**HypoIQ**

Effects of FloTrac IQ

on changing clinician behaviour in the management of intraoperative hypotension

Protocol Version 5.0

18th October 2018

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| **Authorised by:** | |  |  |  |  |
| Name: | Dr Simon Davies | |  | Role: | Chief Investigator |
| Signature: |  | |  | Date: |  |

General Information

This document describes the trial and provides information about procedures for entering patients into it. The protocol should not be used as an aide-memoire or guide for the treatment of other patients; every care was taken in its drafting, but corrections or amendments may be necessary. Clinical problems relating to this trial should be referred to the Chief Investigator.

Compliance

The trial will be conducted in compliance with the protocol, GCP, Data Protection Act, NHS research governance, the Declaration of Helsinki, and the terms of the favourable opinion from the National Research Ethics Service.

Sponsor

York Teaching Hospital NHS Foundation Trust will act as Sponsor for the study.

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Funder

Funding will be from Edwards Lifesciences Ltd

Authorisation

Dr Simon Davies and Dr David Yates are authorised to sign the final protocol and protocol amendments.

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# 1.Background

Intra-operative hypotension is a poorly defined phenomenon partly due to the lack of a standardised definition, however regardless of the definition the incidence is high in the perioperative population. If we look at relative extremes then in one cohort1 56% and 27% of patients experienced a drop in mean arterial pressure of greater than 40% from baseline for a duration of 1 and 10 minutes respectively, whilst 50% and 24% experience a systolic blood pressure drop of >40% at these time scales. This data is consistent with other studies examining intraoperative hypotension.

In a retrospective study of 33 000 patients undergoing non cardiac surgery2, the authors calculated the time that MAP was less than various thresholds ranging from 55-75mmHg and examined post operative renal and cardiac complications as well as 30 day mortality. The overall incidence of acute kidney injury (AKI) was 7.4% and myocardial injury after non-cardiac surgery (MINS) 2.3%. A MAP of < 55 mmHg was associated with both AKI and MINS and the risk rapidly escalated with the amount of time spent below this blood pressure. There was in addition some association with poor outcomes with MAP between 55-59mmHg , particularly for kidney injury. These end points are significant as both AKI and MINS are associated with worse outcomes after surgery both in terms of morbidity and mortality.

More recent work has added to this evidence looking at the association of acute kidney injury and intraoperative hypotension in elective non cardiac surgery3. There was a graded relationship between hypotension both in terms of magnitude and duration and the severity of kidney injury. A MAP < 55 mmHg for more than 10 mins is a poor outcome predictor in terms of kidney injury and a suggestion that prolonged period of time (>20 minutes) spent at mean arterial pressure of 60-64mHg may also lead to injury.

The most recent study and the largest to date also confirms the association between hypotension and myocardial and kidney injury4. It examined 57 000 patients undergoing non-cardiac surgery, and the overall baseline rates of AKI were 5.6% and cardiac injury 3.6% respectively. The authors assessed the relationship between either the relative decrease in Map from baseline or the absolute lowest MAP, the time spent below these thresholds, and outcomes to find the optimal threshold for BP below which injury occurs. They showed that at a MAP below 65mmHg or a decrease of 20% from baseline then the estimated probability of MINS and AKI increases and as the MAP goes lower, either absolute or relative, so does the incidence of the outcome. At a MAP below 65mmHg then a cumulative time spent below this of 13 minutes or more increases the risk of myocardial and kidney injury and as you spend longer under this threshold then the chance of injury is higher.

The Flotrac IQ algorithm incorporates a hypotension probability index (HPI), and a HPI of 85 translates approximately to a 85% chance of hypotension to occur within the following 5 minutes. Additional information on contractility (dp/dt) and dynamic elastance is also available. These variables provide insight into the pathophysiology of the predicted hypotensive episode and enable the treating anaesthetist to provide the appropriate therapy to prevent this hypotension from occurring. Whether clinicians find this information acceptable to use, or that it confers clinical utility remains unknown and for this technology to become accepted, and in turn lead to a reduced incidence of hypotension, this would require change in current behaviours including attitudes and skills.

