APPENDIX 10 to WHiTE Platform Master Protocol

World Hip Trauma Evaluation 10

Lidocaine Intravenous Trial (LIT)

This appendix should be read with the accompanying WHiTE Platform Master Protocol. This appendix describes only the additional details relevant to the conduct of this particular randomised comparison within the context of the overarching master protocol. Based on Protocol Appendix Version 8.0, 24Mar2025.

For Master Platform please refer to

Costa, M et al. The World Hip Trauma Evaluation (WHiTE) platform trial: a framework for randomized comparisons of interventions for fragility hip fracture. Bone Jt. Open 2025 (Apr)2;6(4):383-390.

FUNDED BY

NIHR | National Institute for Health and Care Research

This comparison is funded by the National Institute for Health Research and Care (NIHR) Research for Patient Benefit Programme. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

PLAIN ENGLISH SUMMARY

This study has been designed following a James Lind Alliance Patient and Public Research Priority Setting Partnership, which identified the following question as a top research priority: "What are the best treatments to prevent and treat confusion and delirium after surgery in adults with a broken bone in the leg?" The study has been co-produced with the UK Musculoskeletal Trauma Patient and Public Involvement Group.

A broken hip (hip fracture) is a very serious injury that requires surgery to repair or replace the broken bone followed by a long period in hospital to recover. Around a quarter of patients with hip fracture die within a year and those that survive have a permanent loss of their quality of life. Worldwide there are 1.3 million hip fractures each year, with more than 70,000 in the UK.

Around a quarter of patients who have a hip fracture have an episode of 'delirium' after their surgery. Delirium is a condition where the patient loses awareness of themselves and their environment, and has difficulty thinking clearly. For relatives and friends, as well as the patient, delirium is very disturbing. The symptoms of delirium are similar to those of patients with dementia but develop over a short period and tend to vary over time. The great majority of patients suffering with delirium recover quite quickly, but delirium leads to longer hospital stays and a greater risk of complications. Delirium is also associated with an increased risk of developing dementia in later life.

Inflammation, caused by the hip fracture and by the surgery to repair the hip, is thought to be the root cause of delirium. This study will investigate the use of a drug called 'lidocaine' to see if it reduces the risk of delirium after surgery for a hip fracture. Lidocaine is already used very widely in the NHS as a local anaesthetic, but it also has a strong anti-inflammatory effect. If lidocaine is given to a patient during surgery to reduce inflammation, it may reduce the severity of delirium after surgery.

This study is open to all patients aged over 60 years with a hip fracture, apart from the very small number of patients who have an allergy or another reason not to have lidocaine. Eligible patients will be approached about the study before their treatment where possible. Patients who are unable to consent for themselves may take part in the trial with the agreement of their relatives or an independent doctor, who will be known as legal representatives.

Patients from at least 12 hospitals in the UK will be approached to take part in the study. 564 participants will take part. Half will be allocated by chance to a slow injection of lidocaine during their surgery, and half to a placebo injection containing no lidocaine. Neither the patients nor their doctors will know which treatment they had to make the study fair. All other elements of the patients' treatment will follow the normal care pathway for all hip fracture patients at the hospital.

We will use a series of simple questions to measure symptoms of delirium in the first five days after surgery. We will also assess the patients' mobility, quality of life and complications and review if they develop symptoms of dementia in the 12 months after surgery. We will also work out the cost of the treatment – for the individual, for the health service and in terms of social support in the year following the fracture. We will also ask people for their permission to monitor their long-term health outcome from national databases that are already being routinely collected. Any information collected from these databases will not contain any details which could identify the patient.

The results will be presented at scientific meetings and published in medical journals. Patient representatives will produce a lay summary and take the results to patient advocacy groups and share them through social media.

1 BACKGROUND AND RATIONALE

1.1 What is the clinical problem being addressed?

Delirium is a common neuropsychiatric syndrome defined as disturbance of attention, awareness and cognition which develops over a short period of time, represents a change from baseline and tends to fluctuate during the course of the day.[1] Older patients with hip fracture are at particularly high risk of developing post-operative delirium due to the physiological stress and inflammation from the injury, pain and associated analgesia, and the surgery required to treat the broken bone.[2]UK national audit data for 2018 showed that 25% of all patients with hip fracture suffered with post-operative delirium.[3] As well as being distressing for patients and their families, post-operative delirium is associated with poor functional outcomes, reduced quality of life, longer hospital stays and increased mortality.[4] People with hip fracture admitted from their own home who develop delirium are twice as likely to die while in hospital, and nearly four times more likely to need placement in a nursing home, compared to those who do not develop delirium in the post-operative period.[5] Furthermore, post-operative delirium is also closely associated with long-term cognitive impairment.[6–13]

In this trial we will investigate if an infusion of the local anaesthetic lidocaine during surgery, will have an effect on delirium symptoms in the immediate post-operative period and on the development of cognitive impairment, quality of life and mortality in the following year.

1.2 How does the existing literature support this proposal?

The development of delirium and long-term cognitive impairment has been shown to be associated with the inflammatory response following surgery. The cytokines released in the periphery as a result of the injury and the surgical trauma lead to increased permeability of the blood brain barrier,[14] ingress of activated leucocytes and activation of central nervous system microglia, which lead to neuronal injury and delirium.[5] A wide variety of inflammatory mediators have been implicated in the development of delirium, including TNF, IL-4 and IL-6.[15]

In 2016, a Cochrane review of interventions for preventing delirium in hospitalised patients found only six trials including a total of merely 866 patients.[16] They found that just one study of 126 hip fracture patients comparing proactive geriatric consultation with usual care was sufficiently powered to detect a difference in the primary outcome, incident delirium. The review concluded that "*Research evidence on effectiveness of interventions to prevent delirium is sparse*" and "*Further studies of delirium prevention are needed*"

We systematically reviewed the literature since that Cochrane review. There have been trials investigating blood transfusion,[17] rivastigmine patches,[18] post-operative analgesia regimes,[19] and types of anaesthesia/sedation,[20–22] but most of these studies were designed to treat the symptoms of delirium, rather than the underlying inflammation which causes it.

One trial investigated the effect on delirium of methylprednisolone (an anti-inflammatory drug) vs placebo in patients having surgery for hip fracture. This study found some evidence of a benefit in secondary outcomes, including suppression of cytokine response, but no significant difference in the primary outcome of delirium severity score over the first three post-operative days.[23] However, that was a small, single centre trial excluding those who lacked capacity, so therefore those at most risk.

There are no trials registered using intravenous lidocaine in the context of hip fracture, or other interventions designed specifically to target inflammatory pathways in the peri-operative period. At the

time of developing this appendix, the ALLEGRO trial[24] is investigating the effect of lidocaine on gastrointestinal function in patients undergoing gastrointestinal surgery. Gastrointestinal surgery is a different population with a much lower risk of delirium, and delirium is not the primary outcome of that study. The results of that study will therefore be complementary to this proposal but not addressing the same questions.

The trials reported above, with the exception of the methylprednisolone trial, have used agents aimed at treating delirium symptomatology, whereas our trial will act directly on the potential inflammatory mechanism.

