Spinal Medial Branch Nerve Root Block (MBNB) Intervention compared to Standard Care-Vertebroplasty (VP) for the Treatment of Painful Osteoporotic Vertebral Fractures in Hospitalised Older Patients: A Feasibility Study.

Short title: The AVERT (Acute VertEbRal AugmentaTion) Study

**Study Protocol**

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| **IRAS** | **293210** |
| **REC** |

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| 21/YH/0065  |

 |
| **Study ID** | 21HC001 |
| **Funder** | NIHR RfPB-201937 |
| **ISRCTN** | xxxx |

**PROTOCOL VERSION 1.2**

**Date : 07 May 2021**

**This protocol has been designed in line with HRA guidance**

**FULL/LONG TITLE OF THE TRIAL**

Spinal Medial Branch Nerve Root Block Intervention compared to Standard Care-Vertebroplasty for the Treatment of Painful Osteoporotic Vertebral Fractures in Hospitalised Older Patients: A Feasibility Study.

**SHORT STUDY TITLE / ACRONYM**

The AVERT (Acute VertEbRal AugmentaTion) Study

**RESEARCH REFERENCE NUMBERS : xxx**

**IRAS TRIAL REGISTRY NUMBER AND DATE : 293210**

**SPONSOR NUMBER : 21HC001**

**FUNDERS NUMBER: NIHR RfPB-201937**

**ISRCTN NUMBER : xxx**

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**SPONSOR**

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**PROTOCOL VERSION NUMBER AND DATE**

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| **Version No.** | **Date** |
| Version 1.0 | 25 Feb 2021 |
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# SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor’s SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

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| **For and on behalf of the Study Sponsor:** |
| Signature: ...................................................................................................... |  | Date: ....../....../...... |
| Name (please print):...................................................................................................... |  |  |
| Position: ...................................................................................................... |  |  |
| **Chief Investigator:** |
| Signature: ...................................................................................................... |  | Date: ....../....../...... |
| Name: (please print):Professor Opinder Sahota |  |  |
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|  |  |

**TRIAL SUMMARY**

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| --- | --- |
| Trial Title | Spinal Medial Branch Nerve Root Block (MBNB) Intervention compared to Standard Care-Vertebroplasty (VP) for the Treatment of Painful Osteoporotic Vertebral Fractures in Hospitalised Older Patients: A Feasibility Study. |
| Internal ref. no. (or short title) | The AVERT (Acute VertEbRal AugmentaTion) Study |
| Study Design | Randomised controlled feasibility study |
| Study Participants | 30 patients (Quantitative, intervention study)10 patients and 5 clinicians (Qualitative study) |
| Follow up duration | 8 weeksVisit time points (post intervention)Week 1 : face-to-face Week 4: telephone interviewWeek 8: telephone interview |
| Planned Study Period | 18 months |
| Aim | To undertake a preliminary study to inform the design of a future trial to evaluate the clinical and cost effectiveness of MBNB compared to VP spinal surgery.  |
| Eligibility criteria | Inclusion* Patients aged 70 years and over admitted to hospital
* Ambulatory prior to injury
* < 3 weeks from date of injury
* Numeric Rated Pain Scale (NRS) 7 or more on standing
* MRI confirmed oedema at the site of fracture
* Ability to adhere to study procedures and complete follow-up

Exclusion* Chronic back pain requiring opiate use;
* Substantial fracture retropulsion; acute infection , spinal malignancy
* 3 or more acute vertebral fractures;
* Bed bound prior to fracture
* Receiving palliative care
* Lack of capacity and no consultee
* Spinal deformity which contraindicates VP
 |
| Intervention  | Intervention:VP (routine standard care) or MBNB (trial intervention) |
| Outcome measures | Feasibility outcomes: * Number of eligible patients
* Rate of participant recruitment and randomisation
* Reasons why participants are not recruited or randomised
* Rate of participant adherence to randomisation (cross-over) and retention
* Completion of study rates and reasons for non-completion
* Completeness of data
* Non-inferiority margin
* Standard deviation and effect size of potential outcomes for subsequent definitive trial
* Time from randomisation to delivery of the intervention

Outcomes for subsequent definitive trial measured at 1, 4, and 8weeks from the time of intervention* Functional disability as measured by the 24 point Roland Morris Disability Questionnaire (RMDQ)
* Pain as measured by the 0-11 NRS
* Quality of Life as measured by the EQ5D-5L and (where appropriate) proxy EQ5D-5L
* Activities of daily living as measured by the Nottingham Extended Activities of Daily Living (NEADL) scale
* Record of pain medication use (using the opioid dose equivalence table)

 *Time point defined by the point of intervention* |
| Data analysis plan | Data analysis will primarily be descriptive in order to address the aims of the feasibility study. All analyses will be documented in a Statistical Analysis Plan which will be finalised prior to database lock. Findings from the qualitative study will be analysed thematically.  |

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1. **LIST OF ABBREVIATIONS**

AE Adverse Event

AMT Abbreviated Mental Test

CI Chief Investigator

CRF Case Report Form

CFS Clinical Frailty Scale

GCP Good Clinical Practice

ICF Informed Consent Form

ISF Investigator Site File (This forms part of the TMF)

ISRCTN International Standard Randomised Controlled Trials Number

MoCA Montreal – Cognitive Assessment

PIS Participant Information Sheet

QA Quality Assurance

QC Quality Control

RCT Randomised Control Trial

REC Research Ethics Committee

RMDQ Roland Morris Disability Questionnaire

SAE Serious Adverse Event

SOP Standard Operating Procedure

TMF Trial Master File

TMG Trial Management Group

 TSC Trial Steering Committee

1. FUNDING AND SUPPORT IN KIND

|  |  |
| --- | --- |
| **FUNDER(S)** | **FINANCIAL AND NON FINANCIALSUPPORT GIVEN** |
| NIHR Research for Patient Benefit grant | Research Funder |
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# iv. ROLE OF STUDY SPONSOR

Nottingham University Hospitals NHS Trust is the research sponsor for this study.

The study sponsor will monitor the study conduct against applicable regulatory standards. The study sponsor and study funder will have no role in the design, data analysis, interpretation, manuscript writing and dissemination of the results. The sponsor and funders will be consulted for the final decision/s regarding any aspects of this study.

For further information regarding sponsorship, please contact:

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The sponsor did not have direct input in the study conduct, data analysis, data interpretation, manuscript writing and dissemination of findings.

# vi. ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITTEES/GROUPS & INDIVIDUALS

Trial Management Group

Day to day management of the study will be the responsibility of the Trial Management Group (TMG). The TMG will be responsible for ensuring high quality delivery of the trial according to the agreed protocol and timelines. The TMG will include the Chief Investigator (CI), Trial Manager, Trial Statistician, Sponsor Representative and Patient and Public Involvement (PPI) co-applicant. Other members of the research team will be invited to attend as needed. The group will meet regularly.

Trial Steering Committee

The TMG will report to the independent Trial Steering Committee (TSC) who will be responsible for oversight of the trial. Given this is a feasibility trial, we will include the Data Monitoring Committee (DMC) as part of the TSC. The TSC will comprise majority independent membership for voting purposes including 2 clinical experts and a statistician. The TSC will meet in person at the commencement and near the end of the study; and by teleconference in the middle of the study. The TSC will be responsible for reviewing the trial progress, addressing study-related problems and ensuring timely publication of the study findings. They will also be responsible for assessing the safety of the participants, and confidentially reviewing interim data, if considered appropriate.