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# 2. Rationale and Aim

The underlying rationale is that by using the HPI and the secondary information intra operative hypotension can be reduced and appropriately treated. However, hypotension can also be avoided simply by requiring the treating clinician to keep the MAP>65mmHg, although the treatments may be inappropriate to the pathophysiology. Therefore we aim to show that through the use of the HPI and the secondary information clinician behaviour to the treatment of hypotension is altered compared to standard practice.

## 2.1 Risks and benefits.

A reasonable body of evidence now exists to support the use of haemodynamic optimisation during surgery to reduce complications and hospital length of stay in patients undergoing major abdominal and orthopaedic surgery. The evidence for this in patients undergoing vascular and head and neck surgery is less robust. Increasing evidence is emerging that intraoperative hypotension is deleterious to patients. The potential changing of clinician behaviour towards hypotension is not deemed to have any negative connotations.

There are no additional benefits for individuals taking part in this study

We do not expect any additional risks above that of ‘conventional care’

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# 3. Study Sites

This study will take place in the surgical unit, operating theatres and post anaesthetic care unit, York Hospital, Wigginton Road, York YO31 8HE, and the surgical unit, operating theatres and post anaesthetic care unit University Medical Centre Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands.

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# 4. Selection of Patients

## 4.1 Patient inclusion criteria.

Patients due to undergo elective major abdominal, orthopaedic, head and neck or vascular surgery requiring invasive arterial monitoring (decided at the discretion of the treating clinician) under general anaesthesia with positive pressure ventilation, and with an expected duration of greater than 90 minutes, who will have goal directed fluid therapy performed as part of their standard care.

## 4.2 Patient exclusion criteria

* Requirement for an intraoperative mean arterial pressure of less than 65mmHg as decided by the treating surgeon and/or anaesthetist.
* A preoperative MAP of lower than 65mmHg documented on 2 seperate occasions at preoperative assessment clinic.
* Significant right or left ventricular heart failure
* Known intra cardiac shunt.
* Known severe aortic stenosis (peak velocity greater than 4m per second and/or aortic valve area less than 1cm2)
* Cardiac arrythmias
* Planned positive pressure ventilation with tidal volume < 7ml/kg
* Hepatic surgery
* Subjects requiring dialysis.
* Subjects who do not have the capacity to consent
* Subjects aged less than 18 years of age.

## 4.3 Number and source of patients and participants .

Structured interviews will be performed with 20 clinical staff across both sites at each stage of the interventions. In addition, questionnaires will be distributed to as many staff as possible at all sites to obtained attitudes pertaining to the treatment of hypotension, the barriers that they perceive, and the attitudes towards the new technology (HPI).

The total number of patients to be recruited will be 150 which will allow clinicians undergoing the structured interviews adequate exposure (1-3 cases per clinician) to the differing approaches to treat hypotension . All patients will be undergoing major surgery as described in the inclusion criteria at either York or UMCG. Seventy-five patients will be recruited at each site, with an estimated recruitment of 10-15 clinicians interviewed per intervention.

## 4.4 Identification, recruitment and consent.

The identification and consent process is described below, and only patients with capacity will be recruited

Patients scheduled for major elective surgery that meet the inclusion criteria will be given the Patient Information Leaflet at the earliest opportunity. Patient Information Leaflets will be posted to potential participants with their pre-operative assessment information, or alternatively given out by one of the researchers or research nurses at the pre-operative assessment clinic. During normal working hours, a member of the research team will be available to answer any questions relating to the research project. All members of the research team will have an in-depth knowledge of the protocol and all have been involved in various research projects about haemodynamic optimisation. Once the Patient Information Leaflet has been given out, a sticker will be placed in the clinical notes stating that the patient is eligible for the study and has been given the information. This sticker will be timed and dated. Those patients eligible to take part will be asked to consent having had time to consider the proposal. Consent will be received either by the Chief Investigator, the Co-Investigators or an appropriately trained Research Nurse, and will normally take place at either the pre-operative assessment clinic or on admission to hospital depending on when the individual received the patient information sheet. Another sticker will be placed in the notes stating that informed consent has been received. Again, this will be timed and dated. Three copies of the consent form will be taken – the original for the site file, one copy for the patient and one to go into the patient’s notes.

