

## PROTOCOL

Can continuous non-invasive monitoring improve stability of intraoperative blood pressure  
(iSTABILISE)

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**TRIAL SUMMARY**

<b>Trial Title</b>	<i>Can continuous non-invasive monitoring improve stability of intraoperative blood pressure – A feasibility study in hip fracture surgery</i>
<b>ref. number</b>	2019003AN
<b>Clinical Phase</b>	<i>Phase III feasibility</i>

<b>Trial Design</b>	<i>Feasibility before-and-after trial</i>	
<b>Trial Participants</b>	<i>Adults undergoing surgery for repair of hip fracture</i>	
<b>Planned sample size</b>	<i>30 (15 control and 15 intervention patients)</i>	
<b>Treatment Duration</b>	<i>Intra-operative only.</i>	
<b>Follow-up Duration</b>	<i>In-hospital follow up to discharge, and mortality follow up to 30 days</i>	
<b>Planned Trial Period</b>	<i>From 01/06/2019-01/08/2019</i>	
	<b>Objectives</b>	<b>Outcome Measures</b>
<b>Primary</b>	<i>Demonstrate feasibility</i>	<i>Proportion of patients recruited who received the intervention, and completed follow up.</i>
<b>Secondary</b>	<i>Evaluate the incidence of intra-operative haemodynamic instability and post-operative adverse outcomes</i>	<i>Proportion of anaesthetic time with mean arterial pressure below set thresholds. Lowest recorded blood pressure. Amount of vasopressor and fluid given intraoperatively Post-operative incidence of acute kidney injury, myocardial infarction, stroke and death.</i>

## LIST OF ABBREVIATIONS/GLOSSARY

<b>Abbreviation</b>	<b>Explanation</b>
AE	Adverse Event
CI	Chief Investigator
CNIBP	Continuous non-invasive blood pressure
CONSORT	<i>Consolidated Standards of Reporting Trials</i>
CRF	Case Report Form
GCP	Good Clinical Practice
HRA	Health Research Authority
iABP	Invasive arterial blood pressure
ICF	Informed Consent Form
IRAS	Integrated Research Application System
NIBP	Non-invasive Blood Pressure
PACU	Post Anaesthetic Care Unit
PI	Principal Investigator
PPI	Patient & Public Involvement
QoL	Quality of Life
REC	Research Ethics Committee
R&D	Research and Development
SAE	Serious Adverse Event
SOP	Standard Operating Procedure

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## 1. BACKGROUND

### 1.1 Epidemiology and burden of the condition

#### *Number of operations*

There are approximately 4.5 million procedures performed in operating theatres in England alone, with 1.3 million of these considered major procedures due to duration or complexity [1]. Depending on the definition applied, intraoperative hypotension occurs for some time period in 30–68% of non-cardiac surgery [2, 3]. The risk of post-operative death increases with time spent exposed to mean arterial pressure (MAP) lower than 80 mmHg, with shorter exposures required to experience harm at lower pressures. Additionally, the risk of acute kidney injury, myocardial injury, delirium and stroke all increase with increased duration and magnitude of exposure to mean arterial pressures (MAP) less than 70, again in a graded fashion related to severity and duration of exposure [4].

Trials examining whether different strategies to prevent intraoperative hypotension, or improve intraoperative haemodynamic stability have begun, in an effort to determine whether preventing the hypotension observed to be a risk factor for these important post-operative outcomes can reduce their incidence.

What follows is a discussion of how intraoperative hypotension is defined, a more detailed examination of the associations between intraoperative hypotension and certain post-operative outcomes and summary of the current evidence from clinical trials aiming to prevent intraoperative hypotension. Additionally, there will be a discussion of the use of non-invasive and invasive methods of blood pressure measurement, including a systematic review of the use of continuous non-invasive blood pressure measurement as an intervention to prevent intraoperative haemodynamic instability.

### 1.2 Existing knowledge

#### *What is intraoperative hypotension (IOH)?*

Despite the attempts of many studies, a clear definition of what intraoperative hypotension is has not been agreed. It has not been clear whether there is an absolute value of blood pressure below which organ damage accumulates, or whether a relative fall from the patient's own baseline is in fact the determinant of when low blood pressure becomes problematic. Indeed, even whether it is systolic pressure or mean arterial pressure which is more dominant in determining risk is not clear.

A recent systematic review by Wesselink and colleagues has gone a long way to addressing these questions. They included 42 prospective studies (randomised controlled trial, case-control study, or cohort study), examining the association between intraoperative hypotension and mortality or one of a number of post-operative outcomes in elective non-cardiac surgery. Outcomes studied were acute kidney injury, myocardial injury, stroke, delirium and hospital length-of-stay.

They found that the risk of end-organ injury was increased by prolonged exposure to MAP < 80 mmHg, and was increased with shorter durations to lower MAPs, with any exposure to a MAP < 55–50 mmHg increasing the risk. Given the increase in risk of post-operative organ dysfunction is graded in terms of severity and duration of exposure, it is likely that the threshold that hypotension becomes deleterious varies from patient to patient.



The re-analysis of the *ASAP-1* data by White and colleagues examined anaesthetic technique and post-operative outcomes in 11,085 patients who underwent surgical repair of neck of femur fracture in the UK. They found that overall mortality was 165/11,085 (1.5%) at 5 days, and 563/11,085 (5.1%) at 30 days. Importantly they found that more than half of the patients suffered 'significant hypotension' and found incremental increases in risk of death associated with intra-operative systolic and mean blood pressures, with the highest risk population being those who experienced a MAP<55 [5].

#### *What is the incidence of adverse outcomes*

Abbot and colleagues [6] found that 2.8% of patients in the VISION study (Vascular events in non-cardiac surgery cohort evaluation) experienced myocardial injury (MINS; a transient post-operative rise in troponin levels which are associated with death [7]).

Maheshwari and colleagues found that in a retrospective study of 42,000 cases of non-cardiac surgery, 5% [95%CI 2-7%] of patients developed post-operative acute kidney injury [8]. O'Connor and colleagues [9] found that the acute kidney injury occurs in 10.9-16.4% of patients undergoing major abdominal surgery, and found this associated with a 12.6-fold [95% CI, 6.8-23.4] increase in the risk of death. Other studies have found similarly strong associations between post-operative acute kidney injury and death [10].

Estimates of the incidence of post-operative delirium vary depending on the population. Rudolph et al., (2009) found that delirium occurred in 8.5% of patients over 60 years of age undergoing non-cardiac surgery who did not have pre-existing neurocognitive dysfunction [11]. Bruce and colleagues found post-operative delirium occurred in 3-28.3% of patients undergoing elective orthopaedic surgery following a meta-analysis of 26 publications [12]. Hirsch and colleagues found that intra-operative hypotension was not associated with an increased risk of post-operative delirium, but the degree of intra-operative blood pressure fluctuation was [13].

#### *Current trials on how to prevent IOH and their outcomes*

Futier and colleagues studied 292 patients over the age of fifty years undergoing major surgery who were at high risk of developing post-operative AKI (See Kheterpal et al [14]). They randomised patients to two arms. The control arm received "standard care" [boluses of ephedrine triggered by the systolic blood pressure dropping either 40% from baseline or below an absolute level of 80mmHg]. The intervention arm received a peripheral infusion of Noradrenaline to maintain blood pressure between  $\pm 10\%$  of the pre-operative blood pressure. Both groups received maintenance fluid at 4ml.kg-1.hr-1, and received a fluid bolus of 6% hydroxyethyl starch to optimize stroke volume index. The study showed its primary outcome to be true; a reduction in the composite outcome of systemic inflammatory response syndrome (SIRS) in conjunction with any of AKI, cardiovascular, pulmonary or neurological complications, coagulopathy in the 7 days following surgery [adjusted relative risk 0.73; 95% CI, 0.56-0.94; p.02). Additionally they found a reduced rate of renal dysfunction, altered consciousness, sepsis by 30days (note. Rate of sepsis and severe sepsis/septic shock similar at 7 days, and rate of severe sepsis/septic shock similar at 30d). 30 day mortality was similar in both groups (adjusted relative risk 1.11; 95% CI 0.44-2.81; p=0.82). Importantly, the study showed that in patients at high risk, only 7 patients needed to be treated according to this algorithm to prevent one case of acute kidney injury. However, a major criticism of the study is that it is already recognised that allowing patient's systolic blood pressure to drop 40% from their baseline value is excessive, and likely not to represent current practice, and would put them at risk of organ dysfunction in the trial setting that is not representative of the real world. Such thresholds in the control arm favour finding a positive primary outcome that lacks external validity.

## Description of CNAP

Continuous non-invasive blood pressure (cNIBP) monitoring is available from a number of manufacturers, marketed under the names CNAP by CNSystems, ClearSight from Edwards Life Sciences, Finapres from Finapres Systems to name three. These systems work by applying the Penaz Principle; if arterial blood flow into a finger can be detected by photoplethysmography the pressure required in a cuff around the finger to arrest blood flow will be proportional to the pressure driving blood into the finger; the arterial pressure. cNIBP can be measured using this principle with systems calibrated by more traditional upper-arm oscillometrically derived measurements.