Patient and Public Involvement Group

The PPI group consist of representatives from the Royal Osteoporosis Society (ROS) Nottingham support group. This group meets regularly and are active in promoting all aspects of bone health. They are also highly supportive of research and some are already involved in ongoing research projects. They have provided input into the grant application and will continue to be involved. They will provide input into the design, trial conduct, TMG decisions, dissemination of study findings, and support writing of the definitive future trial grant application.

**vii. KEY WORDS:** vertebral fragility fracture, medial branch nerve root block, vertebroplasty, osteoporosis, feasibility,

**viii. TRIAL FLOW CHART**

**Injury and admission to hospital**

**<21 days from injury**

**Not eligible,**

 **No further contact**

**Confirmation of eligibility and consent undertaken (with/without capacity)**

**DAY 0**

**RANDOMISATION**

**Baseline data collected**

**Potential eligible patients identified on the medical and surgical wards or via hospital systems**

**Week 8 Telephone interview**

**Week 4 Telephone interview**

**Week 1 Face to face interview on the ward**

**Week 8 (+/- 7d)**

**Week 1 (+/- 3d)**

**Week 4 (+/- 7d)**

**Medial Branch Nerve Root Block (MBNB)**

**Routine Vertebroplasty (VP) surgery**

**≤ 3 days from day 0**

**Formal semi-structured interviews with clinicians at week 4**

**Clinicians selected to take part in the Qualitative Study**

**Thematic Analysis**

**Formal semi-structured interviews with participants on the ward on week 1 and telephone interview on week 8**

**Participant selected to take part in the Qualitative Study**

**Data Analysis**

**viii. GANTT CHART**

1. **BACKGROUND**

**Vertebral Fragility Fractures (VFF)**

Osteoporosis is a common chronic disease. Across Europe, 22 million women and 5 million men have osteoporosis, with 4 million new fragility fractures occurring a year, at an estimated health and social care cost of £37 billion (1). One in 2 women and 1 in 5 men over the age of 50 will experience an osteoporotic fragility fracture in their lifetime, and with ageing demographics, fragility fractures are expected to rise by 25% over the next 5 years (2). Fractures of the spine, ‘vertebral fragility fracture-VFF’ are the most common osteoporotic fracture. These constitute a major health problem, leading to both acute and chronic back pain, substantial spinal deformity, functional disability, decreased quality of life and increased mortality (3-4). The risk of one VFF increases the risk of a new VFF five-fold, and up to twelve-fold in the presence of two or more VFF (5-6). These fractures frequently occur with very little trauma from day-to-day activities, such as bending forward, twisting, lifting light objects, and even sitting from a standing position onto a low chair (7)

Many patients who sustain a VFF have mild to moderate symptoms, however a significant proportion develop substantial pain and disability and require admission to hospital (8). The incidence of hospitalisation ranges from 10 to 20 per 10,000/year, rising to 50 per 10,000/year in those aged 80 years and over (9). Hospitalised VFF patients tend to be older (mean age 81 years), frail, with coexisting comorbidities and a significant number have cognitive impairment. Increasing age and multiple comorbidities are associated with longer hospital stay and higher mortality (9-10). Data from Nottingham, serving a population of 800,000, identified 176 hospitalised patients presenting with VFF over a 12 month period, mean age 79.7 years, multi-morbid (69% had ≥ 3 comorbid conditions), frail (56% had a Clinical Frailty Scale score ≥ 5/9) with significant cognitive impairment (54% had a MoCA score of < 23/30) (11). Conservative (medical) treatment for these patients consists of bed-rest, analgesia and, in some units, thoracolumbar bracing (12), but these are poorly tolerated, with the adverse effects of analgesia and immobilisation leading to additional health problems (13). Bed-rest leads to muscle wasting, impaired rehabilitation and further bone loss. It can also lead to medical complications such as chest infections, deep venous thrombosis and pulmonary embolus. Potent morphine based analgesia, which are frequently required, lead to nausea, constipation and particularly in those with cognitive impairment, delirium (14). Moreover, 1 in 5 patients are re-admitted within 30 days (15).

Vertebral augmentation is a general term for several techniques used to treat painful VFF, with the aim of consolidating the fracture and, when possible, achieve height restoration. Vertebroplasty (VP) is a minimally invasive, image-guided key-hole procedure that involves injection of radio-opaque bone cement into the fractured vertebral body, in an effort to provide pain relief and stability (16). Percutaneous balloon kyphoplasty (PBK) attempts to restore vertebral body height by inflating a balloon prior to bone cement injection (17). The National Institute for Health and Care Excellence (NICE) (18) recommends the use of both VP and BKP for:

*‘the treatment of osteoporotic VFF in people who have severe ongoing pain after a recent, unhealed VFF despite optimal pain management and in whom the pain has been confirmed to be at the level of the fracture by physical examination and imaging’.*

However, more recent guidelines recommend VP as the first line treatment for VFF, given its efficacy, cost and minimally invasive nature compared to BKP, with BKP reserved for more traumatic fractures in younger people (19). A recent UK national survey with members of the British Geriatrics Society, Falls and Bone Health Section, UK members of the Fragility Fracture Network Vertebral Fracture Special Interest Group and the British Association of Spinal Surgeons, all actively managing older patients hospitalised with VFF, highlighted that VP remains the first line treatment for these patients (20). The Academy of Medical Royal Colleges, UK, in their recent guidance, gives particular recommendation for VP in hospitalised older people <https://www.aomrc.org.uk/wp-content/uploads/2020/12/EBI_list2_guidance_1220.pdf>

VP has been shown to reduce pain, pain related disability and hospital length of stay compared to conservative (medical) treatment (15,21-23). An analysis of 13,624 hospitalized patients with VFF from the French Hospital National Database demonstrated that a higher proportion of patients were discharged in 7 days after VP compared with conservative treatment, 68% versus 47%, P < 0.001 (23). A large Taiwanese study using National Health Insurance data for 9238 hospitalized patients with VFF demonstrated a 2-day-earlier discharge and lower 30-day readmission rates after VP (15). Most importantly, VP has also been shown to reduce in-hospital and long-term mortality compared with conservative treatment. In an analysis of 1,038,956 VFF from the US Medicare data-set, 75,364 patients treated with VP, who were propensity matched, the mortality risk was significantly higher after conservative treatment compared with VP (adjusted hazard ratio, 1.32; 95% CI, 1.29–1.35) (24). Similar reductions in mortality have been reported in analyses of German (25) and Taiwanese health insurance data (26). In the Taiwanese dataset that identified 10,785 elderly (older than 70 years) patients hospitalised with a painful VFF, the risk of death was 39% higher in patients receiving conservative treatment (hazard ratio, 1.39; 95% CI, 1.09–1.78; P=0.008) compared with VP. Although the recent Cochrane review concluded that VP has no important benefits (27), limitations in the review are recognised (28-29). Emerging evidence suggests that the optimal benefits are seen when VP is performed within 3 weeks of fracture in elderly hospitalised patients (30-31).