If people withdraw from the study, data collected until the point of withdrawal will be included in the study.

Clinicians and allied staff will be consented to take part in the structured interviews and questionnaires prior after educational intervention stage 1 (see section 6.2), this will ensure that all clinicians that are exposed to the differing methods to treat hypotension in patients are willing to take part in qualitative data collection.

## 4.5 Screening procedures and pre-randomisation investigations.

Electronic theatre lists will be screened to find patient subjects eligible for the trial. This is the only screening procedure. No other investigations are necessary for the conduct of this trial. Patients will receive their standard pre-operative work-up, irrespective of whether they participate in the trial or not.

Patients and clinicians who consent to take part in the study, will be free to withdraw at any time and without providing a reason. A decision to withdraw, or a decision not to take part will not affect the standard of care that the patient receives.

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# 5. Allocation

## 5.1 Allocation to treatment

This will be a prospective non randomised trial with three sequential cohorts of 50 patients. The first cohort will act as the control group representing standard practice at the institution, whilst the subsequent 2 cohorts will have different interventions applied to treat hypotension, as described in the protocol (section 6). Randomisation was not considered appropriate due to the potential for observation bias (Hawthorn effect). Clinicians will not be randomised to provide treatment to the different arms, and will be allocated as per the institutions normal practice to operating lists on which those patients occur. There is no limit to the number of clinicians that may provide care in the standard practice arm, however in cohort 2 once 10 clinicians have treated patients in each, clinician enrolment will cease and those 10 clinicians will be allocated to treat any subsequent patients in both cohorts 2 and 3.

## 5.2 Co-enrolment guidelines.

For the duration of their involvement in this study, patients may be co enrolled in other perioperative studies as long there is no intervention performed during the intraoperative period. This would include observational studies and interventional studies where the intervention is performed after recovery from anaesthesia.

# 6. Treatment of Patient Participants

## 6.1 Cohort 1-Standard institutional care (GDFT)- phase 1

Study participants will receive standard institutional care for patients undergoing major surgery. All patients will have an arterial line connected to a FloTrac IQ transducers and haemodynamic data will be displayed on the EV 1000 platform. Patients will receive goal directed fluid therapy intraoperatively to maintain a stroke volume variation of less than 12% (15% in laparoscopic surgery with pneumoperitoneum) (Appendix 1) and clinicians will have access to the all haemodynamic data except for hypotension probability index, Eadyn and dP/dT.

Management of hypotension will be entirely at the discretion of the attending anaesthetist both in terms of the threshold for treatment and mode of treatment.

All fluid management and administration of vasopressor therapy will be at the discretion of the anaesthetist as per the current practice at the host institution.

All interventions relating to the treatment of hypotension will be entered on to the EV1000 platform, and at the end of surgery data will be downloaded from the EV1000 platform that will provide measurements of cardiac output, cardiac index, stroke volume variation, stroke volume, stroke volume index, hypotension probability index, pulse rate variability, pulse rate, and systolic, diastolic and mean arterial pressure. Anonymised raw waveform data will be sent to Edwards Lifesciences for data capture of dP/dT, Eadyn and PPV.

## 6.2 Education intervention 1 – phase 2

All clinicians who will treat patients enrolled into cohort 2 will receive a short presentation via email or at a departmental meeting that outline the current evidence of the association with intraoperative hypotension and adverse clinical outcomes. All clinicians will be required to sign a statement acknowledging that they have received and understood this education package.

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## 6.3 Cohort 2 (GDFT and intraoperative MAP>65mmHg)

All patients will have an arterial line connected to a FloTrac IQ transducers and haemodynamic data will be displayed on the EV 1000 platform. Patients will receive goal directed fluid therapy intraoperatively to maintain a stroke volume variation of less than 12% (15% in laparoscopic surgery with pneumoperitoneum) and clinicians will have access to the all haemodynamic data except for hypotension probability index, Eadyn and dP/dT.