There have been a number of observational studies examining whether cNIBP is equivalent or inferior to continuous *invasive* blood pressure monitoring (iABP), in terms of accuracy (or bias; the difference between the measured value, in this case with cNIBP and the reference value, in this case with iABP), and precision (the extent to which the measured value varies due to random error). Additionally, the ability to reflect changes in arterial blood pressure in a timely, or real-time fashion have been evaluated.

Kim et al [15] included a number of photoplethysmographical devices as well as the 'T-Line' tonometry in a systematic review of continuous non-invasive blood pressure measurement systems. They found that in 7 studies using CNAP, when compared to invasive intra-arterial blood pressure monitoring, the bias for systolic arterial pressure was  $-1.8 \pm 12.8$  (95% LOA: -26.8 to 23.2 mmHg), the bias for diastolic blood pressure was  $7.2 \pm 8.5$  (-9.5 to 24.0 mmHg) and the bias for mean arterial pressure was  $5.5 \pm 9.3$  (-12.7 to 23.6 mmHg).

There are far fewer studies comparing cNIBP systems to conventional intermittent oscillometric blood pressure measurement. Chen et al., [16] compared non-invasive blood pressure measurements made using an intermittent cuff and the Nexfin device in 25 patients undergoing supine abdominal or orthopaedic surgery, and found an overall bias in measurements of systolic blood pressure of  $-1 \pm 12$  mmHg. Importantly, they found that the trending ability of the cNIBP system was at least equivalent to that of the intermittent cuff device.

Juri et al., [17] performed Bland-Altman analysis in 20 patients undergoing elective knee arthroplasty found a MAP bias of  $-1.8 \pm 8.1$  mmHg when comparing the ClearSight device to intermittent cuff measurements of MAP during the intra-operative period. However, during induction of anaesthesia they found a mean bias in MAP of  $-8.7 \pm 14.4$  mmHg with 95% limit of agreement of 28.3 mmHg, giving an overall MAP bias of  $-3.9 \pm 10.3$  mmHg with 20.5 mmHg 95% limit of agreement.

Balzer et al., [18] found that the bias in blood pressure measurements by the Nexfin cNIBP device compared to invasively measurement blood pressure was smaller than that of intermittent oscillometrically measured blood pressure compared to the same (MAP; Nexfin  $-1 \pm 13$ , Intermittent cuff  $13 \pm 13$ , mmHg, percentage error 27 vs 30%).

Although cNIBP measurement appears to be slower at detecting hypotension (see [19]; the lowest systolic blood pressure was detected 10.5 seconds slower by cNIBP than by iABP), it is significantly quicker than by an intermittent oscillometrically obtained measurement, which takes 30-60 seconds to complete, and in many cases is only performed every 3-5 minutes. As such, although based on current evidence, and supported by Kim's systematic review and meta-analysis, cNIBP cannot yet replace invasive blood pressure monitoring in those who need it, it offers significant advantages over intermittent non-invasive blood pressure monitoring which are worth exploring.

A number of trials have supported the view that cNIBP monitoring is superior to intermittent NIBP monitoring. Illies and colleagues studied connected CNAP monitoring to 65 pregnant women iStabilise Protocol – IRAS 261698

undergoing elective caesarean section, but blinded the treating anaesthetist to the values recorded. They found that hypotension was detected in 55% of patients using traditional intermittent non-invasive blood pressure measurement, was detected in 91% of patients using CNAP continuous monitoring [20]. Additionally, Wagner and colleagues connected continuous non-invasive blood pressure monitoring to 130 patients in the emergency department resuscitation area, and found that 46 patients had episodes of hypotension with either systolic pressure <90mmHg or mean arterial pressure <65mmHg for >4 minutes that was *not* detected by the standard monitoring, and thus the clinical team was unaware of [21].

### *Should we prevent intraoperative hypotension?*

Given the significant body of evidence describing the deleterious effects of intra-operative hypotension, a number of clinical trials have investigated whether using continuous non-invasive blood pressure monitoring can reduce exposure to hypotension.

#### *Systematic review of CNAP interventional trials*

We have undertaken a systematic review of all clinical trials using continuous non-invasive blood pressure monitoring as an intervention, where there was an outcome measure which fell into any of the following categories; outcomes related to intra-operative process (eg. Time spent with a blood pressure below a set threshold), post-operative outcomes (eg. 30 day mortality), or economic outcomes (eg. Length of stay). The work was registered before commencing the search with PROSPERO (CRD42018093082). The search identified 2244 papers after removal of duplicates. 2238 of these were excluded after abstract screening, leaving 6 papers, all of which were included in the qualitative synthesis.

Benes and colleagues [22] carried out a single centre randomised controlled trial carried out on 120 patients undergoing elective hip or knee arthroplasty. They were randomised into one of 3 arms. The first was a control arm. The second was the 'pressure' arm, where the patients received CNAP monitoring, and management of measured pressures such that when MAP fell by 20% from baseline if the HR was >100 a fluid bolus was administered, and if HR was <100, a vasopressor bolus was given. The third arm received CNAP monitoring and management of measured pulse pressure variation (PPV), using a protocolised combination of fluid and vasopressor boluses to keep PPV<13%. They found that their primary outcome, the proportion of patients experiencing any post-operative organ or infection complication, was reduced in the group who had their intraoperative haemodynamics managed to a target PPV. (C vs Pressure vs GDFT 83 vs 65 vs 55%\*: p<0.05 for GDFT only). Additionally, they found that the rate of post-operative infectious complications was significantly lower in both groups receiving CNAP based protocolised management (C vs Pressure vs GDFT 57 vs 22 vs 22% (p<0.001)).

Benes and colleagues [23] carried out a further randomised controlled trial in 40 adults undergoing elective thyroid surgery. Patients were randomised to have either intermittent or continuous blood pressure measurement using CNAP. Both groups were treated with a standardised approach to haemodynamic variation, aiming to keep blood pressure within  $\pm 20\%$  of the baseline value recorded in the pre-operative clinic. The absolute time spent in hypotension was reduced in the group with continuous CNAP monitoring [12 min (4–20) vs. 27 min (16–34); p = 0.001], as was the proportion of time spent in hypotension [14 % (7–20) vs. 33.5 % (17.5–53); p = 0.003]. They also found significant reductions in absolute and proportional time spent with SBP more than 30% lower than baseline.

A further study by Han et al [24] randomised ASA I-II patients undergoing elective caesarean section to receive standard intermittent blood pressure monitoring or continuous blood pressure monitoring

with CNAP. Both groups received a standardised approach of phenylephrine boluses for SBP<80% of baseline or <90mmHg. They found that the maximum decrease in SPB was reduced in the group with continuous BP monitoring [26.7 vs 31.9% (p=0.01)], and the time of recording of hypotension was significantly shorter [240 vs 349s (p<0.001)]. Interestingly, they found there was no difference in the quantity of phenylephrine given, indicating that CNAP led to quicker identification and treatment of hypotension without needing more doses of vasopressor. Additionally, the incidence of severe hypotension was significantly reduced in those patients who received continuous monitoring (11.1 vs 28.9% (p=0.035))

Juri and colleagues [17] performed a randomised controlled trial in patients undergoing total knee arthroplasty under general anaesthesia, comparing intermittent and continuous blood pressure monitoring with a standardised anaesthetic, and blood pressure aims (80-110% of baseline systolic blood pressure). They found that their primary outcome, 'haemodynamically stable time', was increased in the group receiving continuous blood pressure monitoring (87.7% vs 61.9% (p<0.001)). Additionally, fewer patients experienced an episode of hypotension during induction or during the operation, and urine output was increased in the patients who received continuous monitoring. Of note, those patients receiving continuous monitoring received more phenylephrine and less ephedrine than those with intermittent monitoring.

Meidert and colleagues [25] performed another single centre RCT comparing continuous BP monitoring (with the ClearSight device) to intermittent BP monitoring in adult patients having a general anaesthetic for orthopaedic surgery. Although their primary outcome was poorly defined, and the powering of the study was unclear, they found that continuous blood pressure monitoring led to a reduction in the systolic blood pressure fall after induction of anaesthesia. However, there are a number of criticisms of this study; 31 patients were excluded following randomisation due to protocol deviation (anaesthetist stopped the cuff recording in order to insert an IV cannula). Additionally, the outcomes reported are poorly defined.

In a similar vein, Gupta and colleagues [26] published a randomised study of blood pressure management in patients undergoing elective caesarean section. They randomised patients to receive CNAP or NIBP monitoring, and allowed the anaesthetist to manage blood pressure based on these, within a suggested protocol of maintaining MAP within  $\pm 20\%$  of baseline and SBP>100mmHg. They did not state any primary outcome, or effective power calculation, did not comment on whether the treating anaesthetist was blinded, did not account for 16 patients who were randomised but did not take part, and did not state any *a priori* plan for statistical analysis. They reported that 'CNAP readings were more likely to be in systolic hypotensive phases (<100mmHg)' than NIBP readings, suggesting that more hypotensive episodes were detected by the continuous monitor than the intermittent version, but the study outcomes are not clear.