The number of patients requiring VP is increasing each year and in Nottingham alone 81 patients underwent VP last year (local audit data). Most patients required a single level procedure, but some required 2-3 levels due to the presence of multiple painful VFFs. A single level VP costs £4,500, thus the approximate costs of treating these patients in Nottingham alone was £650,000 over the last 12 months. Published data have placed the symptomatic complication rates of VP at 2.2–3.9%, and include cement leakage, infection, bleeding at the injection site, fractures of the ribs, posterior elements or pedicle (32). Risk of the adjacent vertebral body collapse still remains a controversial topic despite numerous conducted clinical and biomechanical in vitro studies. Some suggest that VP may increase biomechanical stress levels and lead to new adjacent fractures, while others found no such correlation (33-34). Two recent systematic reviews found that VP was not related to increasing incidence of subsequent adjacent vertebral fractures (35-37).

However, of more concern nationally is the access to VP. As part of our UK survey (20), a total of 60 statements were generated using a case vignette methodology. Consensus was achieved in 52 statements over a number of areas of hospital fracture treatment including fracture diagnosis, pain relief, rehabilitation and hospital discharge. Consensus was agreed that in older patients failing to mobilise, despite optimal analgesic intervention, that surgical VP intervention should be considered. Many of the non-surgical respondents acknowledged limited access to VP services and questioned the role of less invasive nerve block interventions, which could be delivered more readily either through anaesthetic pain services or radiology intervention services across the country.

Recent studies have shown that steroid injections at the facet joint may be effective in managing pain in patients with VFF (38). Facet arthropathy is a known cause of back pain, and injecting local anaesthetic with or without steroids has been used to block the medial branches from the dorsal rami spinal nerve roots-medial branch nerve block (MBNB). Nonetheless, the role of MBNB in treating people who have *‘severe ongoing pain after a recent, unhealed VFF despite optimal analgesia pain management’* has not been well defined. A recent retrospective study showed that in patients with VFF after 2 years of follow-up, VP and MBNB both had similar efficacy in terms of pain relief and radiological changes (39). Furthermore, the incidence of adjacent vertebral fracture was lower and there were no complications of cement leakage in the MBNB group. Additionally, MBNB was more cost effective than VP. No study has prospectively compared the benefits and cost savings of MBNB to VP. If MBNB proves to be ‘as effective’ and is ‘cost saving’ when compared to VP, this will have significant implications in the way in which future healthcare is delivered for these patients admitted to hospital with painful VFF who require surgery.

**2. RATIONALE**

We hypothesise that MBNB will be ‘as effective’ as VP in reducing acute pain and allowing early return to function. This would change the way these patients are treated, but also result in significant financial savings. Given the scale of this problem and the simplicity of the proposed intervention, we believe that if the results are successful, they will be rapidly adopted by the healthcare community.

**3 OBJECTIVES AND OUTCOME MEASUREMENT**

Aim:

Our ultimate aim is to design and conduct a multi-centre, randomised controlled trial of hospitalised older people with painful VFF to evaluate the clinical and cost effectiveness of MBNB compared to those patients awaiting VP as part of their routine surgical treatment. However, before we conduct a definitive larger RCT trial, it is important to undertake a study, to explore the feasibility of such a trial. This will have the following objectives:

3.1 Objectives

* Determine the number of patients who meet the eligibility criteria along with recruitment (including willingness to be randomised) and retention rates of those eligible patients;
* Test several outcome measures for assessment of mobility, pain and quality of life, for their potential use in a future definitive trial;
* Produce means and standard deviations for the quantitative measures to allow hypothesis testing and development of the analysis plan for a future definitive trial;
* Evaluate ease of access and availability of information from primary and secondary care databases, to determine the most efficient way of measuring patient level healthcare costs.
* Use a qualitative nested interview study to assess participants’ and clinicians’ views on trial acceptability, trial processes and define the ‘non-inferiority’ margin to inform the design and conduct of a future definitive trial.

3.2 **Outcome measurement**

Feasibility Study outcomes:

* Number of eligible patients
* Rate of participant recruitment and randomisation
* Reasons why participants are not recruited or randomised
* Rate of participant adherence to randomisation (cross-over) and retention
* Completion of study rates and reasons for non-completion
* Completeness of data
* Non-inferiority margin
* Standard deviation and effect size of potential outcomes for subsequent definitive trial
* Time from randomisation to delivery of the intervention

Planned outcomes for the future definitive trial

* Functional disability as measured by the 24 point Roland Morris Disability Questionnaire (RMDQ) (40) (This is the most commonly used outcome measure in previous studies)
* Pain as measured by the 0-11 Numeric Pain Rating Scale (NRS-11) (41)
* Quality of Life as measured by the EuroQol (EQ5D-5L) and where appropriate, proxy EQ5D-5L (42)
* Activities of daily living as measured by the Nottingham Extended Activities of Daily Living (NEADL) scale (43)
* Record of pain medication use (using the opioid dose equivalence table)

**4. RESEARCH METHODS**

**Research Plan**

The study will inform the design and conduct of a future trial to compare the clinical effectiveness and cost effectiveness of MBNB to routine VP surgical care in hospitalised older people with painful VFF. Data will be used to explore the recruitment process, monitor recovery and outcome of the treatment, assess patient experience and assess different outcome measures. Participants will be followed up for 8 weeks: the duration of the overall study will be 18 months.

**5. TRIAL DESIGN**

Parallel, two-arm randomised controlled feasibility trial with participants individually allocated on a 1:1 ratio to continue with their planned surgical care-VP or MBNB treatment. Embedded within the feasibility study will be a health economic analysis to understand resource utilisation and implication of such an intervention; and a qualitative study which will focus on the experiences of participants and clinicians involved in the study, their insights and further recommendations for improving trial acceptability and processes.

**6. PARTICIPANT ELIGIBILITY CRITERIA**

Eligibility Criteria

Participants presenting to the Nottingham University Hospital NHS Trust with an acute painful VFF and awaiting spinal surgery will be recruited into the study.

6.1 Inclusion criteria

* Patients aged 70 years and over admitted to hospital;
* Ambulatory prior to injury;
* < 3 weeks from date of injury;
* NRS pain score 7 or more on standing;
* MRI confirmed oedema at the site of fracture;
* Ability to adhere to study procedures and complete follow-up

6.2 Exclusion criteria

* Chronic back pain requiring opiate use;
* Substantial fracture retropulsion; acute infection, spinal malignancy;
* 3 or more acute vertebral fractures
* Bed bound prior fracture
* Receiving palliative care
* Lack of capacity and no consultee
* Spinal deformity which contraindicates VP

**7. TRIAL PROCEDURES**

**7.1 Recruitment**

The target population for recruitment is patients admitted to the Queens Medical Centre, Nottingham University Hospitals NHS Trust (catchment population 800,000) with an acute painful VFF.

**7.1.1 Participant Identification**

Patients admitted to hospital who fulfil the inclusion / exclusion criteria will be informed of the study by the ward clinical staff on admission to hospital. Those who indicate that they are interested in hearing more about the trial will be introduced to the research team. The research team will explain the details of the study provide a patient information sheet (PIS) and answer any questions. Patients will have the opportunity to discuss this with their family and to ask any questions they might have. Whenever possible, they will have at least 24 hours to consider participation in the study before giving informed consent

For patients who lack capacity to consent, (as determined by an abbreviated mental test score of 7 or less out of 10), scored as part of routine care, the ward clinical staff will approach and inform the accompanying relative or carer about the study. Relatives or carers who indicate that they are interested in hearing more about the study will be introduced to the research team. The relative or carer will be asked to act as the patient’s personal consultee, who will be able to advise the research team on what they believe the patient’s wishes or feelings would be about taking part in the trial. They too will be given a full explanation of the study, an information leaflet and opportunity to ask any questions related to the study. Whenever possible, they too will have at least 24 hours to consider participation before giving patient assent to participate in the study.