Clinicians will be asked to maintain a MAP>65mmHg. No specific guidance will be issued on how to achieve this target and it will be left to the clinical discretion of the treating clinician. All fluid management and administration of vasopressor therapy will be at the discretion of the anaesthetist.

All interventions relating to the treatment of hypotension will be entered on to the EV1000 platform, and at the end of surgery data will be downloaded from the EV1000 platform that will provide measurements of cardiac output, cardiac index, stroke volume variation, stroke volume, stroke volume index, hypotension probability index, pulse rate variability, pulse rate, and systolic, diastolic and mean arterial pressure. Anonymised raw waveform data will be sent to Edwards Lifesciences for data capture of dP/dT, Eadyn and PPV.

## 6.4 Education intervention 2 – phase 3

All clinicians who will treat patients enrolled into cohort 3 will receive a short presentation via email or at a departmental meeting that describes the hypotension probability index, and the 2 additional parameters of Eadyn and dP/dT and how these may be used clinically. All clinicians will be required to sign a statement acknowledging that they have received and understood this education package

## 6.5 Cohort 3 (GDFT and HPI)

Arterial lines will be placed in patients awake under local anaesthesia All patients will have an arterial line connected to a FloTrac IQ transducers and haemodynamic data will be displayed on the EV 1000 platform. Patients will receive goal directed fluid therapy intraoperatively as per the institutions local policy (see appendix 1), and clinicians will have access to the all haemodynamic data including hypotension probability index, Eadyn and dP/dT.

*Clinicians will be asked to keep MAP >65 and, when an HPI > 85% is alerted, investigate the cause of the pending hypotension and use their knowledge of the advanced haemodynamic parameters for proactive treatment. Guidance on potentially suitable interventions will be provided*. Guidance on potentially suitable interventions will be given (Appendix 2). This guidance has been developed from an expert working group consensus

All interventions relating to the treatment of hypotension will be entered on to the EV1000 platform, and at the end of surgery data will be downloaded from the EV1000 platform that will provide measurements of cardiac output, cardiac index, stroke volume variation, stroke volume, stroke volume index, hypotension probability index, pulse rate variability, pulse rate, and systolic, diastolic and mean arterial pressure. Anonymised raw waveform data will be sent to Edwards Lifesciences for data capture of dP/dT, Eadyn and PPV.

6.6 Anaesthetic technique.Anaesthetic technique will be at the discretion of the anaesthetist as per the current practice at the host institution in both the treatment and control group.

## 6.7 Discontinuation criteria.

Patients will be withdrawn from the trial

1. Voluntary withdrawal (by patient or consultee).

If subjects are withdrawn from the trial, data collected up to that point will be retained. If the intervention has not been performed then an additional subject will be recruited.

## 6.9 Withdrawal of patients.

In consenting to the trial, patients are consenting to trial treatment and data collection. If a patient wishes to withdraw from the trial prior to surgery they shall be free to do so with no detriment to their medical care

## 6.10 Blinding.

Treating clinicians and research nurses will be blinded to the HPI, Eadyn and dP/dT data for cohorts 1 and 2

# 7. Treatment of clinical staff participants

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Structured interview will take place and questionnaires distributed both designed to provide insights into the following research questions and given to clinical staff at the tie scale described below.

7.1 Research question 1: What are the beliefs amongst \*clinical staff of the costs and benefits of controlling hypotension during surgery following initial training?

Interviews with 15-20 clinical staff will be performed across both sites using the Theoretical domains framework (Michie et al., 2005) to structure interviews (Sample interview appendix 3)

7.2 Research question 2: What do clinical staff perceive to be the barriers to effective control of hypotension during phase 2 and 3?

Questionnaires based on information from the above interviews (section 7.1)will be developed as well as the Influences on Patient Safety Behaviour Questionnaire (Taylor et al., 2013) distributed to all staff attending training at phase 2 and phase 3 and others who might be involved in caring for patients before, during or after major surgery. Aim to achieve overall sample of 50+

7.3 Research question 3: How useful and usable is the new technology and can it readily be integrated into routine practice?