In conclusion, there are 4 good quality single centre randomised controlled trials of continuous non-invasive blood pressure monitoring vs intermittent non-invasive blood pressure monitoring, all of which suggest that intraoperative haemodynamics are improved by continuous monitoring, and one finding an improvement in post-operative outcomes. There are no multicentre trials, and trials outside the setting of elective orthopaedic and obstetric surgery.

#### *Data from A-Line survey*

There are two common approaches to intra-operative blood pressure measurement; automated non-invasive intermittent monitoring (such as with Dinamap) and continuous invasive blood pressure measurement using an intra-arterial catheter ('A-Line'). Typically, invasive blood pressure monitoring is used in cases where there are patient factors leading to increased risk of intra-operative difficulties

(eg. Severe cardiovascular disease), surgical factors (such as high risk of haemorrhage), or the requirement for arterial blood sampling (eg. Prolonged procedures or planned ITU admission post-operatively).

Although guidelines are published detailing the broad factors that should be considered when making a decision around the level of blood pressure monitoring to be carried out during an anaesthetic, the guidance does not offer concrete triggers detailing when invasive blood pressure monitoring is mandated [27].

Given the paucity of guidance we undertook a survey of anaesthetists across 5 hospitals offering a variety of district general and tertiary services, including one major trauma centre, to further understand how consultants and registrars currently providing anaesthesia make their decision on who requires invasive blood pressure monitoring. Additionally, we sought information about when they insert the arterial catheter within the time course of anaesthesia. The survey was carried out using 'Google Forms' (see forms.google.co.uk), and was disseminated by trainees within each hospital. In order to reduce responder bias, the form was not offered by email, but rather in person. Participants were free to decline taking part, and all responses were anonymous.

92 anaesthetists (60 consultants, 32 registrars) responded, across 5 hospitals (one major trauma centre, 4 district general hospitals). 78/92 (85%) of anaesthetists felt haemodynamic instability was most likely to occur at induction, while 11/92 (12%) felt it most likely between induction and knife-to-skin. In those cases warranting invasive monitoring, only 3/92 (3%) anaesthetists always insert arterial cannulae awake, while 88/92 (96%) decide on clinical judgement. The anaesthetists surveyed estimated that they insert 22.5% ([10-50%], median [IQR], negatively skewed distribution) of arterial cannulae before induction. When questioned about why the majority of arterial lines are inserted after induction, 58% felt pain/discomfort was greater when inserted awake, 16% felt it was technically more difficult inserted awake, and 9% felt it was more efficient inserted after induction. 30% of anaesthetists surveyed indicated that even in the setting of anticipated haemodynamic instability they would not insert an arterial line pre-induction.

This survey provides an important indication of current practice, poses some interesting dilemmas. The vast majority of anaesthetists rate induction as the most likely timing of haemodynamic instability but at the same time would insert arterial line *before induction* in less than a third of cases they feel invasive monitoring is indicated. To insert arterial line post induction seems counterintuitive. The most commonly cited reason is pain and discomfort. One on hand it would seem prudent to use local anaesthetic liberally and reduce potential harm to patients from exposure to haemodynamic instability in exchange for some procedural discomfort. However, another option may be to employ the use of continuous non-invasive blood pressure monitoring, which can be connected before induction of anaesthesia without discomfort, and act as either continuous monitoring for the duration of anaesthesia, or as a bridge to an 'asleep A-Line' in those who require definitive invasive blood pressure monitoring. Additionally, this would provide continuous blood pressure monitoring for those patients who are perceived to be at increased risk of complications during anaesthesia, but in whom that risk is not sufficiently high to justify insertion of an arterial line.

### 1.3 Objective

This is a feasibility trial, examining whether it is possible to run a full multicentre randomised controlled trial of the following hypothesis; In patients undergoing repair of neck of femur fracture, does the use of continuous non-invasive blood pressure monitoring compared to intermittent non-

invasive blood pressure monitoring improve intraoperative haemodynamic stability and post-operative outcomes.

#### **1.4 Need for a trial**

There is a strong body of evidence demonstrating that patients who experience intraoperative hypotension are at higher risk of death and adverse post-operative outcomes. There is evidence that intermittent non-invasive blood pressure may be inadequate for detecting intraoperative hypotension. There is a lack of high quality evidence examining whether using continuous non-invasive blood pressure monitoring can improve the intra-operative haemodynamic stability by detecting hypotension more effectively and whether doing so leads to a reduction in adverse post-operative outcomes. As the incidence of intra-operative hypotension, and adverse post-operative outcomes is high in patients undergoing repair of fractured neck of femur, this group of patients has a high propensity to benefit from such an intervention if the hypothesis is proved true, and therefore present an ideal study cohort.

#### **1.5 Ethical considerations**

The trial will be conducted in full conformance with the principles of the Declaration of Helsinki and to Good Clinical Practice (GCP) guidelines. It will also comply with all applicable UK legislation. All data will be stored securely and held in accordance with Data Protection Act 2018 and the General Data Protection Regulation (2018)

#### **1.6 CONSORT**

The trial will be reported in line with the CONSORT (Consolidated Standards of Reporting Trials) statement (Lancet 2001, **357**: 1191-1194).

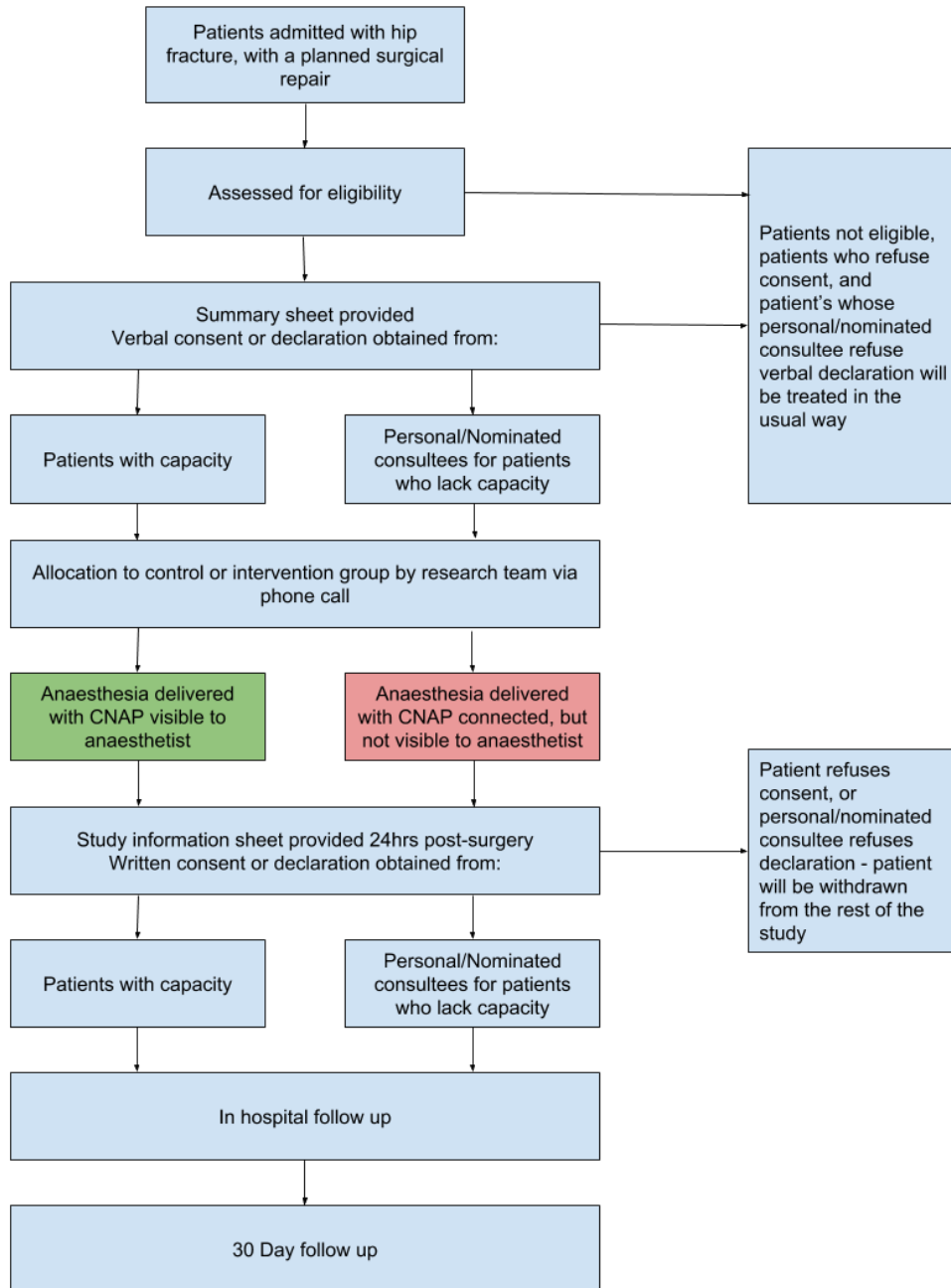
## **2. TRIAL DESIGN**

### **2.1 Trial summary and flow diagram**

This is a feasibility 'before and after' controlled trial, investigating whether it is feasible to conduct a trial testing the hypothesis that the use of continuous non-invasive blood pressure monitoring improves intraoperative haemodynamic stability in patients undergoing repair of fractured neck of femur. The primary endpoint is the proportion of eligible patients who complete the study protocol. Secondary endpoints will include analysis of the effectiveness of patient identification, the reasons for exclusions or failure to complete the study protocol, and an analysis of the incidence of the primary and secondary outcomes planned for the definitive study.