If no personal consultee can be identified then a nominated consultee, (independent practitioner not involved with the study), will be sought and they will be asked to sign the consent form-assent. Once the patient (consultee) has given written informed consent, baseline data will be collected and the participant randomised.

**7.1.2 Screening**

Patients admitted to the medical assessment unit, Nottingham University Hospitals NHS Trust will be screened by the clinical team, supported by the research team, to determine if they meet inclusion / exclusion criteria.

**7.2 Consent**

See flow diagram

Capacity to consent is defined as the patient’s ability to understand the purpose and nature of the research; understand what the research involves, its benefits (or lack of), risks and burdens; understand the alternatives to taking part; be able to retain the information long enough to make an effective decision; and be able to make a decision (Mental Capacity Act 2005). The patient will also be informed that entry into the study will be entirely voluntary and that their treatment and care will not be affected by their decision. They will be informed that if they did agree to participate, they can still withdraw at any time, without giving a reason, and that such decision will not affect future treatment or care. Although consent to take part in the qualitative interview study is included on the main consent form, the researcher will explain that only a small number of participants (10 ) will be selected for the qualitative interview. Participants who choose not to participate in the qualitative interview will still be eligible for the main trial if they have consented to this.

Informed consent for those patients willing to take part will be obtained by those members of the research team delegated responsibility to do so by the Chief Investigator, with appropriate training and expertise, and verified by the Sponsor. Each statement on the consent form will be discussed and initialised by the patient and witnessed by the research team. One copy of the consent form will be given to the participant, one will be retained in the participant’s medical records and the original consent form will be kept by the Research team and stored securely in the site file., Participants G.Ps will be informed of their participation in the study by letter, and will include a patient Information sheet and a copy of the consent form.

**Flowchart Guidance for Consent**

**Fulfils eligibility criteria for AVERT Trial?**

**Fully competent to consent? (e.g. AMT Score >7)**

**Yes**

**No**

**Yes**

Relative/carer present and willing to take on the role of Personal Consultee (PC)?

**Yes**

* PC gives advice about the patient’s participation in the trial
* If the participant regains competency, inform of participation and obtain written informed consent for continuing in the trial
* Written informed consent obtained by research team

Written informed consent obtained by research team

If a participant loses capacity during the study period, they will continue in the study unless there is a known change in their views/perspectives determined by liaising with their relative/carer.

For participants who initially lack capacity but later regain capacity, we will re-approach them, detailing their participation in the study to date, provide a patient information sheet and discuss the purpose and nature of the research, its benefits (or lack of), risks and burdens; understand the alternatives to taking part. If they agree to continue with participation in the study, we will request to sign and updated consent form. If they decline they will be categorised as withdrawn.

For those patients who lack capacity to consent, the consultee will also be informed that entry of their friend/relative into the study is entirely voluntary and that the treatment and care of their friend/relative will not be affected by their decision. It will also be explained that their friend/relative can withdraw from the study at any time, without giving a reason, and that any such decision will not affect future treatment or care. If there is more than one relative or carer willing to act as the patient’s consultee, then they must all agree on the decision for the participant to be included in the study. If the opinion is that the patient would have consented, one person will then be nominated as the personal consultee and sign the declaration form for their friend/relative’s participation in the study. Each statement on the declaration form will be discussed and initialised by the consultee and witnessed by the research team. One copy of the declaration form will be given to the consultee, one will be retained in the participant’s medical records and the original declaration form will be kept by the Research team and stored securely in the site file. Participants GP’s will be informed of their participation in the study by letter, and will include a Patient Information Sheet and a copy of the declaration form.

For participants who initially lack capacity but later regain capacity, we will re-approach them, detailing their participation in the study to date, provide a written patient information sheet and discuss the purpose and nature of the research, its benefits (or lack of), risks and burdens; understand the alternatives to taking part . If they agree to continue with participation in the study, we will request to sign and updated consent form. If participants decline further participation in the study, then they will be categorised as withdrawn and we will keep data collected to this point for analysis. This will not affect their future care and ongoing care will be resumed by the consultant overseeing their care in hospital.

If a participant initially has capacity but then loses capacity during the study period, they will continue in the study unless there is a known change in their views/perspectives by liaising with their relative/carer. The research team will approach them in the role of a ‘personal consultee’ (under Mental Capacity Act section 5) similar to what has been described earlier.

Should there be any subsequent amendment to the final protocol, which might affect a participant’s participation in the study, continuing consent will be obtained using an amended declaration form which will be signed by the participant or consultee.

For patients who decline to take part, or consultees who decline the patient’s participation in the study, they will be asked if they would be willing to share their reasons for declining. It will be made clear that this is in order to help us improve the design and acceptability of the study and that there is no obligation to talk to us. The findings will be tabulated into the final results.

* 1. **Randomisation**

Participants will be randomly allocated to routine vertebroplasty (VP) or MBNB. Allocation will be in a 1:1 ratio via a secure web based system (RedCap Cloud). VP and MBNB will be undertaken within 72 hours of randomisation. The research assistant (RA) will electronically access the web based system and each participant will receive a randomisation number. Participants and their GPs will be notified of allocation to VP or MBNB arm of the study and a record of randomisation will be made in the participant’s medical notes.

**7.4 Blinding**

Due to the nature of the study, it will not be possible to blind the participant to VP surgery or MBNB.

**7.5 Baseline data**

This will include data collected from the medical and nursing notes and where appropriate the participant and/or carer:

* Sociodemographic data (age, sex, deprivation/health economic) and fracture details;
* Cognitive Assessment as measured by the 30 point Montreal Cognitive Assessment (MoCA) tool (35). The MoCA assesses several cognitive domains: the short-term memory recall task (5 points) involves two learning trials of five nouns and delayed recall after approximately five minutes; visuospatial abilities are assessed using a clock-drawing task (3 points) and a three-dimensional cube copy (1 point); multiple aspects of executive functions are assessed using an alternation task adapted from the trail-making B task (1 point), a phonemic fluency task (1 point), and a two-item verbal abstraction task (2 points); attention, concentration, and working memory are evaluated using a sustained attention task (target detection using tapping; 1 point), a serial subtraction task (3 points), and digits forward and backward (1 point each); language is assessed using a three-item confrontation naming task with low-familiarity animals (lion, camel, rhinoceros; 3 points), repetition of two syntactically complex sentences (2 points), and the aforementioned fluency task; orientation to time and place is evaluated by asking the subject for the date and the city in which the test is occurring (6 points);
* Charlson Co-morbidity Index (36). The Charlson comorbidity index predicts the one-year mortality for a patient who may have a range of comorbid conditions, such as heart disease, AIDS, or cancer (a total of 22 conditions). Each condition is assigned a score of 1, 2, 3, or 6, depending on the risk of dying associated with each one. Scores are summed to provide a total score to predict mortality.
* Clinical Frailty Scale (CFS) is used in an outpatient clinical setting to determine frailty of a geriatric patient, which is a predictor of short-term and long-term mortality. This will be completed by the study team at the baseline assessment and requires no additional equipment or further input from the patient. The assessor will determine where the patient sits on a scale of 1 (Very Fit) to 9 (Terminally ill).
* Roland Morris Disability Questionnaire (RMDQ) (38) designed to assess self-rated physical disability caused by low back pain.
* Numeric Pain Rating Scale (NRS) (39). This is an eleven-point unidimensional measure of pain intensity, which has been widely used in diverse adult populations, ranging from 0-no pain to 10-worst imaginable pain. Participants will be asked to give their average pain score on mobilising.
* Quality of Life as measured by the EQ-5D-5L, a self-assessed, health related quality of life measure used for health economic analysis (40). Scores range 0 to 1, with 1 indicating perfect health and it also includes a 0 to 100 VAS (Visual Analogue Scale) to assess general health.
* Nottingham Extended Activities of Daily Living (NEADL). This scale is used to reflect performance in ADLs (activities of Daily Living) in the last few weeks. Each performance item is rated on this scale with a given number of points assigned to each level or ranking. A higher number is indicative of a greater degree of independence. Maximum score is 22.
* Pain medication prescribed