Items from Standardised Normalisation Process Theory questionnaire (NOMAD, 2016) and Implementation of medical devices questionnaire (Green et al., 2009) used in testing of usability of new devices to be distributed to all staff as in section 7.2 approximately 2 months post-training and FloTrac IQ implementation. In addition

observations of practice during 6-8 surgical procedures at York and Groningen will occur with post-procedure interviews with key staff

7.4 Research question 4: What are the attitudes of other clinicians (outside of the two sites) to the use of FloTrac IQ technology? What is the likelihood of wider adoption?

Workshop with 30+ Yorkshire and Humber clinicians including embedded focus group discussions and brief exit questionnaires.

\*Clinical staff refers primarily to anaesthetists, but surgeons, ODPs, recovery staff may also have a role in supporting the monitoring and control of hypotension, so while sampling will attempt to represent at least 40%+ of anaesthetists in each unit, other clinical staff will also be included represented.

## 7.5 Discontinuation criteria.

Clinical staff will be withdrawn from the trial if the voluntarily request

If subjects are withdrawn from the trial, data collected up to that point will be retained. If the intervention has not been performed then an additional subject will be recruited.

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## 7.6 Withdrawal of subjects.

In consenting to the trial, clinical staff are consenting to take part in interviews and/or questionnaires and data collection. If a clinician wishes to withdraw from the trial prior to completion they shall be free to do so .

# 8. Regulatory issues.

A notice of no objection from the MHRA is not necessary as the FloTrac IQ is a CE marked medical device that is being used for its intended purpose.

The study also does not require a Clinical Trial Authorisation from the MHRA as it is not a Clinical Trial of an Investigational Medicinal Product.

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# 9. Assessments

## 9.1 Chart for pre and intra-operative data.

See Case Record File

## 9.2 Loss to follow-up.

It is highly unlikely that there will be any loss to follow up as data collection ceases and the end of surgery

## 9.3 Trial closure.

The trial shall end when the last patient has been has completed surgery.

At the point of trial closure the Chief Investigator shall notify the Sponsor in writing that the trial has ended. This shall be done in accordance with the York Teaching Hospitals NHS Foundation Trust R and D unit SOP on Trial Closure. Study data will be archived in accordance with the York Teaching Hospitals NHS Foundation Trust and University Medical Centre Groningen SOP

# 10. Statistical Considerations

## 10.1 Outcome Measures.

## 10.1.1 Primary outcome

 We will be measuring a range of social-cognitive determinants of behaviour change including attitudes, self-efficacy, social norms, skills, as well as factors relating to the normalisation of technology into routine practice through qualitative data analysis.

## 10.1.2 Secondary outcomes

* Description of treatment of hypotension in the different cohorts
* Incidence of hypotension defined as no of episodes with MAP <65mmHg lasting for > 1, 3, 5, 10, and 20 minutes respectively in each cohort
* Time weighted average spent in hypotension.
* Change in the amount of fluid and dose and type of vasopressors/inotropes given between the different cohorts
* Proportion of interventions deemed sub optimal to treat hypotension compared to the cohort 3 treatment protocol
* Effects of interventions (fluid, vasopressors and inotropes) on secondary parameters including SVV, PPV, CI, SVI, Eadyn and dP/dT.

## 10.2 Sample Size.

A model of theoretical sampling and saturation will be used to determine the number of clinical staff that will need to be recruited for the structured interviews. It is estimated that a minimum of 5 clinical staff will undergo structured interviews at each site with each clinician undergoing exposure to at least 3 patients in each cohort. This will require a patient population of approximately 25 patients at each site per cohort to allow for this.

Questionnaires will be distributed to as many relevant clinical staff as possible aiming for at least 50 responses per site per questionnaire.

In addition the inclusion of 25 patients per site per cohort (50 per cohort, 150 patients in total) will also allow for an estimate of the treatment effect and impact on the incidence hypotension between the groups as described below

A reduction in the incidence of hypotension defined as a MAP < 65mmHg for greater than 5 minutes from 65% in cohort 1 to 43% in cohort 2 would require 47 patients per group (40% risk reduction), with a power 80% to detect a difference with a significance of p< 0.05

A reduction in the incidence of hypotension defined as a MAP < 65mmHg for greater than 5 minutes from 43% in cohort 2 to 18% in cohort 2 would require 50 patients per group (60% risk reduction) with a power 80% to detect a difference with a significance of p< 0.05.