Use of intravenous lidocaine is associated with significant reductions in interleukin-6 in the early post-operative period (SMD -1.70 [-3.17—0.24]); elevated IL-6 is the most commonly identified cytokine change in people with delirium. Lidocaine prevents leucocyte adherence to endothelium when administered before and after injury.[25,26] There is also some evidence of a direct neuroprotective effect on neuronal energy balance and homeostasis following hypoxic injury.[27]

Recent consensus statements have recognised the importance of safe use of intravenous lidocaine, particularly when used outside of the operating theatre (distinct to this protocol).[28] This protocol has been developed with full reference to these statements, and the views of other clinicians and researchers. The need for research to demonstrate the benefits (or lack of benefit) of intravenous lidocaine is recognised. In summary, there is evidence that intravenous lidocaine may have beneficial effects on delirium, mediated through its effects on inflammation, but this hypothesis needs to be tested in the context of a large randomised trial.

1.3 Need for this comparison

Avoiding post-operative delirium is a priority for the NHS; reducing delirium is a 'Key Performance Indicator' for the UK National Hip Fracture Database (NHFD) and is linked to Best Practice Tariff payments in England.[29] Delirium is a devastating acute neuropsychiatric syndrome, common in people with hip fracture, and associated with adverse outcomes.[2] Despite this, there are no treatments to prevent or ameliorate delirium, in part due to our poor understanding of the underlying biology.

A recent NIHR James Lind Alliance Research Priority Setting Partnership, identified: "*What are the best treatments to prevent and treat confusion and delirium after surgery in adults with a fragility fracture of the lower limb?"* as a key research priority. It also addresses a key research question in the forthcoming Association of Anaesthetists' guidance on perioperative management of hip fracture: "*What are the best anaesthetic interventions to prevent and treat confusion and delirium after surgery for hip fracture?"* This proposal falls within the remit of the current NIHR *injuries, accidents and urgent and emergency care* themed call, in particular the management and treatment of the commonest major injury in older people.

2 OBJECTIVES AND OUTCOME MEASURES

2.1 Primary objective

To compare peak delirium in the 5 days following hip fracture surgery between the treatment groups.

2.2 Secondary objectives

1. To compare cognitive impairment scores at 4 and 12 months post-diagnosis of a hip fracture between the treatment groups.
2. To compare peak delirium screening in the 5 days following hip fracture surgery between the treatment groups.
3. To compare pain in the 5 days following hip fracture surgery between the treatment groups.
4. To compare health-related quality of life at 4* and 12 months post-diagnosis of a hip fracture between the treatment groups.
5. To compare mortality risk within the first 12 months post-diagnosis of a hip fracture between the treatment groups.
6. To compare mobility at 4* and 12 months post-diagnosis of a hip fracture between the treatment groups.
7. To compare residential status at 4* and 12 months post-diagnosis of a hip fracture between the treatment groups.
8. To compare risk and pattern of complications at 4* and 12 months post-diagnosis of a hip fracture between the treatment groups.
9. To compare the healthcare and broader resource implications at 4* and 12 months post-diagnosis of a hip fracture between the treatment groups.

*These time-points indicate that these objectives are already collected as part of the overarching platform.

2.3 Exploratory mechanistic objective

The following objective will be investigated through analysis of EEG recordings.

i) Explore whether EEG patterns that correlate with inflammation are predictive of the development and severity of delirium.

The collection of EEG recordings will only be conducted in a subset of recruitment centres based on research team capacity and availability of relevant equipment. Consent to collect EEG recordings for the exploratory mechanistic objective will be optional for participants.

2.4 Outcome Measures

The common outcome data described in the Master Protocol at baseline and 4 months post-diagnosis of a hip fracture will be collected and augmented with additional data collection during the first five days after hip fracture surgery and at 4 and 12 months post-diagnosis of a hip fracture.

Primary

Delirium:

The primary outcome measure is peak post-operative delirium as measured by the ***Memorial Delirium Assessment Scale (MDAS).***

Participants will be assessed once daily after the surgical repair of the hip fracture using the MDAS[30] from day 1 to day 5. The MDAS is a validated scale which quantifies the severity of delirium based on 10 features which integrates behavioural observations with objective cognitive testing. MDAS generates a scale from 0 to 30 (30 is most severe) and can be completed by trained research staff in 5 minutes or less.[4,31] The peak MDAS score will be the maximum recorded score reflecting the worst and most delirious state of the participants in the first five days after surgery.

In addition to the expertise and experience within the research team, we sought advice from several external sources with regard to the choice of primary outcome measure in this trial. While several other assessment tools were considered, MDAS has been used widely in previous trials, including large trials in the hip fracture population.[32] The peak MDAS recorded in the 5 days following surgery provides a comprehensive assessment of the severity of delirium, integrating behavioural observations with objective cognitive testing. Furthermore, MDAS is based upon the diagnostic criteria for delirium in the Diagnostic and Statistical Manual of Mental Disorders (DSM); the 10 MDAS features being: reduced level of consciousness/awareness, disorientation, short-term memory impairment, impaired digit span, reduced ability to maintain and shift attention, disorganised thinking, perceptual disturbance, delusions, decreased or increased psychomotor activity, and sleep-wake cycle disturbance. Another key consideration was the feasibility of training staff to use the delirium assessment tool in the context of a large-scale trial. We believe that the peak MDAS in the first five days following surgery will provide a comprehensive assessment of delirium, without requiring extensive training and/or specialist staff to administer it.

The minimum clinically important difference of 2.5 on the 30-point scale, and the Standard Deviation for the peak MDAS in the post-operative period of 7.0, was established specifically in patients with hip fracture.[4] The decision to adopt a Minimal Clinically Important Difference (MCID) of 2.5 using the full scale of the MDAS tool (c.f. a cut-off score) was made based upon a review of the literature and direct discussions and the recommendation of Ed Marcantonio, Professor of Medicine at Harvard, who has investigated this area extensively.[4,31]

Secondary

In addition to the common outcome instruments, described in the master protocol, further information on delirium, the level of cognitive impairment and pain will also be collected:

Delirium Screening: The 4AT is a relatively recently developed tool for assessment of possible delirium.[33–36] AT covers four domains: Alertness; Abbreviated Mental Test; Attention; and Acute change. Total scores range from 0 to 12, with scores of ≥4 indicating possible delirium. It is sensitive, specific, quick (<2 min) and does not require specialist training to perform. 4AT will be collected pre-surgery and on each of the first 5 days post-surgery.

Pain: Pain will be assessed using the Functional Pain Scale (FPS) for use in hospitals,[37,38] which is a validated 5-point scale that assesses the activities that pain limits rather than rating severity of pain. For participants unable to communicate due to mental capacity (estimated to be approximately 10% of the comparison sample) the validated Pain Assessment in People with Advanced Dementia (PAINAD)[39,40] tool will be used. PAINAD is a five-domain score ranging from 0-10. FPS / PAINAD will be collected pre-surgery and on each of the first 5 days post-surgery.

Cognitive impairment: Patients will complete Cognitive Impairment using the Telephone Interview for Cognitive Status (TICS) UK English 2014 questionnaire [41,42]at 4 and 12 months post-diagnosis of a hip

fracture. Since most people treated for a hip fracture in the UK are not followed-up in person after being discharged from hospital, TICS questionnaire is the best tool in this setting. A 3-point difference in TICS score (score=0-41, with lower scores indicating cognitive impairment) is considered clinically significant.

Exploratory

EEG recordings: The non-invasive electrodes will be applied to the participant's head before the start of surgery and intraoperative EEG recordings will be taken. EEG data will be collected as raw data. The EEG recordings will be transferred to the University of Oxford via secure file transfer for analysis.