Analgesia requirement will be recorded as follows: each medication will be classified as a strong opioid (including oxycodone, morphine, fentanyl, pethidine, hydromorphone, buprenorphine and tramadol), mild opioid (including medications containing codeine or dextropropoxyphene) or non-opioid medication (including paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs)). The participant will be given a score of 0, 1 or 2 in each of these three categories depending on the number of concurrent different medications being taken within each category. Opioid medication will also include a calculation of the oral Morphine Equivalent Daily Dose using the Opioid Dose Equivalence score (47).

**7.6 Trial assessments**

Follow up timings will be counted from the time of intervention. Participants will be followed up face to face at week 1 (±3 days) (whilst in hospital), week 4 (±7 days, telephone interviews) and week 8 (±7 days, telephone interviews).

Follow up outcome measures will include:

* Participant still living (established by the hospital’s NHS spine portal enquiry).
* Hospital length-of-stay (ascertained by the hospital electronic database, supplemented by review of medical notes by a different member of staff to maintain blinding, if necessary)
* Unplanned hospital re-admission within 28 and 91 days post discharge (ascertained by the hospital electronic database, supplemented by review of medical notes if necessary).
* Health economics/resource utilisation (patient and NHS costs)
* Time from randomisation to delivery of the intervention.

Participant follow-up assessments will include:

RMDQ, NRS, EQ-5D-5L, NEADL,

In addition, at week 8, to inform the definitive economic analysis, we will assess resource use between VP and MBNB treatments; the ease of access to information about resource use from routine database systems; and the feasibility of collecting such data.

Surgical VP and MBNB treatment resource use will be collected from the medical notes by the research staff. The cost associated with the surgery will be based on the recorded resource use for the surgery (e.g. consumables, equipment, grade and number of nursing staff present during the operation). Further health resource information will be extracted from the hospital electronic

system (NotIS) and the GP electronic systems by the research assistant. This will include any outpatient appointment, outpatient procedures, emergency department visits, inpatient admissions related to the study or GP visits during the 8 week follow up period. The unit costs of these resources will be based on information from the following sources: national databases such as the NHS Healthcare Resource Group (HRG) Tariff (43), the Personal Social Services Research Unit (PSSRU) Costs of Health (44), the Office of National Statistics (ONS) Bulletin Annual Survey of Hours and Earnings (45), and NHS Reference Costs (https://www.gov.uk/government/collections/nhs-reference-costs). Any unit cost that is not available will be estimated in consultation with the hospital finance department.

**7.8 Qualitative assessments**

The study will be complemented by a nested interview study to provide essential insights into the feasibility, design and conduct of a definitive trial. This will focus on the experiences of participants and clinicians in the study, their insights and their recommendations for improving trial acceptability and processes.

Semi-structured Interviews

Semi-structured interviewswill be undertaken with a purposeful sample of up to 10 participants to explore their views on the trial and recruitment process, the presentation of study information, study documentation and their reasons for accepting randomisation. A maximum variation sampling strategy will be employed to ensure we capture a broad range of patients. We aim to interview participants with different characteristics which we believe might lead them to have a different opinion/experience. For example, participants of both genders; participants from both arms of the study, a spectrum of participants on the clinical frailty scale; some patients who may have particular communication needs (eg English as a second language speakers). Personal consultees of participants will also be invited to participate in the interview. If they agree to do so, they will sign a separate consent form for the qualitative interview.

An interview topic guide will be used to ensure similar areas are covered in each interview. Interviews will be undertaken face-to-face, in a private space on the hospital ward between day 7 and day 10 following randomisation. It is expected that by this time the participants will still be in hospital and will have had their surgery. Interviews will last no more than thirty minutes (to minimise disruption to routines) and all interviews will be audio recorded, transcribed in full and anonymised.

These interviews will be followed up by a second shorter interview with participants who complete the study. If possible, this interview will be combined with their week 8 data collection follow up, either as a telephone call. The aim will be to further explore their experience of the trial, experiences of data collection processes, an acceptable non-inferiority margin, and their overall perception in participating.

We will also interview small number of clinicians (n=5) to explore their experiences of the study. These semi structured interviews will explore their thoughts about participant recruitment (eligibility and randomisation), an acceptable non-inferiority margin, as well as reflect upon the process of integrating the research with the clinical service. The study is sampling a small number of staff based on high 'information power' (Malterud et al, 2015) of qualitative interviews with expert professional knowledge and direct involvement with the study. These staff will be identified by the study lead, who will distribute an invitation letter/email (containing details on how to sign up for the study) and information sheet to eligible staff. Staff members are likely to include a physician, a surgeon, a nurse, a physiotherapist and an occupational therapist.

Interviews will be undertaken by telephone or telephone over internet as convenient, and last approximately 15-20 mins. Interviews will be recorded and transcribed in full. All clinicians will be provided with a participant information leaflet, and asked to give written, informed consent, using a dedicated clinician interview consent form. The interviews will be audio taped and transcribed. A professional transcription service will be used to transcribe all data. Clayton Research Support is a registered University of Nottingham (UoN) supplier and as such has an active confidentiality agreement in place, which covers all research data provided by UoN staff. Clayton Research Support will be provided with password-protected access to the relevant folders on the UoN IT network and will be able to directly access audio recordings; this access will also enable Clayton Research Support to directly upload completed transcripts to the same file space

**7.9 Withdrawal criteria**

Participants will be free to withdraw their consent for participation in the trial at any time. The reasons for withdrawing consent will be recorded, but participants will not be obliged to give reasons. Participants will be assured that withdrawing their consent will not affect the care they receive. They will be informed at the start of the trial that data collected up to the point of withdrawal of consent will be retained and may be used in the final analysis. All reasonable attempts will be made to contact any participant lost to follow-up during the course of the trial in order to complete assessments.

Participants who withdraw from the study for any reason, will be referred back to their consultant for further treatment. Participants who withdraw after randomisation will not be replaced.

**7.10 End of trial**

This will be the date of the collection of the last data item of the last participant undergoing the trial, at week 8.

**8. TRIAL INTERVENTION**

 **Surgical treatment**

**Vertebroplasty (VP)**VP is a standard routine care using keyhole surgery that has been shown to reduce pain and is safe in hospitalised older patients. Usual post-operative care and monitoring will follow after the surgery. Participants will be encouraged to mobilise as pain allows and be prescribed analgesia as required.