These are deemed clinically plausible reduction in hypotensions from the methods that will be employed in treating cohorts 2 and 3, and the baseline incidence of 65% in cohort 1 is representative of the current incidence of hypotension.

## 10.3 Interim Monitoring and Analyses.

There is no planned interim analysis.

## 10.4 Analysis Plan.

A full analysis plan will be written prior to data analysis however will include

1. For qualitative data thematic content analysis will be used to decribe the data
2. Questionnaire data will analysed with descriptive statistics - frequencies, means and SDs. Repeated measures t-tests will be performed to investigate change in behavioural determinants over time. In addition, correlations between the factors reported to influence uptake and effective use of the technology will be performed.
3. Perioperative haemodynamic variables.

* Heart rate (bpm)
* Blood pressure (mmHg) – systolic,diastolic and mean
* Stroke volume (ml)

Summary statistics per group (mean and SD or median and IQR) and difference from baseline between the groups at the start and end of surgery.

1. Perioperative fluid volumes.

Summary statistics per group (mean and SD or median and IQR) of volumes of fluid and type given. Comparison of means with a t test or medians with Mann Whitney U if non parametric data.

1. Use of inotropic or vasopressor support

* Number of people in each group receiving inotropic or vasopressor support.
* Odds of receiving inotropic or vasopressor support in each group with 95% CI
* Difference in proportions - Chi squared test
* Summary stats of volume and dose given (mean and SD or median and IQR)

1. Incidence of perioperative hypotension

* Number of people in each group with hypotension as defined in the protocol
* Odds of having hypotension in each group with 95% confidence interval.
* Difference in proportions between each group – Chi squared test
* Number of people in each group with hypotension
* TWA of hypotension measured by AUC and compared between groups.

1. Descriptive analysis of interventions in cohorts 2 and 3 that would have deviated from the treatment plan for cohort 3.

**Level of significance**

The level of significance will be taken as p< 0.05.

**Additional information**

* Missing data will be coded as missing and no imputation used
* A decision regarding adjustment of data for baseline data will be made when the data has been unblinded.
* Normality of continuous variables will be assessed by plotting the data as histograms and visually inspected. Skewed data will be treated as non parametric and the appropriate tests used.

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# 11. Trial Monitoring.

## 11.1 Clinical site monitoring.

A monitoring plan will be arranged by the Sponsor. Monitoring will take place in accordance with York Teaching Hospitals NHS Foundation Trust’s SOPs and will include, at a minimum, a Trial Initiation Monitoring Review, Trial Closure Review and regular visits to monitor CRF accuracy and completeness. An appropriate interval between monitoring visits is to be decided by the Sponsor.

# 12. Data Protection.

## 12.1 Direct access to data.

Authorised bodies will have direct access to all trial data, including site files and source data, in order to carry out trial-related monitoring, audits, ethics committee review and regulatory inspections. Anonymised data will be sent to Edwards Lifesciences for the derivation of certain variables from raw data. Patients’ consent for this is obtained as part of the consent process.

## 12.2 Patient data.

Patients will be allocated a trial ID number upon allocation to one arm of the study and all personal identifiers will be removed at the earliest opportunity. Any identifiable information such as contact details or consent forms will be stored in a site file held in a locked filing cabinet. Non-identifiable data will be held on a Trust, password protected computer.

## 12.3 Confidentiality.

Full medical confidentiality will be maintained in accordance with law in the UK and The Netherlands and the study will be conducted according to GCP guidelines. No patient’s name or address will be disclosed to any third party. Patients will not be identifiable in any publication that arises as a result of this trial. The trial will comply with the Data Protection Act.

# 13. Ethical Considerations and Approval.

## 13.1 Ethical considerations.

Participants in this study will not have to undergo any additional clinical investigations above and beyond their usual care and will not have to attend any additional hospital appointments.