3 DESIGN

3.1 Concept

This is a randomised comparison embedded within the overarching WHiTE Platform testing clinical superiority between the treatment groups with a parallel economic analysis. The primary outcome is the peak MDAS score over the first five days post-surgery. Participants will be allocated using a 1:1 random allocation, stratified by presence / absence of permanent cognitive impairment at presentation and recruitment centre.

This will be a two-phased comparison. Phase 1 (internal pilot) will confirm the expected rate of recruitment and optimising of procedures in 4 UK hospitals. Phase 2 (main phase) will extend the randomised comparison to a minimum of 12 UK hospitals.

Internal Pilot

The pilot will take place at a minimum of 4 recruitment centres over a period of nine months. The aim of this initial phase will be to determine the number of eligible and recruited patients in the recruitment centres and optimising trial procedures and data collection systems over the course of nine months.

Screening logs will be kept at each recruitment centre to determine the number of patients assessed for eligibility and reasons for any exclusion. The number of eligible and recruited patients, and the number of patients who decline consent or withdraw will be recorded. The Data and Safety Monitoring (DSMC) and Platform Oversight Committees (POC) will closely monitor recruitment during the feasibility phase and review the assumptions regarding the distribution of the primary outcome data in order to make a recommendation regarding continued progress of the comparison against the specified stop/go criteria. Once the comparison is deemed feasible an application for funding for the main phase will be made. If the comparison is stopped –due to feasibility not being shown or further funding not being obtained, then all participants will be followed up per protocol. If the comparison continues into the main phase, participants from the internal pilot will be included in the final analysis.

Main phase

During the main comparison phase, patients will be recruited for a further 9 months from at least a further 8 additional centres, bringing the minimum number of recruitment centres to 12 across the UK.

Participants will be allocated on a 1:1 basis to either placebo or lidocaine infusion treatments.

Assessments will include all those described in the Master protocol, augmented with additional data relevant to this specific randomised comparison. In summary:

Routine pre-operative cognitive assessment will be made using the delirium screening tool (4AT); this score is used throughout the UK as part of routine admission clinical practice. Similarly, as part of routine care, full blood counts are taken pre-operatively; we will record the haemoglobin concentration taken on admission from electronic records. Pain will also be assessed pre-operatively. Further baseline demographic data including pre-injury mobility and residential status will be collected. Participants or their proxy will also be asked to complete the EuroQol EQ-5D-5L to indicate their typical pre-injury health status.

The primary outcome is post-operative delirium recorded using the peak MDAS which will be recorded each day during the first five days after surgery. Secondary short-term outcomes are pain scores and 4AT which will also be measured over the first 5 days.

At 4- and 12-months post-diagnosis of a hip fracture, cognitive function using TICS, EQ-5D-5L,[43] residential and mobility status, pain, complications and participant-completed resource use questionnaires will be collected remotely. We will adopt the techniques used in the WHiTE Cohort[44] to collect self-reported or proxy-reported health states.

4 STUDY PROCEDURES

A comparison flow chart is provided in Annex A.

4.1 PARTICIPANT IDENTIFICATION

4.1.1 Comparison participants

A subset of participants in the overarching WHiTE platform will be eligible for this randomised comparison.

4.1.2 Inclusion criteria

As per the overarching platform protocol; all adults aged 60 years or over diagnosed with a hip fracture that in the opinion of the treating surgeon may benefit from surgical treatment.

4.1.3 Exclusion criteria

In addition to the exclusion criteria stated in the overarching master protocol, the participant is not eligible if ANY of the following apply:

- Body weight estimated to be less than 40 kg or greater than 100 kg
- Known serum albumin less than 30 g/l
- Known subdural haematoma
- Known allergy to local anaesthetics
- Severely impaired renal (eGFR <30 ml.min-1) or hepatic (based on clinical history) function.
- Specific contraindications to lidocaine:
    - all grades of atrioventricular block; severe myocardial depression; sino-atrial disorders
    - acute porphyria
    - current congestive cardiac failure
- Concurrent participation in a clinical trial of a medicinal product or recent participation within 5 half-lives of the last dose of medicinal product
- Local anaesthetic nerve block administered within the previous 6 hours

Eligibility for entry into the comparison will be confirmed by a medically qualified person.

4.2 Consent

Patients will be presumed to have capacity unless established otherwise and the default will be to seek prospective individual consent from every patient. Where patients do not have capacity, those procedures laid down in Section 11.4 of the Master Protocol will apply.

Where participants are recruited in a recruitment centre that is taking part in the collection of the exploratory mechanistic outcome, they will be provided with the option to consent to having their EEG recordings collected. For participants who do not have capacity at the time of consent, the Legal Representative will be given the option to consent for the EEG recordings.

With regard to these provisions, the randomised comparison described in this appendix **is** a clinical trial of an investigational medicinal product.

4.3 Randomisation

Randomisation will be as per the Platform Master Protocol. Randomisation will be on a 1:1 basis to lidocaine or placebo, stratified by the presence/absence of permanent cognitive impairment at presentation and recruitment centre. The allocation sequence will be generated by the trial statistician using variable block sizes and stored securely in a web-based encrypted system provided by OCTRU. Full details will be stored in a separate randomisation and blinding plan stored in the confidential statistics section of the trial master file.

Randomisation will be performed as close to the time of induction of anaesthesia as possible to avoid the risk of postponement of surgery or moving to a different theatre list.

4.4 Blinding and code-breaking

This is a double-blinded comparison, whereby the participant and the local research team members involved in the delirium assessment and data collection process will be blinded to the allocated treatment. An (unblinded) treating anaesthetist will prepare the comparison medications following randomisation. The treating anaesthetist will not be involved in the data collection process.

The participants in this comparison will not be informed which of the two treatments they have received. No formal assessment of the success or otherwise of the blinding will be made.

A 24 hour emergency unblinding function will be available via the secure online randomisation system to reveal which treatment a participant has been allocated to, should this be required. However, the emergency scenario i.e. local anaesthetic toxicity will always be managed using the applicable local and national policy and guidelines, which will not require staff to carry out unblinding first.

4.5 Assessments

4.5.1 Schedule of assessments

The overall schedule of assessments, including the common outcome set and the additional outcomes measured for this comparison, and methods for data collection are described in the table below:

Time Point	Data	Source	Setting
Pre-surgery*	i) 4AT ii) FPS/PAINAD iii) pre-operative haemoglobin levels	Participant or proxy (blood sample: participant only)	Acute inpatient - face to face;
Baseline^	i) Demographics ii) Relevant medical history iii) Injury details Pre-injury (retrospective): iv) EQ-5D v) Residential status vi) Mobility status vii) Resource use	Participant or proxy & medical record	Acute inpatient - face to face; medical record review
Surgery	i) Intra-operative analgesia used ii) Intra-operative EEG recordings	Anaesthetic chart Participant	Medical record review Acute inpatient
Days 1-5 post-surgery*	MDAS 4AT FPS/PAINAD Opioid analgesia use	Participant or proxy Medical records	Acute inpatient - face to face; Medical record review
Up to point of discharge	i) Early complications	Medical records	Medical record review
4 months post-diagnosis of a hip fracture	i) EQ-5D ii) TICS* iii) Complications iv) Residential status v) Mobility status vi) Resource use	Participant or proxy	Telephone, online or postal
12 months post-diagnosis of a hip fracture *	i) EQ-5D ii) TICS iii) Complications iv) Residential status v) Mobility status vi) Resource use	Participant or proxy	Telephone, online or postal

Table 1: Assessment schedule, instruments and means of collection.