**Medial Branch Nerve Root Block (MBNB)**This will be performed by a consultant anaesthetist specialised in Spinal Injections.

Bilateral Medial Branch Blocks (MBNB) will be performed targeting facet joints above and below the vertebral fracture. Contrast media, oblique and lateral XR views will be used to assess optimal position of the needle.

A mixture of 0.5 % Bupivacaine with 40 mg Depomedrone will be used. Each medial branch will be blocked with 1-1.5 mls solution.

Spinal nerve blocks (all types) are currently undertaken three times per week (Monday, Wednesday and Friday) as part of the routine spinal service.

**9. ADVERSE EVENTS /SERIOUS ADVERSE EVENTS**

**9.1 Definitions**

|  |  |
| --- | --- |
| **Term** | **Definition** |
| **Adverse Event (AE)** | Any untoward medical occurrence in a participant  |
| **Serious Adverse Event (SAE)** | A serious adverse event that:* results in death
* is life-threatening

NB: The term "life-threatening" in the definition of "serious adverse event" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.* Requires prolongation of existing inpatient’s hospitalisation
* Results in persistent or significant disability or incapacity
* Other important medical event\*

 \*Other events that may not result in death, are not life threatening, or do not require hospitalisation, may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. |

**9.2 Operational definitions for AEs AND SAEs**

It is important to note that this trial is not testing a new surgical treatment or procedure.

Both VP and MBNB are recognised safe and routinely used procedures, and as such the adverse events are well documented. The use of analgesia, such as opioids, used in a group of older people can lead to side effects, e.g. nausea, constipation and confusion. Periods of bed rest can lead to physical inactivity and deconditioning which is associated with chest infections, deep venous thrombosis, urinary tract infection and may lead to inpatient falls and their associated consequences.

The risks associated with participating in the study and potential adverse outcomes with either group will be explained to the patient and will be detailed in the accompanying participant information sheet. Management of any adverse outcomes will be treated accordingly.

Adverse Events will be reviewed by the CI and PI and recorded as AEs. The severity will be categorised as: 1 = mild, 2 = moderate, 3 = severe. .

**9.3 Reporting and Recording of SAEs**

All AEs will be recorded as part of the study outcome measures. Any SAEs involving death occurring from randomisation to the final study visit will be recorded on the Sponsor SAE Form and sent/e-mailed to the Sponsor within 3 days of the research staff becoming aware of the event. Once all resulting queries have been resolved, the Sponsor will retain the original form and a copy to be retained on site and in the Trial Master File.

Other SAEs (severity =3) that are both related to the study and unexpected (not an expected surgical or post-operative complication or complication of extended bed rest for this injury type) will be reported to the REC using the non-CTIMP safety report form, within 15 days of the researcher becoming aware of the event.

For each SAE the following information will be collected:

* full details in medical terms and case description
* event duration (start and end dates, if applicable)
* action taken
* outcome
* seriousness criteria
* causality (i.e. relatedness to surgical intervention), in the opinion of the investigator
* whether the event would be considered anticipated.

Any change of condition or other follow-up information will be sent to the Sponsor as soon as it is available or at least within 3 days of the information becoming available.

Events will be followed up until the event has resolved or a final outcome has been reached.

**9.4 Responsibilities**

The RA will check for AEs daily until the time of discharge and at each follow up visit.

1. Liaise with the CI/PI to judge the seriousness and causality and providing an opinion on whether the event/reaction was anticipated.
2. Ensure that AEs are recorded and SAEs are reported to the sponsor and LCTU in line with the requirements of the protocol.
3. Ensure that all SAEs are recorded and reported to the sponsor and LCTU within 3 days of becoming aware of the event and provide further follow-up information as soon as available. Ensure that SAEs are chased with Sponsor if a record of receipt is not received within 2 working days of initial reporting.

Chief Investigator (CI):

1. Will ensure clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Use medical judgement in assigning the AE seriousness, causality and whether the event was anticipated where it has not been possible to obtain local medical assessment.
3. Review specific SAEs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.

Sponsor:

1. Ensure central data collection and verification of SAEs according to the trial protocol onto a database.
2. Report safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.
3. Report safety information to the independent oversight committees identified for the trial (Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.

Trial Steering Committee (TSC):

In accordance with the Trial Terms of Reference for the TSC, periodically review the safety data.

### 9.5 Notification of deaths

Deaths will be reported to the sponsor, within 3 days of the research staff becoming aware of the event.

**10 STATISTICS AND DATA ANALYSIS**

The aim of this feasibility study is to provide estimates of the recruitment and retention rates and the variability of important outcome measures in order to inform the design of a future definitive study.

 **10.1 Sample size calculation and data analysis**

Sample Size

Approximately 200 patients present with acute VFF each year (local audit data) of which approximately 1/3 require VP. We propose to recruit for 10 months, in which time we expect to approach approximately 50 patients listed for VP. Assuming 80% are eligible, and a 70% consent rate, we expect to recruit 30 participants. Allowing for a 10% two month attrition rate, 28 participants will complete the study. By recruiting 30 patients we will be able to estimate a recruitment rate of 82% (CI 74%, 92%) and a retention rate of 90% (CI 81%, 99%). Completed follow-up on 28 participants will allow the Roland Morris Disability mean score to be estimated with an approximate standard error of 0.98 assuming a SD of 6, thus enabling future power calculations to be calculated. Sample sizes between 24 and 40 are recommended for a feasibility study (46-49) and thus by recruiting 30 participants, we are confident we can determine whether a definitive trial is feasible.

Data Analysis

A statistical analysis plan will be finalised and approved prior to database lock and commencement of data analysis. Feasibility outcomes will be summarised using appropriate descriptive statistics; mean (95% Confidence Interval) for continuous and frequency (%) for categorical. Completeness and descriptive summaries of outcome data at each follow up time point will be presented. The standard deviation and effect size of potential outcomes for subsequent definitive trial will be estimated to inform future sample size estimations. We will check outcome distributions for suggested floor and ceiling effects. Descriptive summaries of NHS costs (using standard unit costs) data at each follow up time point will be presented.

* 1. **Missing Data**

The data entered into the database will be validated prior to analysis to correct spurious and missing data, if possible, by referring to the original data source. Imputation methods will not be used to replace any missing data.

No sub-group analyses are planned and no formal interim analyses will be conducted. Only descriptive interim data on participant safety and trial conduct will be presented to TSC for the purposes of monitoring the trial and participant safety.

* 1. **Health economic analysis**

We will rehearse the cost-effective analysis, which will inform the study hypothesis and the analysis plan for the definitive trial. The within-trial economic evaluation will determine the cost and outcome of VP and MBNB treatment from a NHS perspective. The evaluation will follow the reference case guidance for technology appraisals as set out by NICE. Effectiveness will be captured using quality adjusted life years (QALYs) as assessed by the EQ-5D-5L. The primary health economic outcome of the evaluation will be the incremental cost per additional quality-adjusted life years (QALY) gained from surgical fixation. To control for the impact of uncertainty, one- and two-way sensitivity analyses will be performed on (but not exclusively) age, gender and baseline scores. The impact of parameter uncertainty will also be addressed using a probabilistic sensitivity analysis, allowing the calculation of 95% confidence intervals for the incremental cost-effectiveness ratio and cost-effectiveness acceptability curves.