Full medical confidentiality will be maintained according to UK law for York Teaching Hospitals NHS Foundation and The Netherlands law for University Medical Centre Groningen nd the study will be conducted according to GCP guidelines.

The trial information and all data will be stored for a period of at least 5 years.

All investigators and research teams will receive training in relevant areas such as GCP, and Standard Operating Procedures (SOPs).

A monitor appointed by the York Teaching Hospitals NHS Foundation Trust will monitor the conduct of the study.

## 13.2 Ethical approval.

Ethics approval will be sought from an ethics committee

## 13.3 Trial withdrawal.

The right of any patient to refuse to participate in the trial without giving reasons shall be respected. After the patient has entered the trial, all clinicians are free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interests of the patient. However, the reason for doing so shall be recorded and the patient will remain within the trial for the purpose of data analysis according to the treatment option to which they have been allocated. Similarly, all patients are free to withdraw at any time from the protocol treatment and trial follow-up without giving reasons and without prejudicing his/her further treatment.

# 14. Safety Reporting

All adverse event reporting will be carried out in accordance with the Sponsor’s Research Related Adverse Event Reporting Procedures.

For all adverse events, the Clinical Investigator will take appropriate action to ensure the safety of all participants and staff in the study.

## 14.1 Definition of Adverse Events/Reactions

Adverse Event (AE)

An adverse event is defined as any untoward medical occurrence that occurs to a trial participant during the course of the study. Information about adverse events will be collected from the beginning of any trial related procedure. For the purpose of this trial this is defined as the induction of anaesthesia

For the purpose of this trial the adverse events that will be recorded are those that may occur as a result of the fluid volume given, or the use of vasopressors. Such adverse events will include, but will not be limited too:

* Pulmonary oedema.
* Myocardial ischaemia.
* Myocardial infarction.
* New peripheral oedema.
* Intraoperative hypertension
* Any other adverse event deemed relevant by the Chief Investigator.

Serious Adverse Event (SAE)

An adverse event is defined as serious if it results in one of the following:

1. Death
2. A threat to life
3. A new in-patient hospitalisation (not including planned, elective treatment)
4. Prolonging of an existing hospitalisation
5. Persistent or significant disability or incapacity
6. A congenital anomaly or birth defect in a subsequent pregnancy (not expected in this sample of patients)

Serious Adverse Reaction (SAR)

An SAE will be deemed to be an SAR if there is thought to be a possible, probable or definite relationship to the volume of fluid therapy, the use of vasopressors, or the omission of clinically significant treatment . Causality will be rated for all SAEs as follows:

*Not related*

There is clear alternative explanation for the AE or it has no reasonable temporal relationship to the volume of fluid therapy or use of vasopressors

*Unlikely to be related*

The AE may be temporarily linked to volume of fluid therapy or use of vasopressors but is much more likely to be due to other causes

*Possible*

The AE has a reasonable temporal relationship with volume of fluid therapy or use of vasopressors but could equally well be explained by these or other causes*.*

*Probable*

The adverse event may be due to an alternative cause but it will follow a pattern of a known response and/or a reasonable temporal relationship to volume of fluid therapy or use of vasopressors.

*Definitely related*

The adverse event cannot be explained by an alternative cause and either follows a pattern of a known response and/or a reasonable temporal relationship to volume of fluid therapy or use of vasopressors

Suspected Unexpected Serious Adverse Reaction (SUSAR)

A SUSAR is an adverse event that is serious, thought to have a possible, probable, or definite relationship to volume of fluid therapy or use of vasopressors and is unexpected.

Expectedness will be rated as:

*Unexpected*

The nature and/or severity of the event is not consistent with the applicable information about volume of fluid therapy or use of vasopressors.

*Expected*

The nature and/or severity of the event is consistent with the applicable information about volume of fluid therapy or use of vasopressors

## 14.2 Clinical Management of Adverse Events

The supervising clinician will manage any adverse events that should occur. Advice will be provided by the Chief Investigator as necessary.

Documentation of any action taken will be recorded in the medical notes and communicated to other relevant parties as necessary.