Key: ^Baseline information will be collected before surgery where possible, otherwise it will be collected as soon as possible after.
**Indicates measurement timepoint or data collected is in addition to the Platform Common Dataset specified in the master protocol*

4.5.2 Visits and Contacts

Contact 1: Pre-operatively, 4AT, FPS/PAINAD will be collected on the hospital ward. Pre-operative haemoglobin levels will be recorded from medical records as a potential prognostic marker for delirium for the mechanistic outcome.

Contact 2: Baseline data collection as per Platform Protocol.

Contact 3: During surgery: EEG recordings will be taken during surgery from consented participants in those centres participating in the exploratory mechanistic part of the protocol. For patients whose EEG recording will be recorded, a list of the anaesthetic drugs received intraoperatively will also be collected.

Contacts 4-8: Days 1-5 after the day of surgery, delirium assessments will be made on the hospital ward by trained staff using the MDAS and 4AT scores. A pain score will also be collected.

Contact 9: Follow-up at 4 months post-diagnosis of a hip fracture as per Platform Protocol with the addition of TICS.

Contact 10: Follow-up at 12 months post-diagnosis of a hip fracture, will be completed directly with the participant or a proxy either via telephone interviews by a member of the central research team, or through electronic means depending on choice expressed by the participant or proxy at the time of consent.

4.6 Sample Handling

No samples, other than those routinely collected as part of clinical care, will be taken for the purposes of this comparison.

4.7 Mechanistic Outcomes Analysis

4.7.1 EEG recordings

The aim of this mechanistic work is to quantify the EEG patterns which correlate with postoperative delirium. The recording will use standard clinical electroencephalography monitors from the start of anaesthesia until the end of surgery. Recordings will be downloaded from the monitor at the recruitment centre after the operation according to relevant recruitment centre SOPs or policies. The digital recording will be sent to the University of Oxford via a secure server that each recruitment centre participating in the mechanistic work will be given upload access to. The recordings will be stored on secure servers at the University of Oxford. Analysis of the patterns of EEG will take place at the University of Oxford with the comparison identification number as the identifier. The anaesthetist caring for the participant will not be required to interpret the raw EEG during surgery.

4.8 Definition of End of Comparison

The end of the comparison is the point at which the follow up of the last participant has been completed, all the data has been entered and all queries have been resolved. The last direct data collection will be at one year post-diagnosis of a hip fracture of the last participant. The Sponsor, MHRA and main Research Ethics Committee will be notified in writing within 15 days if the comparison has been concluded or terminated early.

5 INTERVENTIONS

5.1 Description of the randomised treatments

Participants will be randomly allocated to one of the treatment arms:

- Intervention: Intravenous lidocaine 1.5 mg.kg^{-1} bolus followed by infusion of 1.5 mg.kg^{-1}.h^{-1} for the duration of surgery
- Placebo control: Identical volumes of 0.9% saline

The allowed maximum absolute dose will be 120 mg and 120 mg h^{-1} regardless of weight.

Both lidocaine and saline have market authorisation and are routinely used in clinical practice. They will both be prepared as per section 10.1.2 below prior to administration. The IMP, lidocaine, is described only by its active ingredient and any brand can be used for the trial.

5.1.1 Blinding, Labelling and Storage of the IMP

The IMP will be used from normal standard stock held in the operating theatre and will not be labelled with a Clinical Trial Label; nor will the packaging be blinded.

An appropriately trained anaesthetist not involved in the assessment of any comparison outcomes will carry out the online randomisation. The treating anaesthetist will prepare a syringe with the allocated intervention, in an area away from the rest of the clinical team. The prepared syringe will then be labelled 'lidocaine 1% or saline 0.9%' so as not to reveal the treatment allocation to the blinded assessors accidentally. Lidocaine and saline are clear colourless solutions, indistinguishable to the human eye.

1) Intravenous solution – 50ml 1% lidocaine (10mg.ml^{-1}) (intervention group). This solution will be drawn up directly from ampoules containing 1% lidocaine. No dilution is required.

OR

2) 50ml 0.9% saline (control group). This solution will be drawn up directly from ampoules containing 0.9% saline. No dilution is required.

The attending anaesthetist will give the intravenous medicines as a slow bolus over 5 minutes followed by the infusion at 0.15 ml kg^{-1} h^{-1} (e.g. 9ml bolus followed by 9 ml h^{-1} for a 60 kg participant).

5.1.2 Accountability of the Comparison Treatment

As this is a pragmatic randomised comparison involving a one-off administration of the intervention in a context where it is frequently administered at similar or higher doses, by clinically trained professionals, a risk adapted approach has been employed to ensure the appropriate level of documentation is kept to record IMP accountability as per standard local practice. The total dose of administered treatment will be collected.

5.1.3. Anaesthetic technique

A regional or general anaesthesia technique will be used for each participant as per routine clinical care. Intra-operative analgesia may be achieved by combining a local anaesthetic nerve block, plus paracetamol 1g and opioid analgesia as clinically indicated. All participants will receive a peripheral regional block using

1.0 mg kg^{-1} l-bupivacaine diluted as appropriate with 0.9% saline; either femoral or fascia iliaca blockade will be used at the attending anaesthetist's discretion. Surgery to fix or replace the broken part of the hip will take place using the preferred technique and implants of the operating surgeons as per routine clinical practice. Relevant details of the treatment pathway will be recorded.

5.1.4 Safety of the IMP

The main concerns with use of local anaesthetics in the context of surgery and anaesthesia (whether administered intravenously or part of a regional technique) are cardiovascular and central nervous system toxicity. Severe effects are rare in clinical practice when toxic doses are not administered. Harms, including death, from local anaesthetic administration have been reported due to inadvertent intravenous administration of solutions intended for epidural use (and hence a large intravenous dose rather than the more slowly absorbed epidural dose).

Cardiovascular and neurological toxicity of local anaesthetics is related to concentration. Toxic concentrations vary for the different local anaesthetics, but toxicity of local anaesthetics is effectively additive. Local anaesthetic concentration can therefore be referenced as fractions of a toxic dose. A dose of a single local anaesthetic that is 50% of a toxic dose is therefore equivalent to a combined dose of two different local anaesthetic agents given at 25% of their toxic dose. This is how safe local anaesthetic doses of mixtures of local anaesthetics are calculated in normal, routine clinical practice.

Data from an updated systematic review and meta-analysis of studies reporting concentrations of lidocaine after bolus and infusion are discussed below. Most studies report a loading dose of 1-1.5 $mg.kg^{-1}$ followed by an infusion of 1.5-2 mg $kg^{-1}.h^{-1}$. As shown in Figure 1 below, mean peak lidocaine concentrations are ~ 1.77 $\mu g.ml^{-1}$ with bolus dose <3 mg kg^{-1} and infusion < 3 mg $kg^{-1}.h^{-1}$. The upper 95% confidence interval (CI) of the mean lidocaine concentration is 2.21 $\mu g.ml^{-1}$. The CNS toxic dose of lidocaine is ~5μg ml^{-1}. This therefore equates to ~35% of toxic dose at mean, ~ 45% at upper 95% CI, and ~45% even for the highest individual study 95% CI (Martin). [45]