* 1. **Qualitative analysis**

Data will handled using the NVivo software package and analysed using a framework thematic approach. The framework will be informed by the literature around the challenges of clinical trial methodology (51-55), and initial themes are likely to include elements such as randomisation, outcome measures, communication and feedback. Data from each interview will be mapped to the thematic tables. The generation and population of the thematic tables will be managed by the qualitative research lead, with interpretations and allocation validated by other members of the team. Thematic table summaries will be used to generate recommendations about the nature and form of the subsequent trial; specific detail will also be used to inform recruitment strategies, data collection regimes, and participant information resources.

 **11. DATA MANAGEMENT**

**11.1 Data collection tools and source document identification**

The source data will be the medical and nursing notes, questionnaires, case report form (CRF) worksheets, audio recordings and interview transcripts. Demographic data, including a minimal amount of information that is required for randomisation, will be collected from each participant.

**11.2 Access to Data**

Direct access will be granted to authorised representatives from the Sponsor, and the regulatory authorities to permit trial-related monitoring, audits and inspections- in line with participant consent.

**11.3 Archiving**

The study documents held by the CI on behalf of the Sponsor shall be finally archived at secure archive facilities. This archive shall include all anonymised audio recordings, study databases and associated meta-data encryption codes. NUH NHS Trust via its research arm, Research and Innovation will assist with archiving of data. This will be done by an archiving company subcontracted to NUH. The CI will ensure that any documentation held electronically are printed or placed onto appropriate electronic storage device. Archiving of study documents will be in accordance with NUH standard operating procedure. Electronic records will be stored in a SQL Server database, stored on a restricted access, secure server maintained by the sponsor. Access to the study database will be permission based allocated by the sponsor IT team. Data will be stored for 5 years. Destruction of essential documents (including the database) will require authorisation from the Sponsor

**12. MONITORING, AUDIT & INSPECTION**

**Monitoring**

Trial supervision will be established according to the principles of GCP and in-line with the NHS Research Governance Framework (RGF). This will include establishment of a core Project Team, Trial Management Group (TMG) and an independent TSC. A Trial Monitoring Plan will be developed and will be informed by a Trial Risk Assessment which will consider the safety or physical or mental integrity of the trial patients and the scientific value of the research.

This Trial Monitoring plan will detail the timing and content of reports to monitor trial conduct, implementation, and adherence with the Consolidated Standards of Reporting Trials (CONSORT). Procedures will be in place to assess risk on an ongoing basis with adjustments made accordingly.

**Data Monitoring**

Data will be monitored for quality and completeness by the sponsor and evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures, the Trial Manager or where required, a nominated designee of the Sponsor, will verify that the clinical study is conducted and data are generated, documented and reported in compliance with the protocol GCP and the applicable regulatory requirements.

Processing of trial data and monitoring for consistency, validity and quality will be done as data accumulate by the sponsor. Screening will include computerised checks for out-of range data, and cross-checks for conflicting data within and between data collections forms. Missing data will be chased until they are received, confirmed as not available or the trial is at the point of analysis.

The sponsor will reserve the right to intermittently conduct source data verification exercises on a sample of patients, which will be carried out by staff from the sponsor. Source data verification will involve direct access to patient notes at the participating hospital sites and the ongoing central collection of copies of consent forms and other relevant investigation reports.

**Clinical governance issues**

To ensure responsibility and accountability for the overall quality of care received by participants during the study period, clinical governance issues pertaining to all aspects of routine management will be brought to the attention of the TSC and, where applicable, to the Trust.

 **13. ETHICAL AND REGULATORY CONSIDERATIONS**

**13.1 Research Ethics Committee (REC) review& reports**

* The study will not start until the protocol, consent forms and information sheets have received approval/favourable opinion from the Research Ethics Committee (REC), and the Health Research Authority (HRA) and Confirmation of Capacity and Capability for NUH sponsored studies approval is obtained from the Research & Innovation department.
* Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the trial.
* All correspondence with the REC will be retained in the Trial Master File/Investigator Site File.
* An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended.
* It will be the Chief Investigator’s responsibility to produce the annual reports as required.
* The Chief Investigator will notify the REC of the end of the trial.
* If the trial is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination.
* Within one year after the end of the trial, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

**13.2 Peer review**

The study has been peer reviewed as part of the 2 stage NIHR funding application by clinical and non-clinical reviewers; and internally within the study teams’ local department.

* 1. **Patient & Public Involvement**

The study’s Patient and Public Involvement (PPI) group are members of the National Osteoporosis Society’s Nottingham support group, a 250-member group, with 12 board committee members who meet every month. The group is actively involved in fund raising events, public awareness campaigns and arranging educational bone health meetings. Supporting research features highly as a priority within the group and some of its members are currently already involved as research lay members.

The pain and suffering from vertebral fragility fractures is well recognised among the membership and has been highlighted as important to research, and has been specifically put forward by the group, as an area for further research. The interest in key-hole surgery stemmed from the annual Nottingham lay public medical update meeting in 2018, which featured key-hole surgery for the treatment of vertebral fractures which was approved by NICE. This led to the development to two focus groups which informed and developed the research call.

LW from the PPI group has agreed to be the nominated PPI lead and co-applicant. She will draw on the wider views of the patient group to support the research study. LW has severe osteoporosis and undergone a 5 level vertebroplasty procedure experiences have greatly influenced the design of the research study, in particular, the choice of the proposed outcome measures.

Our members and wider support group will comment further on aspects of the study design and conduct. They will also contribute to the production of questionnaire booklets, information sheets and other documentation as necessary for the trial, to ensure these are understandable and acceptable to patients. Additionally, they will be invited to comment on methods of sharing the study findings, but more importantly, support the writing of the definitive, future trial application. One advantage of Covid-19 is that it has allowed our members to work remotely with each other using Zoom and Microsoft Teams and thus continued our outreach to the whole group

* 1. **Regulatory Compliance**

The study will be conducted according to the Quality Management System of the sponsor. The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 2013; the principles of Good Clinical Practice, and the UK Policy Framework for Health and Social Care Research 2017.

**13.5 Protocol compliance**

* Prospective, planned deviations or waivers to the protocol will not be allowed.
* Accidental protocol deviations will be adequately documented on the relevant forms and reported to the Chief Investigator, and Sponsor immediately.
* Deviations from the protocol which are found to frequently recur, will require immediate action and could potentially be classified as a serious breach.

**13.6 Notification of Serious Breaches to GCP and/or the protocol**

A “serious breach” is a breach which is likely to effect to a significant degree –

* 1. the safety or physical or mental integrity of the participants of the trial; or
	2. the scientific value of the trial

In such cases:

* The Sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase;
* The Sponsor will notify in writing to the REC of any serious breach of the conditions and principles of GCP in connection with that trial or the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach.

**13.7 Data protection and patient confidentiality**

Information about participants will be stored pseudo anonymous, confidentially and securely, and will be managed according to the requirements of all current legislation including the general data protection regulation. All investigators and study staff will also comply with these regulatory requirements. A unique identification number will be automatically attributed to each participant randomised in the study. All evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. Paper based names, addresses and other personal identifiers will be stored separately from questionnaire and clinical data to prevent identification of research records. Electronic records will be stored in a SQL Server database, stored on a restricted access, secure server maintained by the sponsor. Access to the study database will be permission based allocated by the sponsor IT team. This will prevent personal data from being viewed by all members of the research team. All non-electronic records will be kept in a secure storage area with limited access to research staff only. Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the Sponsor or its designee.