## 14.3 AE Follow-up

Adverse events will be followed up by the research team to their conclusion. Follow up of adverse events will cease at hospital discharge or Day 10 whichever is reached first.

## 14.4 SAE/SUSAR Follow-up

All SAEs or SUSARs will be followed up to their conclusion irrespective of the timeframe of the follow-up period. If necessary this will involve telephone interviews or, if deemed necessary and the study participant is willing, an extra out-patient visit to the hospital for review by the research team. Any patient discharged home with an ongoing SAE/SUSAR shall be given 24 hour contact details for the research team.

|  |  |  |
| --- | --- | --- |
|  |  |  |
|  | **SAE NOTIFICATION** |  |
|  | Within 24 hours of becoming aware of anSAE, please fax a completed SAE form to the York Foundation Trust R&D Unit on: |  |
|  | **Fax: 01904 725700** |  |
|  |  |  |

# 16. References:

1. Bijker JB, van Klei WA, Kappen TH, van Wolfswinkel L, Moons KG, Kalkman CJ. Incidence of intraoperative hypotension as a function of the chosen definition: literature definitions applied to a retrospective cohort using automated data collection. Anesthesiology 2007;107:213-20.

2. Walsh M, Devereaux PJ, Garg AX, Kurz A, Turan A, Rodseth RN, Cywinski J, Thabane L, Sessler DI. Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: toward an empirical definition of hypotension. Anesthesiology 2013;119:507-15.

3. Sun LY, Wijeysundera DN, Tait GA, Beattie WS. Association of intraoperative hypotension with acute kidney injury after elective noncardiac surgery. Anesthesiology 2015;123:515-23.

4. Salmasi V, Maheshwari K, Yang D, Mascha EJ, Singh A, Sessler DI, Kurz A. Relationship between Intraoperative Hypotension, Defined by Either Reduction from Baseline or Absolute Thresholds, and Acute Kidney and Myocardial Injury after Noncardiac Surgery: A Retrospective Cohort Analysis. Anesthesiology 2017;126:47-65.

# Appendix 1 : GDFT treatment algorithm

../SVV%20algo%202.pdf

# Appendix 2 : treatment algorithm for cohort 3

../algo4b%20SVV%20GDFT.pdf

Fluid : 250 ml of crystalloid or colloid fluid over 5 minutes.

Inotropes : Ephedrine 3-9 mg as a bolus. If more than 3 consecutive boluses given then consider dobutamine infusion at 2.5mcg.kg/min and titrate to effect.

Vasopressors: Either bolus of phenylepherine 100mcg or metaraminol 0.5mg. If more than 3 consecutive boluses given then consider infusion of either drug titrated to effect. Alternatives would include Noradrenaline either peripherally or centrally as per local protocols.

# Appendix 3 : Sample interview.

**Hypotension management in major surgery: Implementation study**

**Interview Schedule for Health Professionals**

Background

We are conducting interviews as we wish to understand the beliefs amongst clinical staff of the costs and benefits of controlling hypotension during surgery following initial training.

Interview

1. To what extent do you see managing hypotension peri-operatively as a priority. Why?

2. How do you manage hypotension and how have you learnt to do this?

Prompt: Do you refer to any guidance/ training/ literature.

3. In what circumstances would you be less concerned and/or more concerned to manage hypotension.

4. What are the short and long term benefits for the patient/ you/ the team or service of managing hypotension?

5. Are there any negative consequences?

6. Do your colleagues (other anaesthetists) strive to manage hypotension?

7. Thinking about other people you work with in theatres - how you interested are they in managing hypotension?

8. Do you feel you have the knowledge and skills you need to manage hypotension?

9. How difficult is it to manage hypotension? Why is this?

10. What tools or equipment do you have to help you manage hypotension? Is there anything else you need?

11. Is managing hypotension something that you are measured on or encouraged to do by anyone else?

12. Are there situations in which it is difficult or impossible to manage hypotension? How does this make you feel?

13. Is managing hypotension something you do automatically or do you sometimes forget?

14. Is managing hypotension an interesting or satisfying part of the job?

15. To what extent is the ability to manage hypotension a sign that you are good at your job?

16. Is there anything else that you would like to add?