PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Vertebroplasty in multiple myeloma patients with vertebral compression fractures: Protocol for a single-blind randomized controlled trial.
AUTHORS	Wickstroem, Line; Carreon, Leah; Lund, Thomas; Abildgaard, Niels; Lorenzen, Marianne; Andersen, Mikkel

VERSION 1 – REVIEW

REVIEWER	Romero, Andrés National Cancer Institute Mexico City
REVIEW RETURNED	29-Dec-2020

GENERAL COMMENTS	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

REVIEWER	De Leacy, Reade Icahn School of Medicine at Mount Sinai
REVIEW RETURNED	26-Jan-2021

GENERAL COMMENTS	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. 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 ??? 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

VERSION 1 – AUTHOR RESPONSE

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.

VERSION 2 – REVIEW

REVIEWER	Romero, Andrés National Cancer Institute Mexico City
REVIEW RETURNED	21-Jul-2021

GENERAL COMMENTS	I did not find any reference regarding complications.