**Figure 1** Trial flow diagram



**Connection to CNAP monitor (the intervention)**

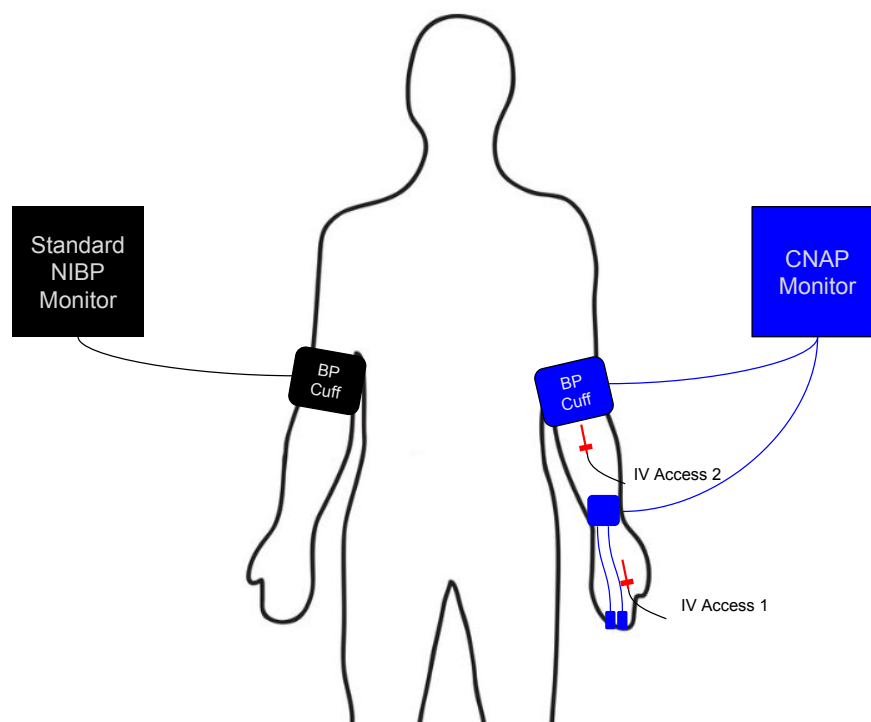
All patients included in the trial will have CNAP monitoring. The first cohort of patients (before) will have CNAP monitoring but the monitoring readings will not be visible to the

treating anaesthetist. The second cohort ('after') will have CNAP monitoring connected and visible for clinical use by the treating anaesthetist. In each case, normal clinical monitoring will be applied (non-invasive intermittent blood pressure monitoring). The systems will be applied on opposite arms, allowing the CNAP monitor to use its own automatic calibration without disturbing the standard monitoring.

The 'Standard monitoring' NIBP cuff will inflate approximately every 3-5 minutes, whereas the CNAP calibration cuff will only inflate every 20-30. As such we will recommend that the CNAP cuff is placed on the same arm as IV access is established, to offer the lowest chance of impeding flow of IV medication. However, this will not be mandatory, and ultimately it is up to the treating anaesthetist to determine the best position for IV access. Where there is an interruption in CNAP use because of IV access, the patient will be excluded from the study. This will form part of the feasibility analysis.



Figure 1 – Arrangement of Standard and CNAP monitoring, including suggested positioning of intravenous access.



## 2.2 Aims and objectives

### 2.2.1 Primary objective

The primary objective of this trial is to evaluate whether it is feasible to undertake before and after controlled trial to test the effect of using continuous non-invasive blood pressure monitoring versus standard intermittent non-invasive blood pressure monitoring on intraoperative haemodynamic stability and post-operative outcomes.

### 2.2.2 Secondary objective

Secondary objectives of the trial are to

- Assess the effectiveness of patient identification and screening
- Assess the effectiveness of the blinding
- Identify reasons for failure to recruit patients and screen fails

▪ Explore barriers and facilitators to recruitment

▪ Evaluate the robustness and completeness of data collection.

- Identify the proportion of patients with complete follow up at 30 days
- Identify the incidence of haemodynamic instability by evaluating the nadir blood pressure, the absolute time spent below blood pressure thresholds, and the proportion of anaesthetic time spent with a blood pressure outside defined limits.
- Identify the frequency of occurrence of technical difficulties with the CNAP equipment.
- Identify the incidence of post operative acute kidney injury, myocardial injury, stroke, and death in the post-operative period.

### 2.2.3 Measures of success

The success of this feasibility trial will be assessed by the trial management group, to consider whether we should apply for funding for a larger, definitive trial. The assessment will be based on the data generated from this feasibility study, and key parameters for assessment will include:

- What is the rate of recruitment
- What is the effectiveness of the process for identifying and screening patients, and what are the reasons for failure to recruit patients if/when this occurs. This will include analysis of reasons patients give for declining consent (if given).
- Are clinicians willing to recruit patients into the study
- Was the CNAP equipment reliable and easy to use?
- Can the CNAP equipment be started by research team and left unattended without any intervention?
- Are the data collection processes during the hospital stay adequate? How complete is the data for the important perioperative parameters?
- What is the rate of follow up of patients at 30 days? What are the reasons for loss of follow-up if any?

## 2.3 Outcome measures

### 2.3.1 Feasibility Outcomes

- Proportion of eligible patients recruited
- Proportion of recruited patients in whom CNAP was successfully applied and full data collected.
- Proportion of patients with complete in-hospital data set
- Proportion of patients with complete follow up data.

### 2.3.2 Intraoperative Outcomes

- Nadir blood pressure; the lowest recorded mean arterial pressure, as per CNAP recording (blinded or otherwise)

- Absolute intra-operative time spent with mean arterial pressure <55mmHg, <65mmHg, <80mmHg.
- Total dose of fluid given intra-operatively
- Total dose of vasopressors given intra-operatively.

### **2.3.3 Post-Operative Outcomes**

- Outcomes as per standardised definitions from the European Perioperative Clinical Outcome standards [28].
- Incidence of acute kidney injury in the 7 days post-operatively
- Incidence of myocardial injury in the first 3 days after surgery (Troponin>0.03ng/ml judged to be due to myocardial injury)
- Stroke: Thrombotic, embolic or haemorrhagic where there is a persistent residual motor, sensory or cognitive dysfunction
- Surgical site infection (superficial or deep, as per CDC definitions – see [29])
- Mortality: in hospital, and at 30 days post-operatively

### **2.3.4 Health Economic Outcomes**

- Hospital length of stay

## **2.4 Eligibility criteria**

Patients are eligible to be included in the trial if they meet the following criteria:

### **2.4.1 Inclusion criteria**

1. Provision of written informed consent (see “2.7 – Informed consent’ for details)
2. Adult patients, undergoing surgical repair of neck of femur fracture
3. Patient can understand and comprehend written and spoken English
4. Patient’s consultee can understand written and spoken English

### **2.4.2 Exclusion criteria**

1. American Society of Anaesthesiologists (ASA) Class I patients
  2. Patients with device-specific exclusions; atrial fibrillation, Raynauds syndrome or disease, peripheral vascular disease, scleroderma, an arteriovenous shunt, valvular heart disease.
- Patients in whom a blood pressure cuff cannot be safely inflated on both arms for any reason (for example, lymphoedema).

4. Patients in whom the treating anaesthetist has judged they will require invasive arterial pressure monitoring.
5. Patients declining consent
6. Patients in whom the treating anaesthetist will use total intravenous anaesthesia (TIVA)
7. Patients in whom there is a >20mmHg difference between non-invasive cuff mean arterial pressure measurements made on opposite arms.

### **2.4.3 The need to recruit patients lacking capacity**

A significant proportion of patients undergoing surgery for hip fracture will lack capacity to consent to involvement in a clinical trial, as a result of pre-existing cognitive dysfunction or acute delirium. These patients are more likely to be comorbid, and may well be at increased risk of developing intraoperative haemodynamic instability, and of developing the complications which have been associated with it. As such, excluding this group of patients would limit the external validity of any findings which could change clinical practice.

Additionally, the intervention is of relatively low burden; it is non-invasive, not painful, and well tolerated in preliminary work and in other trials already published. As such, the burden of taking part is low, and we feel the benefits of producing a trial result which has good generalisability to *all* patients with hip fracture outweigh the burdens of recruiting patients who wouldn't otherwise have capacity.

### **2.4.4 Co-enrolment of patients with other clinical trials**

Where other clinical trials are taking place in the same setting, co-enrolment agreements will be sought. As this is a feasibility study, it will be important to determine whether co-enrolment impacts upon recruitment, and patients who are eligible but not enrolled for this reason.

## **2.5 Participant identification / Screening**

Participants will be identified through daily screening of the 'trauma list' at participating sites by the local research team. Following identification of patients who may be eligible, screening will be carried out by viewing these patient's medical notes to ascertain whether they meet the inclusion criteria, and do not meet any exclusion criteria. If these conditions are met, the patient will be approached by a member of the research team.