The CI and research staff involved with this study will not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee will be obtained for the disclosure of any said confidential information to other parties. In compliance with the ICH/GCP guidelines, regulations and in accordance with the Nottingham University Hospital SOP-RES-028 and research ethics, the CI will maintain all records and documents regarding the conduct of the study. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

**13.8 Financial and other competing interests for the chief investigator, and committee members for the overall trial management**

None.

**13.9** **Indemnity**

As Nottingham University Hospitals NHS Trust is acting as sponsor for this study, NHS indemnity applies. NHS bodies are legally liable for the negligent acts and omissions of their employees. Non-negligent harm is not covered by the NHS indemnity scheme. The Nottingham University Hospitals NHS Trust, therefore, cannot agree in advance to pay compensation in these circumstances. In exceptional circumstances an ex-gratia payment may be offered.

**13.10 Amendments**

It will be the Sponsor’s responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to the REC. If the Sponsor wishes to make a substantial amendment to the REC application or the supporting documents, the Sponsor (or delegate) will submit a valid notice of amendment to the REC for consideration. Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant information sheets (if appropriate) have been reviewed and also received approval/favourable opinion from the REC and R&D department. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately and the REC will be notified as soon as possible and an approval requested. The REC will provide a response regarding the amendment within 35 days of receipt of the notice, informing the HRA of the amendment. Non-substantial amendments will also be notified to the HRA. Some amendments that may be considered to be non-substantial for the purposes of REC may still need to be notified to NHS R&D (e.g. a change to the funding arrangements). Any amendments will be recorded and will be reflected in the protocol (and its versions). Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC subsequently informed.

**13.11 Post trial care**

Following the end of the trial, all participants will continue with routine, standard care.

**13.12 Access to the final study dataset**

In compliance with ICH/GCP guidelines, regulations and in accordance with the Nottingham University Hospitals NHS Trust standard operating procedures (SOP) and Research Ethics, the CI will maintain all records and documents regarding the conduct of the study. These will be retained for at least 5 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The CI will have primary access to the final study dataset. The CI will also designate core members of the study team access to the dataset. If it is envisaged that that data set will be used to support the application for the definitive trial, participants will be informed of this.

**14. DISSEMINATION POLICY**

**14.1 Dissemination policy**

The team’s dissemination strategy aims to target these groups:

**a) Policy makers and planners**

We will submit articles to various periodicals and send updates to relevant websites e.g. Health Service Journal, NHS Primary Care Commissioning. Previous experience of participating in Department of Health (DH) consultations will help us to contact key policy groups to whom we can deliver important lessons regarding our work. In addition, a number of the co-applicants are engaged with (at national executive board level) healthcare planners, practitioners and policy makers: OS-National Osteoporosis Society UK and NP, British Association of Spine Surgeons and CWT-British Geriatrics Society UK. ED- Chartered Society of Physiotherapists.

**b) Researchers**

Methodological papers including those describing the development of methodology and the protocol are likely to be targeted at major online free to access journal, such as Trials. The full report will be available on the NIHR RfPB website. Results from the trial will also be submitted for presentation at scientific meetings and conferences targeted at clinicians working with older people, trauma and spinal surgery, e.g. the BritSpine Meeting, annual congress of the European Society of Spinal Surgery, British Geriatrics Society scientific meeting and the Fragility Fracture Network. Major scientific papers will be submitted to high impact journals (e.g. Lancet), and other papers in the appropriate high impact general or specialist surgical journals.

**c) User groups**

We will work with our PPI Group on the study’s dissemination and engagement strategy with the wider public. This will include publishing articles in their dedicated newsletter, speaking at an annual public forum and using their direct links to the National Osteoporosis Society (<https://www.nos.org.uk>).

**d) Networks and the NIHR faculty**

The study will be adopted by the Clinical Research Network (CRN) musculoskeletal division. This will allow further dissemination of the findings through established network routes and provide a significant contribution to the collective research endeavour of the NIHR Faculty.

More importantly, if the findings from this study indicate that a definitive trial is feasible, the data will be used to prepare an application for funding a future clinical and cost effectiveness RCT, which will determine whether the intervention would:

* Improve patient outcomes;
* Reduce clinician uncertainty about the management of these injuries;
* Change the practice of clinicians who manage these injuries;
* Inform local (i.e. commissioners, hospitals), national (i.e. NICE, DH, NOS, British Association Spine Surgeons) and International (AO Spine Foundation) producers of treatment guidelines.
	1. **Authorship eligibility guidelines and any intended use of professional writers**

A publication policy will be agreed with co-applicants and a systematic plan, including authorship, for the peer reviewed publications. Criteria for authorship will be in accordance with the International Committee of Medical Journal Editors. Individuals that have contributed to the study but not fulfilled authorship criteria will be acknowledged in a separate section.

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27. APPENDICES
* **Appendix 1 Schedule of Procedures**
* **Appendix 2 Amendment History**

**Appendix 1 – Schedule of Procedures**

|  |
| --- |
| **Procedures** |
| **Screening** | **Baseline** | **Day of surgery** | **Week 1****Face-to-face** | **Week 4****Telephone** | **Week 8****Telephone** |
| **Visit Window** | **<21 days from injury** | **Day 0** | **< 3 Days from Randomisation** | **+/-3 days****(or post intervention)** | **+/- 7 days** | **+/- 7 days** |
| **Eligibility Assessment** | **x** | **x** | **x** | **x** | **X** | **x** |
| **Abbreviated Mental Test (AMT)\*** | **x\*** |  |  | **x** |  |  **x£** |
| **Participant and fracture details** | **x** | **x** |  |  |  |  |
| **Informed consent** |  | **x** |  |  |  |  |
| **Randomisation** |  | **x** |  |  |  |  |
| **Surgery details & complications** |  |  | **x1** | **x1** | **x1** | **x1** |
| **Charlson Co-morbidity Assessment** |  | **x** |  |  |  |  |
| **Clinical Frailty Scale (CFS)** |  | **x** |  |  |  |  |
| **Roland Morris Disability Questionnaire** |  |  |  | **x** | **x** | **x** |
| **NEADL** |  | **x** |  | **x** | **x** | **x** |
| **Montreal – Cognitive Assessment (MoCA)++** |  | **x** |  |  |  |  |
| **Numeric Pain Rating Scale++** |  | **x** |  | **x** | **x** | **x** |
| **EQ-5D-5L++** |  | **x** |  | **x** | **x** | **x** |
| **Analgesia requirement** |  | **x** |  | **x** | **x** | **x** |
| **Healthcare resource utilisation \*\*** |  | **x** | **x** | **x** | **x** | **x** |
| **Qualitative study interviews** |  |  |  | **x2** | **x3** |  |
| **Participant safety review** |  |  | **x** | **x** | **x** | **x** |

1 Participants in the surgery intervention arm. 2 10 participants. 3 5 participants

\* AMT will be assessed at the point of hospital admission as part of routine care..

\*\* Healthcare resource utilisation will be captured at discharge and throughout the study. All participant questionnaires will be completed where possible, however for those participants that lack capacity, these will not be obtainable, just the clinically assessed ones.

**Appendix 2 – Amendment History**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Amendment No.** | **Protocol version no.** | **Date issued** | **Author(s) of changes** | **Details of changes made** |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |