each intervention	
32				
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35	Background and	#6b	Explanation for choice of comparators	n/a
36	rationale: choice of			
37	comparators			
38				
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40	Objectives	#7	Specific objectives or hypotheses	n/a
41				
42				
43	Trial design	#8	Description of trial design including type of trial (eg,	4
44			parallel group, crossover, factorial, single group),	
45			allocation ratio, and framework (eg, superiority,	
46			equivalence, non-inferiority, exploratory)	
47				
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49				
50	Methods:			
51	Participants,			
52	interventions, and			
53	outcomes			
54				
55				
56				
57	Study setting	#9	Description of study settings (eg, community clinic,	4-5
58			academic hospital) and list of countries where data will be	
59				
60				

1		collected. Reference to where list of study sites can be	
2		obtained	
3			
4	Eligibility criteria	#10 Inclusion and exclusion criteria for participants. If	5
5		applicable, eligibility criteria for study centres and	
6		individuals who will perform the interventions (eg,	
7		surgeons, psychotherapists)	
8			
9			
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11	Interventions:	#11a Interventions for each group with sufficient detail to allow	5-6
12	description	replication, including how and when they will be	
13		administered	
14			
15			
16			
17	Interventions:	#11b Criteria for discontinuing or modifying allocated	5-6
18	modifications	interventions for a given trial participant (eg, drug dose	
19		change in response to harms, participant request, or	
20		improving / worsening disease)	
21			
22			
23			
24	Interventions:	#11c Strategies to improve adherence to intervention protocols,	n/a
25	adherence	and any procedures for monitoring adherence (eg, drug	
26		tablet return; laboratory tests)	
27			
28			
29	Interventions:	#11d Relevant concomitant care and interventions that are	n/a
30	concomitant care	permitted or prohibited during the trial	
31			
32			
33	Outcomes	#12 Primary, secondary, and other outcomes, including the	6
34		specific measurement variable (eg, systolic blood	
35		pressure), analysis metric (eg, change from baseline, final	
36		value, time to event), method of aggregation (eg, median,	
37		proportion), and time point for each outcome. Explanation	
38		of the clinical relevance of chosen efficacy and harm	
39		outcomes is strongly recommended	
40			
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45	Participant timeline	#13 Time schedule of enrolment, interventions (including any	12, 14
46		run-ins and washouts), assessments, and visits for	
47		participants. A schematic diagram is highly recommended	
48		(see Figure)	
49			
50			
51			
52	Sample size	#14 Estimated number of participants needed to achieve study	6-7
53		objectives and how it was determined, including clinical	
54		and statistical assumptions supporting any sample size	
55		calculations	
56			
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1	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	n/a
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4				
5	Methods:			
6	Assignment of			
7	interventions (for			
8	controlled trials)			
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11				
12	Allocation: sequence	#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
13	generation			
14				
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24	Allocation	#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
25	concealment			
26	mechanism			
27				
28				
29				
30				
31	Allocation:	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5-6
32	implementation			
33				
34				
35				
36	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5-6
37				
38				
39				
40				
41				
42	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	5-6
43	emergency unblinding			
44				
45				
46				
47	Methods: Data			
48	collection,			
49	management, and			
50	analysis			
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54	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
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1		training of assessors) and a description of study	
2		instruments (eg, questionnaires, laboratory tests) along	
3		with their reliability and validity, if known. Reference to	
4		where data collection forms can be found, if not in the	
5		protocol	
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9	Data collection plan:	#18b Plans to promote participant retention and complete	13
10	retention	follow-up, including list of any outcome data to be	
11		collected for participants who discontinue or deviate from	
12		intervention protocols	
13			
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15			
16	Data management	#19 Plans for data entry, coding, security, and storage,	13
17		including any related processes to promote data quality	
18		(eg, double data entry; range checks for data values).	
19		Reference to where details of data management	
20		procedures can be found, if not in the protocol	
21			
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23			
24	Statistics: outcomes	#20a Statistical methods for analysing primary and secondary	7
25		outcomes. Reference to where other details of the	
26		statistical analysis plan can be found, if not in the protocol	
27			
28			
29			
30	Statistics: additional	#20b Methods for any additional analyses (eg, subgroup and	7
31	analyses	adjusted analyses)	
32			
33			
34	Statistics: analysis	#20c Definition of analysis population relating to protocol non-	7
35	population and	adherence (eg, as randomised analysis), and any	
36	missing data	statistical methods to handle missing data (eg, multiple	
37		imputation)	
38			
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41	Methods: Monitoring		
42			
43	Data monitoring:	#21a Composition of data monitoring committee (DMC);	8
44	formal committee	summary of its role and reporting structure; statement of	
45		whether it is independent from the sponsor and competing	
46		interests; and reference to where further details about its	
47		charter can be found, if not in the protocol. Alternatively,	
48		an explanation of why a DMC is not needed	
49			
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54	Data monitoring:	#21b Description of any interim analyses and stopping	n/a
55	interim analysis	guidelines, including who will have access to these interim	
56		results and make the final decision to terminate the trial	
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1	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
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8	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
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13	Ethics and dissemination			
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17	Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	7
18				
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21	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
22				
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28	Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
29				
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34	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
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40	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
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46	Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	8
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51	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
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56	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
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		participation	
1			
2			
3	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate trial
4	trial results		results to participants, healthcare professionals, the public,
5			and other relevant groups (eg, via publication, reporting in
6			results databases, or other data sharing arrangements),
7			including any publication restrictions
8			
9			
10			
11	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of
12	authorship		professional writers
13			
14			
15	Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol,
16	reproducible research		participant-level dataset, and statistical code
17			
18			
19	Appendices		
20			
21	Informed consent	#32	Model consent form and other related documentation
22	materials		given to participants and authorised surrogates
23			
24			
25	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of
26			biological specimens for genetic or molecular analysis in
27			the current trial and for future use in ancillary studies, if
28			applicable
29			
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 34 <https://www.goodreports.org/>, a tool made by the [EQUATOR Network](#) in collaboration with
 35 [Penelope.ai](#)
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