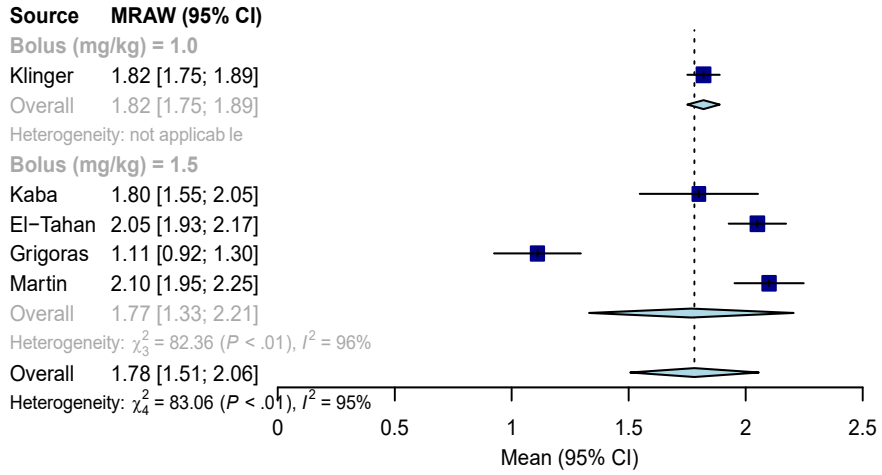

Figure 1: data displaying mean peak lidocaine concentration, gathered from meta-analysis of studies

There are only two studies examining the pharmacokinetics of bupivacaine following regional blockade for hip fracture (Figure 2).[46,47] These data suggest a mean concentration of ~0.8 $\mu g.ml^{-1}$ after 1.39 – 2 $mg.kg^{-1}$ block dose. The toxic concentration of bupivacaine ~ 2.4 – 2.6 $\mu g.ml^{-1}$. This therefore equates to ~33% of 'toxic dose', ~42% at upper 95% CI, ~45% for highest 95% CI.[20]

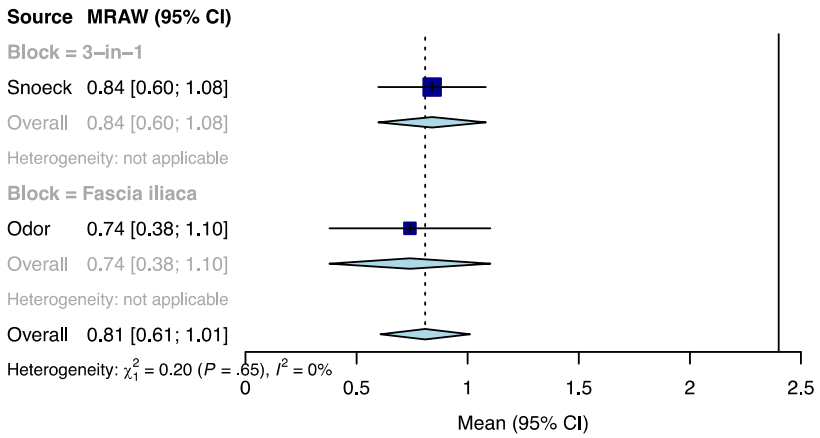

Figure 2: data displaying mean bupivacaine concentrations

The intervention group will be receiving a bolus of 1.5mg.kg^{-1} lidocaine followed by an infusion of 1.5 mg. kg^{-1}.h^{-1}. The most conservative estimate is that this would equate to around 45% of a toxic equivalent. The bupivacaine dose is 1.0 mg.kg^{-1}. This is approximately 70% of the lowest dose (1.39 mg.kg^{-1}) reported in the two studies reported above. Therefore a conservative estimate is that the bupivacaine dose to be used in the comparison is ~30% of a toxic dose (70% of highest concentration (45%) = ~30%).

The total combined dose of the local anaesthetic in the intervention group is therefore ~75% of toxic equivalents, using a conservative estimate of the highest plasma concentrations. Mean concentrations in total equate to ~55% of a toxic dose. The dose for regional block has been reduced by 50% to give an increased margin of safety. The volume of the injection will remain the same for both groups. Since the volume of the injection determines the distribution of the anaesthetic in the relevant soft-tissue plane, and only a fraction of the amount infiltrated is required to anaesthetise the femoral nerve, no patient will be disadvantaged by this reduction in dose. The dose of local anaesthetic used in routine clinical practice for regional block for hip fracture varies considerably. 2mg.kg^{-1} is the generally accepted safe maximum. In clinical practice most anaesthetists use less than this as the aim is for safe, prolonged analgesia (pain relief) rather than anaesthesia (lack of sensation). Analgesia is achieved with lower doses than needed for anaesthesia. Hence, a regional block dose of 1.0 mg.kg^{-1} of bupivacaine is expected to achieve the twins aims of safety and efficacy in both groups.

5.1.5 Efficacy of the IMP

The majority of studies report bolus lidocaine doses of 1.5 – 2.0 mg.kg^{-1} with infusions of 1.5 – 3.0 mg.kg^{-1} h^{-1}.This proposed dose regime is identical to the one used in the ongoing NIHR-funded ALLEGRO study[24] in gastrointestinal surgery).

Standard of care is for a regional nerve block to be offered to all patients having hip fracture surgery. Without clear evidence of the benefit of IV lidocaine, it would be unethical to deny this to participants.

5.1.6 Management of local anaesthetic toxicity

All administration of local anaesthetics (intravenous and regional block) will be carried out by suitably qualified anaesthetists within the setting of an operating theatre. All anaesthetists are trained in the recognition and management of local anaesthetic toxicity. All theatre suites have local anaesthetic toxicity protocols and immediate availability of 20% Intralipid. The Association of Anaesthetics of Great Britain and

Ireland (AAGBI) guidelines should be followed in such instances.[48,49] The availability of local protocols and Intralipid will be checked as part of site feasibility assessments before any site confirms participation in this comparison.

5.1.7 Concomitant Medications

Section 4.5 of the Summary of Product Characteristics should be referred to for concomitant medications to avoid prior to and during dosing with lidocaine.

6 SAFETY REPORTING

Safety reporting for each participant will begin from the time of consent and will end when the participant has reached their final follow up time point, at 1 year post-diagnosis of a hip fracture. As the safety profile of lidocaine is very well known, only serious adverse events (SAEs) will be reported for this comparison. Investigators should follow up serious adverse events until resolved or the participant reaches 1 year post-diagnosis of a hip fracture.

All SUSARs are to be reported according to the guidelines relevant to CTIMPs specified in section 15 of the Master Protocol.

6.1 Related and expected Serious Adverse Events

Across all the comparisons, SAEs which are related to and expected in the course of a hip fracture before, during and after the admission for a hip fracture including standard surgical procedures, will be exempt from reporting as SAEs across all comparisons unless the event is considered related to an IMP intervention. SAEs related to IMPs will be subject to safety reporting as per the instructions in the Platform Master Protocol. Instead, all other events must be reported on a 'Complications Case Report Form'.

Complications will be classified as 'general' complications or 'surgery specific' complications.

<u>General complications:</u>

- Chest Infection/Pneumonia requiring antibiotic treatment
- Urinary Tract Infection requiring antibiotic treatment
- Cerebrovascular Accident diagnosed with a CT/MRI scan of the brain
- Clinically diagnosed Myocardial Infarction/Acute Coronary Syndrome documented in the medical record
- Pulmonary Embolism requiring anti-coagulation or interventional radiology treatment
- Deep Vein Thrombosis requiring anti-coagulation or interventional radiology treatment
- Clinically diagnosed Acute Kidney Injury documented in the medical record
- Blood transfusion
- Clinically diagnosed delirium documented in the medical record
- Death

<u>Surgery-specific complications:</u>

- Intraoperative damage to a nerve, tendon or blood vessel documented in the operation note

- Intraoperative fracture of the bone documented in the operation note
- A wound infection that required treatment with antibiotics
- A dislocation of the hip replacement requiring reduction under sedation (not in an operating theatre)

Surgery specific complications requiring treatment in an operating theatre for:

- Dislocation of the hip replacement requiring closed reduction or revision surgery
- Fracture around the replacement requiring revision surgery
- Failure (or impending failure) of the fixation or bone healing requiring revision surgery
- Washout of a wound Infection
- Wound infection requiring removal or revision of the fixation/replacement
- Other reason for removal of the fixation/replacement

Local anaesthetic toxicity is an SAE that is expected and related to the IMP. This will be exempt from reporting as an SAE unless the reaction is assessed to be more severe than expected, in which case sites must report it on a SAE form. Instances of severe local anaesthetic toxicity which must be reported as SAEs include:

- toxicity requiring treatment with Intralipid
- sudden alteration in mental status
- severe agitation or loss of consciousness, with or without tonic-clonic convulsions
- significant cardiovascular events (including sinus bradycardia, conduction blocks, asystole and ventricular tachyarrhythmias).

Cases of expected local toxicity that do not require expedited reporting include:

- Circumoral and/or tongue numbness.
- Metallic taste
- Light headedness
- Dizziness
- Visual and auditory disturbances (difficulty focusing and tinnitus).

6.2 Expectedness

For SAEs that require reporting, expectedness of SARs will be determined according to the relevant RSI section of the Summary of Product Characteristics. The RSI used (within the SmPC) will be the current Sponsor and MHRA approved version at the time of the event occurrence.

7 STATISTICS & ANALYSES

7.1 Sample Size Determination

The sample size for this comparison will be 564 participants.

The MCID for the MDAS is 2.5 on the 30 point scale and, in patients with hip fracture, prior estimates of Standard Deviation (SD) for the peak MDAS in the post-operative period are around 7.0.[4] However, in the pilot phase of this trial a slightly higher standard deviation of 8.4 was estimated (using blinded data from the first 120 participants). Using this estimate of the standard deviation, assuming 90% power and 5% (2-

sided) significance a sample size of 478 participants (239 per arm) would be required. Allowing for 15% loss to follow-up this is inflated to 564 participants (282 per arm). Although we do not anticipate this level of attrition for the primary outcome measure, this inflation of the sample size calculation will allow us to collect high-quality secondary outcome data.

7.2 Analysis Populations

The primary analysis population will be intention to treat (ITT); that is all participants will be analysed as randomised. Sensitivity analyses will be undertaken on the per-protocol population for the primary outcome and key secondary outcomes.

The ITT population includes all randomised participants including:

1. Participants who are randomised but do not undergo surgery (such as those who died or were found to be ineligible after randomisation but before surgery).
2. Participants who are randomised and found to be ineligible during or after surgery.

Note: participants who withdraw from the comparison between randomisation and 1 year will provide data up to the point of withdrawal.

The per protocol population will be the ITT population excluding participants as described in 1 and 3 above and other major deviations from the protocol which will be fully described in the Statistical Analysis Plan.

7.3 The Level of Statistical Significance

The statistical significance will be assessed at 5% for two-sided tests. All p-values will be reported to 3 decimal places. 95% confidence intervals will be reported throughout.

7.4 Decision Points

A total of 564 participants will be randomised across a minimum of 12 recruitment centres. We will exploit the efficiencies available from nesting this within the Platform. This Platform has been built based upon the experiences of the WHiTE Cohort Study, which has successfully delivered three hip fracture trials[50–52] and three further trials are currently underway (ISRCTN92825709, 18393176, 15606075). The comparison processes are streamlined and harmonised with those of the Platform so that we should be able to achieve 65% recruitment of eligible patients and 90% follow-up of available participants (those alive and not withdrawn) at the primary outcome time-point.

During the 9 months internal pilot phase, we expect to recruit 100-120 patients from the 4 pilot recruitment centres. The DSMC and POC will closely monitor recruitment during the feasibility phase and make a recommendation with regards continued progress of the comparison. If recruitment is below 70 participants, we will consider stopping the comparison for feasibility reasons, if between 70 and 100 participants we will review the recruitment processes and implement the committees' recommendations. In the event that recruitment is lower than anticipated we have a network of 120 hospitals in addition to these 12 that have previously worked with us on multicentre trials.

7.5 Analysis

A full, detailed statistical analysis plan (SAP) will be drafted early in the trial and will be finalised following the recruitment review by the DSMC and POC and prior to the primary analysis data lock. Any subsequent changes to the SAP will be fully justified in the final report. Stata (StataCorp LO) or other appropriate validated statistical software will be used for analysis.

Baseline demographic data will be summarised by treatment groups to assess comparability between treatment arms. Binary and categorical data will be summarised as frequencies and percentages, normally distributed continuous data will be summarised as means and standard deviations, and non-normally distributed continuous data as medians and interquartile ranges. Primary and secondary outcomes will be explored graphically.

The main analysis will investigate differences in the primary outcome measure, the peak (maximum) Memorial Delirium Assessment Scale (MDAS) scores during the first five days post-operatively. The principal analyses will be conducted on the intention-to-treat (ITT) population using mixed-effects linear regression. Stratification factors will also be included within the models with centre included as a random effect to allow for any heterogeneity in response between centres, and the presence or absence of permanent cognitive impairment pre-surgery will be included as a fixed effect. Models will also adjust for important baseline covariates to maximise precision, which will include age as a continuous variable, sex, type of surgery as either fixation or total hip replacement, and type of anaesthesia as either general anaesthetic or spinal anaesthetic. The treatment difference will be based on the estimate of adjusted means and 95% confidence intervals, with a 2-sided significance level of 5% being used for comparative tests. The sensitivity of the primary outcome data to the underlying population will be assessed using the per-protocol (PP) population; the definitions of this population will be fully defined in the SAP.

The analysis of secondary clinical outcomes will use multi-level mixed effects regression models and will include all time-points, where appropriate. Continuous outcomes will be analysed using linear mixed effects regression, and binary outcomes will be analysed using logistic mixed effects regression. During the recruitment period, the data collection tool used for the assessment of mobility (secondary objective) was changed from the 'NHFD mobility questions' to the 'modified New Mobility Score (mNMS)'. Data collected through these two outcome tools will be summarised separately at the end of the study. The change in outcome collection tool was made during the early stages of recruitment and the majority of study participants will provide data on mobility through this mNMS tool. The primary analysis with regards the mobility objective will therefore be performed on the mNMS data. The NHFD mobility data will be used as supportive evidence.

Missing data will be minimised through careful data management. Missing data will be described with reasons given where available; the number and percentage of individuals in the missing data category will be presented by treatment groups. The nature and mechanism for missing variables and outcomes will be investigated and sensitivity analyses will be undertaken to assess the underlying missing data assumptions, in particular whether it can be treated as missing completely at random (MCAR). Missing data may be imputed in sensitivity analyses if considered beneficial to the interpretation of the main findings. Any imputation methods used for scores and other derived variables will be carefully considered and justified. Reasons for ineligibility, non-compliance, withdrawal or other protocol violations will be stated and any missing data patterns summarised.

Adverse events will be explored to assess if they differ between groups.

7.6 Health Economic Analysis

A fully detailed health economic evaluation analysis plan (HEAP) will be drafted early in the trial and finalised after review by the DSMC and POC. The within-trial economic evaluation will determine cost-effectiveness in relation to quality-adjusted life years (QALYs) from an NHS and personal social services (PSS) perspective at four months post-diagnosis of a hip fracture. Fractures in this elderly population may

burden their carers and it is possible that different treatment pathways will have different consequences on their families and friends. As such, we will report separately the broader resource use such as any private expenses, informal care, and productivity losses incurred in both arms due to the injury.