Eligibility can be confirmed by any member of the research team who has received appropriate training and has been delegated by the Principle Investigator to do so. This will be confirmed and recorded on a screening proforma prior to randomisation.

## **2.6 Site Staff Training**

Under the supervision of the PI, trained members of the research team will be responsible for identifying potential participants, obtaining consent and conducting study related follow up. Protocol training will be provided to members of the research team by the trial coordinating team at the site on the first visit and throughout the trial, as necessity dictates. This may include device specific training from the manufacturer.

## **2.7 Informed consent**

### **2.7.1 Consent Considerations**

Patients with hip fractures are typically operated on between 12-48hrs of admission to hospital. Due to the urgent nature of surgical repair, there can be a short time between research staff approaching the patient, and the patient going to theatre. As such, there will be occasions where there is limited time for the patient, or their consultee if they lack capacity, to review the trial documentation and make an informed choice about their participation.

Additionally, owing to the fact patients with hip fracture are in pain, and likely to have received strong analgesia, it is possible they may be finding their time in hospital disorientating and confusing. In the same vein, family and carers may be anxious and distressed by what is going on.

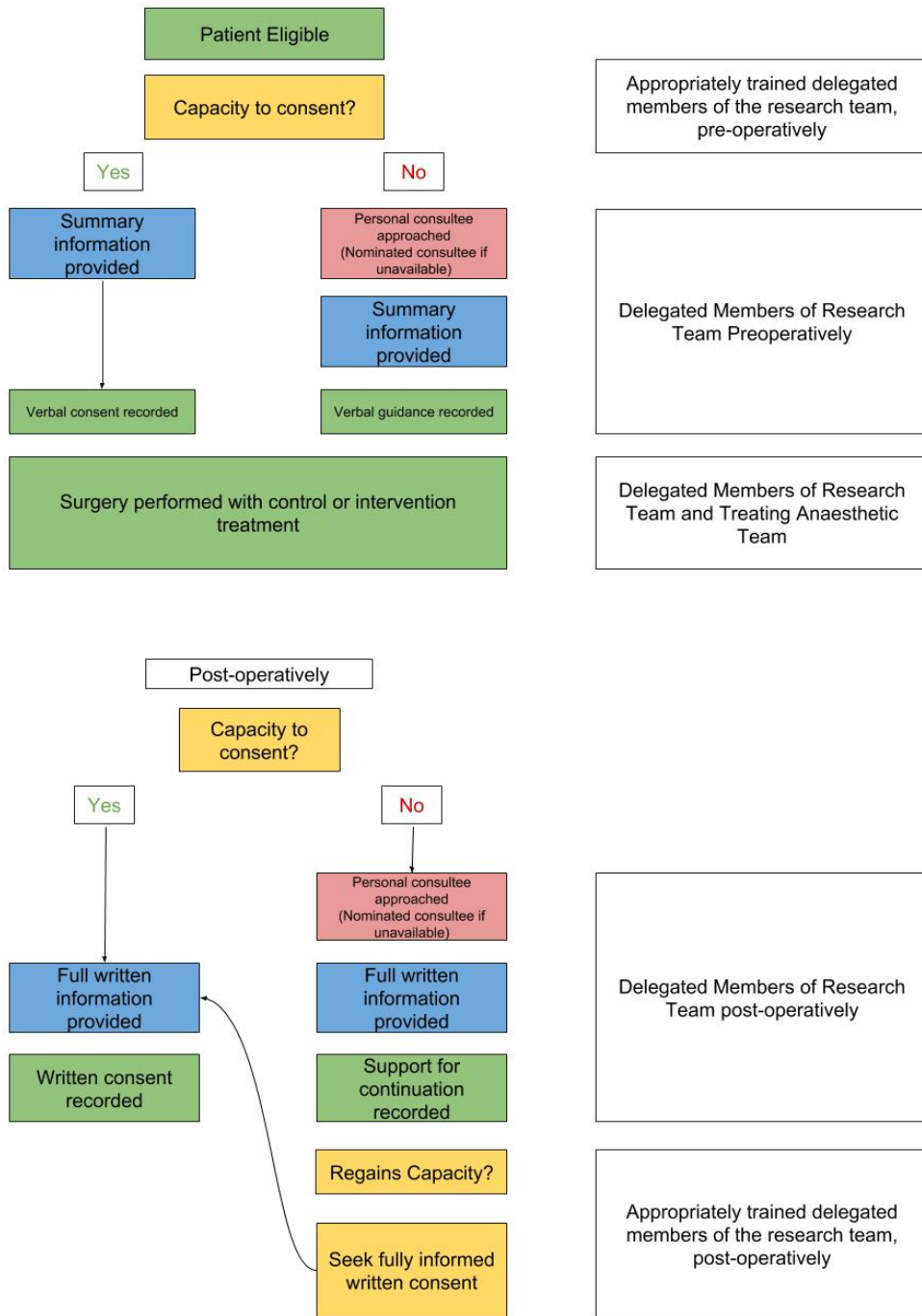
As this research will be conducted in the 'emergency setting', it is regulated by the Mental Capacity Act 2005. As patients may lack capacity for the reasons described above, and because of the urgent nature of the treatment limiting access to, and appropriate discussion with Personal Consultees, we will act in accordance with Section 32, subsection 9b of the Mental Capacity Act following a process approved by the relevant research ethics committee.

### **2.7.2 Summary of consent process**

We will apply a layered, proportionate approach to consent; patients and consultees will be approached for Verbal Consent prior to surgery using a study summary sheet. Patients and consultees will be approached post-surgery with a full study information sheet where full informed written consent will be sought. If the patient wishes, they can receive full study information before surgery, and provide full informed written consent at this point.



iStabilise Consent Flowchart



patients with hip fracture have a diagnosis of dementia [30] and a third of patients have cognitive dysfunction at the time of admission [31]. Given that this lack of capacity more commonly occurs in those patients who are more likely to have other comorbidities, and thus more likely to come to harm due to intraoperative haemodynamic instability, it is important that these patients are included in the trial; they have the greatest propensity to benefit from improvements in this area, and their exclusion would severely limit the external validity of the study. Additionally, the burden of taking part in the trial is very low (the use of an additional non-invasive monitor which has already been proven equivalent to standard monitoring, in patients who are either under general anaesthetic or often sedated), we do not feel that exclusion of patients without capacity to consent is needed, where a consultee indicates their preferences on the patient's behalf.

### **2.7.3 Assessment of Mental Capacity**

This trial will recruit from a patient population with pre-existing conditions which may affect their capacity of make decisions. It is anticipated that the study population will contain a significant number of patients unable to give informed consent due to lack of capacity.

Members of the research team who will be performing mental capacity assessment and taking consent from patients and or consultees will be trained in mental capacity assessment according to the Mental Capacity Act 2005 and GCP Informed Consent in Adults Lacking Capacity training. An assessment of a patient's mental capacity will be completed before obtaining consent, after the patient is identified as potentially eligible.

### **2.7.4 Patients with capacity**

If a patient has been assessed as having capacity, a delegated member of the research team will discuss participation in the trial. This approach will take place after the patient has undergone the clinical assessments and admissions process as part of their normal clinical care, and has been scheduled for surgery.

#### **2.7.4.1 Verbal consent before surgery**

The research team will provide a verbal description of the trial, as well as a short written summary sheet, allowing the patient adequate and reasonable time to take in the information and ask questions about the trial. At this point, if the patient agrees that they are happy to take part in the trial, the research staff will record the verbal consent on the enrolment log and the summary sheet, and the patient will proceed to treatment allocation. If the patient expresses that they do not want to take part in the study, non-identifiable information will be recorded on the screening log, with details of the reason for declination. There is a full study information sheet that will be available should the patient want to read this before giving verbal consent. The participant will remain free to withdraw agreement at any time up to the time of surgery without giving reasons, and without prejudice to further treatment.

#### **2.7.4.2 Written informed consent after surgery**

The majority of patients who give verbal consent will regain consciousness and be comfortable the day after surgery. At the first available opportunity the research team will visit the patient to discuss the trial in detail and provide a full study information sheet. Patients will be given reasonable and adequate time to consider or raise any questions. If the patient agrees to continue in the study, at this point written informed consent will be obtained. If they choose to withdraw their participation at this point, they are free to do so with no further research follow-up or consequences to their clinical care. Research staff will ask for consent to keep anonymised data already collected as part of

### **2.7.4.3 Written informed consent before surgery**

If the patient has capacity, and wishes to do so, they be provided with full study information before surgery, and if they wish, can provide fully informed written consent. In this situation, no further consent will be required post-surgery.

### **2.7.5 Patients lacking capacity to consent**

If a patient is assessed as lacking capacity to make an informed decision on whether or not to take part in the trial, the site research team will approach a member of the family, a friend or a carer to act as a personal consultee on behalf of the patient. If a personal consultee cannot be found before surgery, the research team will approach a nominated consultee. A nominated consultee can be a registered medical practitioner who is not involved in the organisation or conduct of the research project. The Nominee (independent clinician) must not be the same clinician conducting the consenting process for surgery or anaesthesia. The Consultee (either personal or nominated) will be provided with the relevant information including medical notes and must consider, so far as is reasonably ascertainable

- a. The person's past and present wishes and feelings (and, in particular, any relevant written statement made by them when they had capacity),
- b. The beliefs and values that would be likely to influence their decision if they had capacity, and
- c. The other factors that they would be likely to consider if they were able to do so.

#### **2.7.5.1 Verbal declaration before surgery**

The research team will present the consultee with the same information as patients with capacity receive, and will offer the opportunity to discuss the study and ask questions. If the consultee gives verbal declaration for the patient to be involved in the trial, the patient will proceed to treatment allocation. The research team will record the name of the consultee and verbal declaration on the screening log and study summary sheet. If the consultee refuses to give verbal declaration on behalf of the patient, this will also be noted on the screening log. There is also a full consultee study information sheet available should the consultee want to read this before giving verbal declaration. The participant will remain free to withdraw agreement at any time up to the time of surgery without giving reasons and without prejudice to any further treatment. Additionally, as with patients who have capacity, if the personal or nominated consultee wishes to provide full written consent at this point they are free to do so. If the patient regains capacity their consent to continue will be sought.

#### **2.7.5.2 Verbal declaration over the phone**

In the case of patients who do not have capacity, where a personal consultee is unavailable in person, but contactable over the phone, if they are willing to provide a verbal declaration over the telephone after having the summary information sheet read to them, they can do so, and this will be documented on the verbal declaration form.



### **2.7.5.3 Written declaration after surgery**

The majority of these patients will regain consciousness and be comfortable the day after surgery. On the day after surgery, or the first available opportunity the research team will reassess the patient's mental capacity. If they are assessed to lack capacity, the research team will make all reasonable effort to contact the patient's family or known carer to act as a personal consultee. If a personal consultee cannot be reached via telephone call, then the research team will seek a nominated consultee. Where possible, the research team will seek to approach the same nominated consultee that previously agreed to the patient's participation upon review of the summary information sheet.

The consultee (either personal or nominated) will be given a consultee study information sheet and time for discussion with the research team. If the consultee agrees for the patient to continue in the study, they will be asked to sign a written declaration. The written declaration will state that in their view the person who lacks capacity would have wanted to continue to take part in the trial. If the consultee chooses to withdraw their participation at this point, the research staff will ask for consent to keep anonymised data already collected as part of the study.

### **2.7.6 Participants who regain mental capacity**

Mental capacity will be reassessed at the follow up visit where informed written consent is sought. If the patient is deemed by the research team to have regained capacity, written informed consent will be sought in the same fashion as described for those who had capacity to give verbal consent before surgery.

### **2.7.7 Participants who lose mental capacity**

If a participant loses mental capacity during their participation, before they are approached for informed written consent, the research team will seek a consultee. The consultee (either personal or nominated) will be given a consultee study information sheet and time for discussion with the research team. If the consultee agrees for the patient to continue in the study, they will be asked to sign a written declaration. The written declaration will state that in their view the person who lacks capacity would have wanted to continue to take part in the trial. If the consultee chooses to withdraw their participation at this point, the research staff will ask for consent to keep anonymised data already collected as part of the study.

### **2.7.8 Responsibilities**

The Principal Investigator (PI) is responsible for ensuring that the consent processes described above are followed at the hospital site.

The consultation and consent process will be undertaken by a registered medical practitioner or other healthcare professional who is a member of the research team with the approval of the site PI.

## **2.9 Trial treatments / intervention**

### **2.9.1 Trial treatment(s) / intervention**

The trial intervention is the use of continuous non-invasive blood pressure monitoring, visible to the anaesthetist from before induction of anaesthesia, until the patient has left the theatre and

moved to the post-anaesthetic care unit (“recovery”; PACU). All other aspects of the trial will be the same as the control/comparison group.

### **2.9.2 Trial control/comparison group**

The trial control/comparison group will have continuous non-invasive blood pressure monitoring applied by the research team. The readings will not be available, or visible to the clinical team treating the patient. Additionally, the alarms will be disabled, to ensure no information is obtained through visual or audible cues.

### **2.9.3 Measures common to the intervention and control groups**

The vast majority of the perioperative care provided to the control and intervention groups will be similar. Pre-operative care will be unaltered. Once group allocation has occurred, there will be no restrictions on choice of anaesthetic technique (for example, choice of general or regional anaesthesia, choice of drugs).

Management of the patient’s blood pressure will be at the sole discretion of the anaesthetic team treating the patient. Baseline blood pressure (systolic, mean, and diastolic) will be calculated as the average of 2 readings 5 minutes apart before administration of any anaesthetic drugs. Both control and intervention groups will have ‘standard non-invasive blood pressure monitoring’ regardless of the availability of CNAP to the treating anaesthetist, as shown in the trial diagram. The frequency of readings will be chosen by the treating anaesthetist

Continuous non-invasive blood pressure monitoring will continue until the patient moves to the PACU.

### **2.9.4 Compliance/contamination**

Compliance with treatment will be indicated by a number of measures

We anticipate that there will be times during the trial where the CNAP monitor is not recording. This can be for a number of reasons

- Calibration; every 30 minutes the CNAP cuff finger is switched. Recalibration takes place at this point. During this, a new blood pressure reading is unavailable for between 1m45s and 2m15s. At this point a non-invasive blood pressure reading from the native monitoring will be used to calibrate the CNAP monitoring. Blood pressure will be assumed to be unchanged during this period. As part of the feasibility study, the total recording time lost to calibration will be noted, and the method for managing this developed if required in the full study.
- Disconnection; The reasons for disconnection will be noted. If disconnection leads to >5 minutes without CNAP blood pressure monitoring, the patient will be excluded from the study analysis.
- Equipment malfunction; if the CNAP device malfunctions such that blood pressure monitoring is unavailable for >5 minutes the patient will be excluded from the study. The patient will receive routine care thereafter.

- Patient deterioration; If the patient deteriorates such that the treating clinician judges invasive blood pressure measurement is required, the patient will be excluded from the study.
- For other reasons not anticipated, anything that leads to >5 minutes of CNAP monitoring being unavailable will lead to patient exclusion. Details will be noted.
- For other reasons not anticipated, anything that leads to <5 minutes of CNAP monitoring being unavailable will not lead to patient exclusion, but an event marker will be included with details of the reason, and these will be collated to inform the refinement of the full study protocol, and will be an important part of the feasibility study.

## **2.10 Blinding**

### **2.10.1 Methods for ensuring blinding**

The treating anaesthetist, and clinical team in theatre will not be blinded to the patient's treatment allocation, as they need to use the equipment in question.

The team performing follow up, which will involve reviewing the patient's notes and viewing their electronic blood test results and information will be blinded to the treatment the patient received, except where this is not possible due to organisational constraints. This part of the follow up will not require any viewing of the anaesthetic chart, and will be a review of entries in the notes *after* theatre. As such it should not be difficult for them to remain blinded.

The team performing statistical analysis will be blinded to the treatment allocation during the analysis phase.

The effectiveness of blinding will be reviewed as part of the feasibility outcomes, and if required altered for any further large-scale study based on this feasibility trial.

## **2.11 Concomitant illness and medication**

### **2.11.1 Concomitant illness**

Details of concomitant illness of relevance to the inclusion and exclusion criteria will be recorded. This will include presence of atrial fibrillation, peripheral vascular disease, scleroderma, an arteriovenous shunt, valvular heart disease. Details of concomitant illness of relevance to the analysis of the data will include known diagnosis of chronic arterial hypertension, chronic heart failure, ischaemic heart disease, chronic kidney disease, and diabetes mellitus.

### **2.11.2 Concomitant medication**

A record will be made of any patients who have taken an angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, calcium channel blocker or thiazide diuretic in the 24 hours immediately prior to surgery, as well as a record of any antibiotics the patient is being treated with.

## 2.12 Assessment of feasibility outcomes and improvements to trial protocol

### 2.12.1 Anaesthetic questionnaire

Following the final participation of a centre in the study, anaesthetists who took part in the study will be approached to fill out a questionnaire seeking to further understand their views on how the trial protocol can be improved, problems with the CNAP monitor and what they felt went well. This will be used to inform any future application for a full trial.

## 2.13 End of trial

The trial will be stopped when 30 patients have been recruited.

The trial will be stopped prematurely if:

- Mandated by the Research Ethics Committee (REC) or Health Research Authority (HRA)
- Mandated by the Medicines and Healthcare products Regulatory Agency (MHRA)
- Funding for the trial ceases

The Research Ethics Committee will be notified in writing within 90 days when the trial has been concluded or within 15 days if terminated early.

## 3. METHODS AND ASSESSMENTS

### 3.1 Schedule of delivery of intervention and data collection

*Describe the timescale over which the intervention is delivered, the times at which data will be collected and the type of data to be collected.*

*It is good to summarise the participant assessments in a table. This section should tally with what is being recorded in the CRF.*

**Table 1** Trial assessments

Visit	1	2	3	4
Visit Window	Pre-operative	Intra-operative	Post-operative D1-7	Follow up 30d
Verbal ( $\pm$ written consent)	✓			
Inclusion/exclusion criteria	✓			
Medical history	✓			
Intervention		✓		
Full written consent	(✓)		✓	
Adverse events		✓	✓	✓
Mortality			✓	✓

### 3.2 Laboratory assessments

There will be no laboratory assessments carried out specifically *by* the study. However, the study will record laboratory results of the serum creatinine concentration, serum troponin concentration, serum C-reactive Protein concentration, blood white cell count. These will be recorded from information available to the treating clinician only, and will not involve any research-specific samples.

### 3.3 Long term follow-up assessments

In hospital, and 30day mortality will be measured.

## 4. ADVERSE EVENT MANAGEMENT / PHARMACOVIGILANCE

### 4.1 Definitions

#### 4.1.1 Adverse Events (AE)

An Adverse Event (AE) is defined as any untoward medical occurrence in a participant and which does not necessarily have a causal relationship with this treatment/intervention.

iSTABILISE is a feasibility study that will look at the impact of continuous non-invasive blood pressure monitoring on intra- and post-operative patient outcomes. It is expected that patients undergoing hip fracture surgery may often suffer medical complications, up to and including death (see [32]). It follows that a large number of iSTABILISE trial participants will experience complications of surgery, which are completely unrelated to the trial intervention. Adverse events that are potentially related to study interventions will be recorded on study CRFs and if they fit the criteria for seriousness, then they will be reported as a SAE.

Adverse events which are expected, and do not need to be reported as such are not limited to, but include all of those measured as *outcomes*, as well as

- Constipation
- Pain
- Post-operative infections including sepsis
- Delirium
- Venous Thromboembolism
- Gastro-intestinal Bleeding
- Anaemia
- Electrolyte disturbances

#### 4.1.2 Serious Adverse Events (SAEs)

A Serious Adverse Event is an AE that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical condition.

## Reporting SAEs

All **SAEs** occurring from the time of **treatment allocation** until 30 days later must be recorded on the SAE Form and communicated to the Sponsor **within 24 hours** of the research staff 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 intervention), in the opinion of the investigator
- whether the event would be considered expected or unexpected.

Any change of condition or other follow-up information should be faxed to the Sponsor as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

SAEs will be reported using the SAE form in the participant's CRF. The Principal Investigator in each centre must report any SAEs to the trial coordinating centre within 24 hours of them becoming aware of the event. The SAE form should be completed and emailed to the trial SAE Reporting email address. The trial coordinator will liaise with the investigator to compile all the necessary information. The trial coordinating centre is responsible for reporting any related and unexpected SAEs to the sponsor and REC within required timelines.

The causality and expectedness of SAEs (i.e. relationship to trial treatment) will be assessed by both the principal and chief investigator(s) on the SAE form.

Relationship to trial intervention	Description
Unrelated	There is no evidence of any causal relationship
Unlikely to be related	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial intervention or device). There is another reasonable

	explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).
Possible relationship	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial intervention or device). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
Probable relationship	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely related	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

## 4.2 Responsibilities

### Principal Investigator (PI):

Checking for AEs when participants attend for treatment / follow-up.

1. Using medical judgement in assigning seriousness, causality and expectedness
2. Ensuring that all SAEs are recorded and reported to the Sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs are chased with Sponsor if a record of receipt is not received within 2 working days of initial reporting.
3. Ensuring that AEs are recorded and reported to the Sponsor in line with the requirements of the protocol.

### Chief Investigator (CI) / delegate or independent clinical reviewer:

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgement in assigning seriousness, causality and expectedness of SAEs where it has not been possible to obtain local medical assessment.
3. Using medical judgement in assigning expectedness.
4. Immediate review of all related and unexpected SAEs
5. Review of specific SAEs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.
6. Production and submission of annual reports to the relevant REC.

### Sponsor:

1. Central data collection and verification of AEs, and SAEs, according to the trial protocol.
2. Reporting 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. Reporting safety information to the independent oversight committees identified for the trial (Data Monitoring Committee (DMC) and / or Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.
4. Expedited reporting of related and unexpected SAEs to the REC within required timelines.

5. Notifying Investigators of related and unexpected SAEs that occur within the trial.

### **4.3 Notification of deaths**

Deaths are expected in this population and will be reported to the TMG on a monthly basis and to the TOC.

### **4.4 Reporting urgent safety measures**

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the relevant REC of the measures taken and the circumstances giving rise to those measures.

## **5. DATA MANAGEMENT**

Personal data collected during the trial will be handled and stored in accordance with the 1998 Data Protection Act. Following recruitment, participants will be identified using a unique identification number and initials only to maintain anonymisation of research data.

All data will be handled as per data management plan, current data protection legislation.

### **5.1 Data collection and management**

The Case Report Forms (CRFs) will be developed to collect all required trial data. On completion, original CRFs will be sent to Heartlands Hospital MIDRU, and a copy retained at the study site within research site files. The maintenance and upkeep of research files will fall to site specific research team and site PI. These files will be routinely checked upon monitoring visits conducted by MIDRU staff as per monitoring plan.

Data up to hospital discharge, and information on survival at 30 days will be recorded by the site research staff, based on the visit schedule detailed in table one and all data will be collected within CRF and stored in the research site file. Any information that is relevant to the participant's clinical care will be recorded in both researcher site file and patient care records, as to allow for transparency between clinicians and researchers of the participants health.

Data will be entered on to the trial database by staff based at the study site. The data entry clerk will enter data on to the trial database as soon as possible after receipt as per data management plan. The CRF will be reviewed for missing data, conflicting data, and other apparent errors. Where necessary, a data query will be raised for resolution by the study site.

#### **5.1.1 Haemodynamic monitoring data**

Lidco CNAP recordings will be stored on the secure trust-based file system. Analysis will be performed using 'Lidcoview SE' software.

### **5.2 Data storage**

All essential documentation and trial records will be stored by MIDRU in conformance with the applicable regulatory requirements and access to stored information will be restricted to authorised personnel.



### **5.3 Data access and quality assurance**

At treatment allocation, each study participant will be allocated a unique study identification number which, along with the participant's initials, will be used to identify the study participant.

Participant names and other contact details will not be disclosed to anyone other than iSTABILISE research study staff (at both site and coordinating centre) directly involved in running the trial.

Direct access to participant's medical records and other source data (e.g. intensive care unit charts) will be required for trial-related monitoring or audit by NHS Trust R&D departments, and regulatory authorities. This is covered in the patient informed consent form.

### **5.4 Archiving**

Trial documentation and data will be archived for at least ten years after completion of the trial.

The study will be archived in line with University Hospitals Birmingham NHS Foundation Trust's archiving policy.

## **6. STATISTICAL ANALYSIS**

### **6.1 Determination of sample sizes**

This is a feasibility study, and as such the primary outcome is whether it is feasible to run the trial. However, secondary outcomes include;

- Nadir blood pressure; the lowest blood pressure recorded.
- Cumulative time spent with MAP <55mmHg, <65mmHg, 80mmHg.
- Post-operative incidence of acute kidney injury, myocardial infarction, stroke, infective complications and death.

The data produced during this feasibility study, and information currently available in the literature will be used to determine sample sizes for a full large-scale randomised controlled trial.

The main feasibility outcome is ability to successfully carry out the intervention, including screening, identification, consent, randomisation, and use of the equipment intra-operatively. It is anticipated that recruiting 30 cases will be sufficient to demonstrate feasibility, and allow improvements to the protocol to be made and tested.

## **7. TRIAL ORGANISATION AND OVERSIGHT**

### **7.1 Sponsor and governance arrangements**

University Hospitals Birmingham NHS Foundation Trust will act as the Sponsor to this study. Delegated responsibilities will be assigned to the Chief Investigator and the NHS Trust taking part in this study. The non-commercial model clinical trials agreement will be used with all participating sites detailing their local responsibilities.

University Hospitals Birmingham NHS Foundation Trust holds standard NHS Hospital indemnity and insurance cover with NHS Litigation Authority for NHS Trusts in England, which apply to this study.

## 7.2 Ethical approval

We will request ethical approval for this study by a Research Ethics Committee (REC) and Health Research Authority (HRA), flagged for studies involving adults lacking capacity. The required regulatory approvals for the trial will be sought using the Integrated Research Application System (IRAS). The trial will be conducted in accordance with all relevant regulations.

Before enrolling patients into the trial, each trial site must ensure that relevant NHS Trusts have given their confirmation of capability and capacity to undertake a study. Sites will not be permitted to enrol patients into the trial until written confirmation of REC and HRA approval for the trial is received by the iSTABILISE coordinating centre study team. Additionally, sites can only begin recruitment once the sponsor issues greenlight for sites to proceed post-confirmation of capability and capacity.

Email to each site and PI will be used to communicate substantial and minor amendments (e.g. changes to eligibility criteria, outcomes, analyses) to relevant parties i.e. investigators and NHS Trusts.

Annual reports 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. The REC will be notified of the end of the trial (whether at planned time or prematurely).

CI will submit a final report to the required authorities with the results, including any publications within one year of the end of the trial.

## 7.3 Trial Registration

The trial will be registered with [clinicaltrials.gov](http://clinicaltrials.gov)

## 7.4 Notification of serious breaches to GCP and/or trial protocol

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

- (a) the safety or physical or mental integrity of the subjects of the trial; or
- (b) the scientific value of the trial

The sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase

## 7.5 Indemnity

NHS indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS bodies carry this risk themselves or spread it through the Clinical Negligence Scheme for Trusts, which provides unlimited cover for this risk.