Any missing QALYs and costs will be jointly imputed using multiple imputation chained equations. Cost and QALY estimates will be bootstrapped and adjusted for trial stratification variables (centre) and other potential variables as per the statistical analysis plan, such as age, gender and cognitive impairment, in secondary analyses. “All available” and “imputed” cost categories and QALY data, will be reported by trial arm in a cost-consequences framework. An incremental cost-effectiveness analysis comparing the cost-effectiveness of different trial arms will be expressed in terms of incremental cost per QALY gained from the NHS and PSS perspective at four months post fracture diagnosis for the base-case analysis. Results will be presented using incremental cost-effectiveness ratios (ICERs) and cost-effectiveness acceptability curves (CEACs) will be generated via non-parametric bootstrapping to accommodate sampling (or stochastic) uncertainty and varying levels of willingness to pay for an additional QALY. The ICER will be compared with willingness-to-pay thresholds of £20,000 and £30,000 per QALY, which are commonly assumed in the UK by bodies such as the National Institute for Health and Care Excellence. An additional £15,000 cost-effectiveness threshold will also be included to reflect recent trends in health-care decision-making. The net monetary benefit (NMB) of intervention versus control will also be computed and presented in a graph across different cost-effectiveness thresholds. In order to gauge the robustness of the results, deterministic sensitivity analysis will be performed. First, a societal perspective that includes broader resource use will be considered. Second, a complete-case analysis in which only patients with completed data on all cost and outcome data at all follow-up time points will be performed. Last, a time frame of 12 months post-diagnosis of a hip fracture will be investigated.

8 DISSEMINATION POLICY

Outputs for LIT will be released within 12 months of the end of the final data collection time-point at one year post-diagnosis of a hip fracture.

Trial slide-decks will be provided to clinicians through the network of WHiTE investigators and presented at local and regional multidisciplinary meetings. In addition, we will produce:

- Plain English outputs, led by the UK Musculoskeletal Trauma PPI group and distributed via paper, web and blog media
- Major international free-to-access publications including the protocol and Statistical Analysis Plan, as well as the main trial results
- National presentations – Orthopaedic Trauma Society, Age Anaesthesia & British Geriatrics Society
- International presentations – Global Fragility Fracture Network Congress, Orthopaedic Trauma Association Congress.

9 REFERENCES

1 American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. American Psychiatric Association, 2013 DOI:10.1176/appi.books.9780890425596.

2 Marcantonio ER, Flacker JM, John Wright R, Resnick NM. Reducing delirium after hip fracture: A randomized trial. *J Am Geriatr Soc* 2001; **49**: 516–22.

3 Royal College of Physicians. The National Hip Fracture Database. https://www.nhfd.co.uk/ (accessed Aug 19, 2020).

4 Marcantonio E, Ta T, Duthie E, Resnick NM. Delirium severity and psychomotor types: Their relationship with outcomes after hip fracture repair. *J Am Geriatr Soc* 2002; **50**: 850–7.

5 Alam A, Hana Z, Jin Z, Suen KC, Ma D. Surgery, neuroinflammation and cognitive impairment. EBioMedicine. 2018; **37**: 547–56.

6 Cole MG. Persistent delirium in older hospital patients. Curr. Opin. Psychiatry. 2010; **23**: 250–4.

7 Kat MG, Vreeswijk R, De Jonghe JFM, *et al.* Long-term cognitive outcome of delirium in elderly hip surgery patients: A prospective matched controlled study over two and a half years. *Dement Geriatr Cogn Disord* 2008; **26**: 1–8.

8 Krogseth M, Watne LO, Juliebø V, *et al.* Delirium is a risk factor for further cognitive decline in cognitively impaired hip fracture patients. *Arch Gerontol Geriatr* 2016; **64**: 38–44.

9 Krogseth M, Bruun Wyller T, Engedal K, Juliebø V. Delirium is an important predictor of incident dementia among elderly hip fracture patients. *Dement Geriatr Cogn Disord* 2011; **31**: 63–70.

10 Krogseth M, Wyller TB, Engedal K, Juliebø V. Delirium is a risk factor for institutionalization and functional decline in older hip fracture patients. *J Psychosom Res* 2014; **76**: 68–74.

11 Lee KH, Ha YC, Lee YK, Kang H, Koo KH. Frequency, risk factors, and prognosis of prolonged delirium in elderly patients after hip fracture surgery. *Clin Orthop Relat Res* 2011; **469**: 2612–20.

12 Witlox J, Slor CJ, Jansen RWMM, *et al.* The neuropsychological sequelae of delirium in elderly patients with hip fracture three months after hospital discharge. *Int Psychogeriatrics* 2013; **25**: 1521–31.

13 Goldberg TE, Chen C, Wang Y, *et al.* Association of delirium with long-term cognitive decline: A meta-analysis. *JAMA Neurol* 2020; **77**: 1373–81.

14 Rochfort KD, Cummins PM. The blood-brain barrier endothelium: A target for pro-inflammatory cytokines. *Biochem Soc Trans* 2015; **43**: 702–6.

15 Clark IA, Vissel B. The inflammatory nature of post-surgical delirium predicts benefit of agents with anti-TNF effects, such as dexmedetomidine. *Front Neurosci* 2018; **12**. DOI:10.3389/fnins.2018.00257.

16 Siddiqi N, Harrison JK, Clegg A, *et al.* Interventions for preventing delirium in hospitalised non-ICU patients. Cochrane Database Syst. Rev. 2016; **2016**. DOI:10.1002/14651858.CD005563.pub3.

17 Blandfort S, Gregersen M, Borris LC, Damsgaard EM. Blood transfusion strategy and risk of postoperative delirium in nursing homes residents with hip fracture. A post hoc analysis based on

the TRIFE randomized controlled trial. *Aging Clin Exp Res* 2017; **29**: 459–66.

18 Youn YC, Shin HW, Choi BS, Kim SY, Lee JY, Ha YC. Rivastigmine patch reduces the incidence of postoperative delirium in older patients with cognitive impairment. *Int J Geriatr Psychiatry* 2017; **32**: 1079–84.

19 Freter S, Koller K, Dunbar M, MacKnight C, Rockwood K. Translating Delirium Prevention Strategies for Elderly Adults with Hip Fracture into Routine Clinical Care: A Pragmatic Clinical Trial. *J Am Geriatr Soc* 2017; **65**: 567–73.

20 Du X, Yu J, Mi W. The effect of dexmedetomidine on the perioperative hemodynamics and postoperative cognitive function of elderly patients with hypertension: Study protocol for a randomized controlled trial. *Med (United States)* 2018; **97**. DOI:10.1097/MD.0000000000012851.

21 Numan T, van den Boogaard M, Kamper AM, Rood PJT, Peelen LM, Slooter AJC. Recognition of Delirium in Postoperative Elderly Patients: A Multicenter Study. *J Am Geriatr Soc* 2017; **65**: 1932–8.

22 Li T, Yeung J, Li J, *et al.* Comparison of regional with general anaesthesia on postoperative delirium (RAGA-delirium) in the older patients undergoing hip fracture surgery: Study protocol for a multicentre randomised controlled trial. *BMJ Open* 2017; **7**. DOI:10.1136/bmjopen-2017-016937.

23 Clemmesen CG, Lunn TH, Kristensen MT, Palm H, Foss NB. Effect of a single pre-operative 125 mg dose of methylprednisolone on postoperative delirium in hip fracture patients; a randomised, double-blind, placebo-controlled trial. *Anaesthesia* 2018; **73**: 1353–60.

24 ISRCTN - ISRCTN52352431: Does intravenous lidocaine speed up gut recovery after large bowel surgery? https://www.isrctn.com/ISRCTN52352431 (accessed Feb 15, 2021).

25 Klinger RY, Cooter M, Berger M, *et al.* Effect of intravenous lidocaine on the transcerebral inflammatory response during cardiac surgery: a randomized-controlled trial. *Can J Anesth* 2016; **63**: 1223–32.

26 Luostarinen V, Evers H, Lyytikäinen M -T, Scheinin A, Wahlén A. Antithrombotic Effects of Lidocaine and Related Compounds on Laser-Induced Microvascular Injury. *Acta Anaesthesiol Scand* 1981; **25**: 9–11.

27 Lopachin RM. Intraneuronal ion distribution during experimental oxygen/glucose deprivation. Routes of ion flux as targets of neuroprotective strategies. In: Annals of the New York Academy of Sciences. New York Academy of Sciences, 1999: 191–203.

28 Foo I, Macfarlane AJR, Srivastava D, *et al.* The use of intravenous lidocaine for postoperative pain and recovery: international consensus statement on efficacy and safety. *Anaesthesia* 2021; **76**: 238–50.

29 2019/20 National Tariff Payment System-A consultation notice: Annex DtD Guidance on best practice tariffs A joint publication by NHS England and NHS Improvement National Tariff Payment System-A consultation notice Annex DtD: Guidance on best practice tari. 2019 https://improvement.nhs.uk/resources/national-tariff-1920-consultation/ (accessed Feb 15, 2021).

30 Breitbart W, Rosenfeld B, Roth A, Smith MJ, Cohen K, Passik S. The memorial delirium assessment scale. *J Pain Symptom Manage* 1997; **13**: 128–37.

31 Schuurmans MJ, Deschamps PI, Markham SW, Shortridge-Baggett LM, Duursma SA. The measurement of delirium: review of scales. Res. Theory Nurs. Pract. 2003; **17**: 207–24.

32 Gruber-Baldini AL, Marcantonio E, Orwig D, *et al.* Delirium outcomes in a randomized trial of blood transfusion thresholds in hospitalized older adults with hip fracture. *J Am Geriatr Soc* 2013; **61**: 1286–95.

33 Bellelli G, Morandi A, Davis DHJ, *et al.* Validation of the 4AT, a new instrument for rapid delirium screening: A study in 234 hospitalised older people. *Age Ageing* 2014; **43**: 496–502.

34 Welch C, McCluskey L, Wilson D, *et al.* Delirium is prevalent in older hospital inpatients and associated with adverse outcomes: Results of a prospective multi-centre study on World Delirium Awareness Day. *BMC Med* 2019; **17**. DOI:10.1186/s12916-019-1458-7.

35 Saller T, MacLullich AMJ, Schäfer ST, *et al.* Screening for delirium after surgery: validation of the 4 A's test (4AT) in the post-anaesthesia care unit. *Anaesthesia* 2019; **74**: 1260–6.

36 Shenkin SD, Fox C, Godfrey M, *et al.* Delirium detection in older acute medical inpatients: A multicentre prospective comparative diagnostic test accuracy study of the 4AT and the confusion assessment method. *BMC Med* 2019; **17**. DOI:10.1186/s12916-019-1367-9.

37 Arnstein P, Gentile D, Wilson M. Validating the Functional Pain Scale for Hospitalized Adults. *Pain Manag Nurs* 2019; **20**: 418–24.

38 Gloth FM, Scheve AA, Stober C V., Chow S, Prosser J. The Functional Pain Scale: Reliability, validity, and responiveness in an elderly population. *J Am Med Dir Assoc* 2001; **2**: 110–4.

39 Lichtner V, Dowding D, Esterhuizen P, *et al.* Pain assessment for people with dementia: A systematic review of systematic reviews of pain assessment tools. *BMC Geriatr* 2014; **14**. DOI:10.1186/1471-2318-14-138.

40 Warden V, Hurley AC, Volicer L. Development and psychometric evaluation of the pain assessment in advanced dementia (PAINAD) scale. *J Am Med Dir Assoc* 2003; **4**: 9–15.

41 Brandt J, Folstein MF, Breitner JCS, Welsh KA, Helms M, Christian JC. Hereditary Influences on Cognitive Functioning in Older Men: A Study of 4000 Twin Pairs. *Arch Neurol* 1993; **50**: 599–603.

42 Telephone Interview for Cognitive Status | TICS. https://www.parinc.com/Products/Pkey/445 (accessed Nov 26, 2021).

43 Herdman M, Gudex C, Lloyd A, *et al.* Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011; **20**: 1727–36.

44 Costa ML, Griffin XL, Achten J, *et al.* World Hip Trauma Evaluation (WHiTE): Framework for embedded comprehensive cohort studies. *BMJ Open* 2016; **6**. DOI:10.1136/bmjopen-2016-011679.

45 Fletcher D, Martin F, Cherif K, *et al.* Lack of impact of intravenous lidocaine on analgesia, functional recovery, and nociceptive pain threshold after total hip arthroplasty. *Anesthesiology* 2008; **109**: 118–23.

46 Odor PM, Cavalier AG, Reynolds ND, *et al.* Safety and Pharmacokinetics of Levobupivacaine Following Fascia Iliaca Compartment Block in Elderly Patients. *Drugs and Aging* 2019; **36**: 541–8.

47 Snoeck MMJ, Vree TB, Gielen MJM, Lagerwerf AJ. Steady state bupivacaine plasma concentrations and safety of a femoral '3-in-1' nerve block with bupivacaine in patients over 80 years of age. *Int J Clin Pharmacol Ther* 2003; **41**: 107–13.

48 Management of severe local anaesthetic toxicity | Association of Anaesthetists. https://anaesthetists.org/Home/Resources-publications/Guidelines/Management-of-severe-

local-anaesthetic-toxicity (accessed Feb 15, 2021).

49 Association of Anaesthetists Quick Reference Handbook T. 3-10 Local anaesthetic toxicity v.2. https://anaesthetists.org/Portals/0/PDFs/QRH/QRH_complete_June_2023.pdf?ver=2023-06-23-141011-603 (accessed Aug 12, 2024).

50 Griffin XL, Parsons N, Achten J, Costa ML. A randomised feasibility study comparing total hip arthroplasty with and without dual mobility acetabular component in the treatment of displaced intracapsular fractures of the proximal femur the warwick hip trauma evaluation two : White two. *Bone Jt J* 2016; **98**-**B**: 1431–5.

51 Masters JPM, Achten J, Cook J, Dritsaki M, Sansom L, Costa ML. Randomised controlled feasibility trial of standard wound management versus negative-pressure wound therapy in the treatment of adult patients having surgical incisions for hip fractures. *BMJ Open* 2018; **8**. DOI:10.1136/bmjopen-2017-020632.

52 Sims AL, Parsons N, Achten J, Griffin XL, Costa ML, Reed MR. A randomized controlled trial comparing the Thompson hemiarthroplasty with the Exeter polished tapered stem and Unitrax modular head in the treatment of displaced intracapsular fractures of the hip. *Bone Jt J* 2018; **100B**: 352–60.

10 ANNEX A: FLOW CHART