## 7.6 Trial timetable and milestones

	Month	Recruitment
Set-up	1-3	-
Recruitment	4-8	30
Follow up	5-9	-

Analysis	9-10	-
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## **7.7 Administration**

The trial coordination team will be based at MIDRU, Heartlands Hospital, Birmingham. The team will be made up of a trial coordinator, senior project manager, CI and possibly admin support staff. All staff coordinating team staff members will be listed and signed off on the delegation log.

## **7.8 Trial Management Group (TMG)**

The Trial Management Group, consisting of the project staff and co-investigators involved in the day-to-day running of the trial, will meet regularly throughout the project. Significant issues arising from management meetings will be referred to the Trial Steering Committee or Investigators, as appropriate.

## **7.9 Essential Documentation**

The Trial Master File will be held in MIDRU, Birmingham Heartlands Hospital, Bordesley Green East, Birmingham B9 5SS. It will be held in a secure office. The coordinating centre will provide Investigator Site Files to all recruiting centres involved in the trial.

## **7.10 Financial Support**

The trial has been funded through an NIHR Academic Clinical Fellowship for Dr William Rook. The CNAP monitors required for the trial have been provided free-of-charge by Lidco Limited (16 Orsman Road, London, United Kingdom, N1 5QJ). Lidco Limited have had no input into the design or conduct of the study.

# **8. MONITORING, AUDIT AND INSPECTION**

## **8.1 Training**

All research study staff involved in the assessment and eligibility assessment of participants will receive training at least once as detailed in section 2.6. It will not be possible to train all clinicians/allied health professionals in GCP but key GCP principles for relevant personnel will be covered during the training programme. The site PI is responsible for the delegation of tasks to appropriately trained site staff. Anaesthetists who are delivering anaesthesia as part of routine clinical care so do not need trial specific training, except for overview of treatment SOP. The CI, PIs, University Hospitals Birmingham administration staff and site staff involved in obtaining consent and follow-up data will be required to complete a GCP course. The CVs and evidence of GCP training for these individuals will be held in staff specific training folders at the coordinating centre, or site specific Investigator Site Files where appropriate. Any new staff to the trial within the University Hospitals Birmingham administration team will complete a trial induction plan. Training will also be carried out for University Hospitals Birmingham administration staff who may answer phone calls from patients or legal representatives and need to deal sensitively with their questions.

## 8.2 Data Quality and visits to sites

Data entered into the trial database will be checked for accuracy. Quality assurance checks will be carried out in accordance to monitoring plan which will be created after a thorough risk assessment has taken place. Additional monitoring may be carried out at the discretion of University Hospitals Birmingham NHS Foundation Trust. This may be triggered by events such as evidence of protocol breaches, poor data quality, repeated late return of CRFs, or late reporting of SAEs. The PI at each site will be responsible for ensuring that the sponsor has access to site files and source data at each monitoring visit. The chief investigator and trial coordinator will have regular telephone and email contact with hospital sites. The trial coordinator(s) will check investigator site file documents are up to date at monitoring visits

## 8.3 Monitoring and Audit

The study will be monitored and/or audited by University Hospitals Birmingham NHS Foundation Trust under their remit as Sponsor and other regulatory bodies to ensure adherence to Good Clinical Practice and the UK Health Policy Framework for Health and Social Care.

Monitoring of study data shall include confirmation of informed consent; source data verification; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. The Trial Co-ordinator, or where required, a nominated designee of the Sponsor, shall carry out monitoring of study data as an on-going activity.

The first study participant who has been randomised, received surgery and completed up to the in hospital follow up stage of the protocol will be monitored by the Sponsors QA Manager to ensure the protocol is fit for purpose and review protocol adherence. Monitoring of study participants by the Sponsors QA manager will then occur at random intervals throughout the study based on recruitment.

Study conduct will be subject to systems audit of the Study Record for inclusion of essential documents; permissions to conduct the trial; Study Delegation Log; CVs of study staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, timeliness of visits); accountability of study materials and equipment calibration logs. This will be led by the Trial co-ordinator and reported back to the Sponsor.

Entries on CRFs will be verified by inspection against the source data. A sample of CRFs (10%) will be checked on a regular basis for verification of all entries made. In addition the subsequent capture of the data on the study database will be checked. Where corrections are required these will carry a full audit trail and justification.

Study data and evidence of monitoring and systems audits will be made available for inspection by the regulatory authority as required.

## 9. PATIENT AND PUBLIC INVOLVEMENT (PPI)

In support of PPI in clinical research, a local group called Clinical Research Ambassador Group (CRAG) has been formed at University Hospitals Birmingham. The CI has presented this study from an early stage, and developed its protocol and aims in accordance with what the PPI group were important outcomes for them.

Following an initial meeting with the West Midlands Research the strategy for involving the key stakeholders in this study was developed; involvement of patients and members of the public from an early stage in the design to ensure the outcomes chosen, and the methodology to achieve them was acceptable and appropriate, and involvement of the anaesthetists who would be needed to both deliver the study, but also to change their practice based on the results, to help make the most deliverable, and relevant clinical trial for them.

## 9.1 Clinical Research Ambassador Group of PPI representatives

Discussions with the CRAG group included the following points.

- Would it be acceptable to withhold the true purpose of the study [to see whether knowledge of blood pressure from CNAP monitoring alters their behaviour, and reduces haemodynamic instability] in order to reduce the ‘Hawthorne’ effect. [Question posed as Meidart et al [25] *did* blind their treating anaesthetists to the purpose of the study.
  - Answer: It would be ideal to do so, but may cause mistrust within the anaesthetic community and harm future recruitment, and so unless there is a clear way to do so without risking creating mistrust with anaesthetic colleagues then overall the harm outweighs the benefit of this form of blinding.
- Would it be acceptable to take additional blood tests?
  - Answer: It would be reasonable to take additional blood to look for things such as kidney or heart problems if it was required, but need to inform the patients what the blood tests would be, and must be clearly stated on the consent form.
- If a member of the research team was present, and looked at the monitor, and it showed a very low blood pressure and the anaesthetist wasn’t aware of it because they were blinded, would you expect the trial to unblind the anaesthetist and tell them?
  - Answer: Yes, but only when this falls well outside acceptable normal practice

In addition to these specific questions, the CRAG group have reviewed, and significantly improved the quality and clarity of the patient-facing documentation, and supported the proportionate approach to consent that we are proposing.

## 9.2 Anaesthetists

Information has been sought by presentation of draft forms of the research proposal to groups of consultant and junior anaesthetists at several departmental meetings in University Hospitals Birmingham.

- Is it a trial worth doing?
  - Answer: Not clear whether preventing hypotension will in itself reduce the adverse outcomes associated with it, or whether the hypotension association is simply a surrogate marker of those at risk of these complications anyway. Therefore it will be helpful to have as much prospective interventional evidence as possible, but clear that given the event rates, this would require a much larger study which may not be possible.

- Answer: A randomised approach will be difficult. If any anaesthetist takes part in the study, and looks after a patient in the interventional arm, where they have the monitoring available, and finds it shows more hypotension than expected [as the literature would predict], then they are likely to change their practice in any patients they are subsequently caring for, be they in a control or interventional arm. This would create bias, and make it likely that the trial outcome would be susceptible to type II error [failing to reject the null hypothesis where it is false]. A better trial would be before and after [which is what, after review, the study team decided to proceed with].
- Is including patients who lack capacity required?
  - Answer: Yes, they are a different group of people, who are generally sicker, and would have more propensity to benefit if the intervention proves to be helpful. Additionally, if the trial excluded this group, it would have severely limited generalisability, as it would exclude a clearly different, and large portion of patients with hip fracture.

## 10. DISSEMINATION AND PUBLICATION

The results of the trial will be reported first to trial collaborators. The main report will be drafted by the trial co-ordinating team, and the final version will be agreed by the Trial Steering Committee before submission for publication, on behalf of the collaboration.

The success of the trial depends on the collaboration of doctors, nurses and researchers from across the UK. Equal credit will be given to those who have wholeheartedly collaborated in the trial.

The trial will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines ([www.consort-statement.org](http://www.consort-statement.org)).

- Publications in specialist journals, such as anaesthetic, trauma, geriatric journals and also high impact peer-reviewed general journals such as BMJ.
- Results will be presented at national anaesthetic, geriatric and surgical meetings such as those organised by Age Anaesthesia Association, Health Service Research Centre UK Peri-operative Clinical Trials Network Research Forum, Royal College of Anaesthetists, Association of Anaesthetists in Great Britain and Ireland, British Geriatric Society.
- A layperson summary will be produced to inform public and patient groups by using our links with National Osteoporosis Society and Clinical Research Ambassador Group at Public Involvement Team at University Hospitals Birmingham NHS Foundation Trust.
- Patients will be asked if they wish to be contacted with results of the trial at the time of consent, and if they do, they will be asked to write the contact details they wish to use on the consent form. These consent forms will be reviewed at the conclusion of the trial and contact made appropriately.

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