THE IMPACT OF CONTINUOUS HAEMOFILTRATION WITH HIGH VOLUME FLUID EXCHANGE DURING CARDIOPULMONARY BYPASS SURGERY ON THE RECOVERY OF PATIENTS WITH IMPAIRED RENAL FUNCTION - A PILOT TRIAL – HTA REF 08/53/33

Short Title: Filtration On Bypass Surgery – **FOBS Trial**

HTA Ref: 08/53/33

R&D STUDY Number: 853

Protocol version 6

ISRCTN protocol registration number **49513454**

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Confidentiality statement

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1 CONTACT DETAILS AND KEY PERSONNEL

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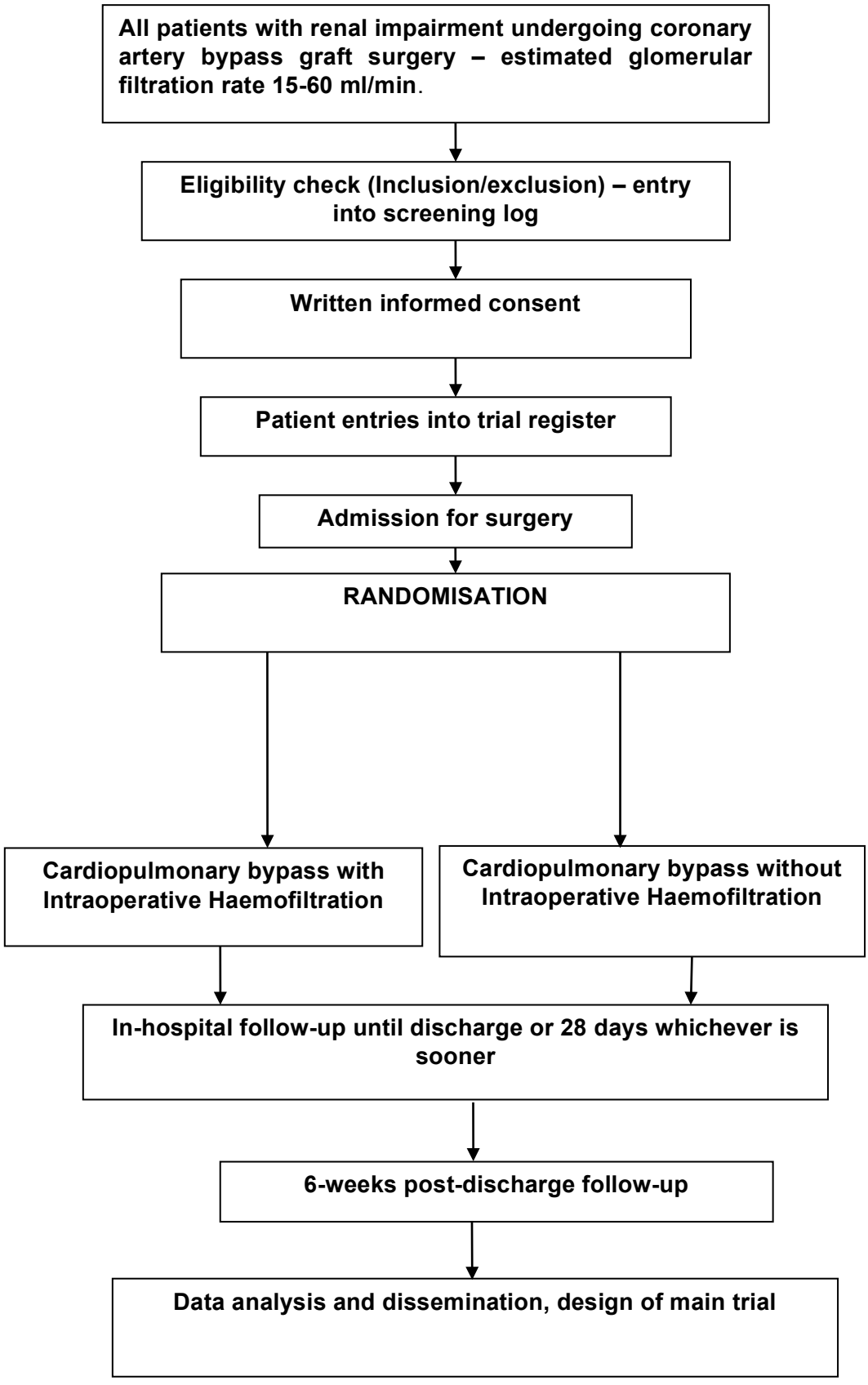
2. STUDY SUMMARY

Title of study	**The Impact of continuous haemofiltration with high volume fluid exchange during cardiopulmonary bypass surgery on the recovery of patients with impaired renal function - A pilot randomised study**
Lay title	Impact of blood purification devices on well-being of patients with moderately impaired kidney function and undergoing cardiac surgery
Study design	Single-centre, randomised, prospective clinical trial
No of subjects	60
Study timelines	Planning, ethics and start-up **Mar 2010 – Oct 2010** Recruitment **Nov 2011 – Mar 2012** End of follow-up **Mar 2012** Analysis and reporting **Mar 2012** Final report **May 2012**
Inclusion criteria	Consenting men and women must be at least 18 years old, high-risk patients elective for on-pump coronary artery bypass graft surgery (CABG). They must also have impaired renal function established preoperative by an <60 ml/min measured within 4 weeks before surgery.
Exclusion Criteria	Patients undergoing surgery on the great vessels (aortic surgery) or valve surgery, have significant impaired liver function (serum bilirubin >60 or INR>2 without anticoagulation), patients who are further down the line of renal failure or on-dialysis, have malignancy and those that are pregnant.
Primary outcome measure	Incidents of ICU stay >3 days for patients with renal impairment identified as an estimated glomerular filtration (eGFR) <60 ml/min.
Secondary outcome measures	**Clinical** 1. Composite of perioperative incidences: Bleeding, sepsis, death, arrhythmias, stroke, and myocardial infarction 2. Need for postoperative continuous veno-venous haemofiltration (CVVH) in the ICU- Indications for requirement of postoperative continuous veno-venous haemofiltration must adhere to our surgical guidelines. 3. Mechanical ventilation time 4. Hospital stay 5. eGFR at 6 weeks follow-up **Secondary Economic Outcomes:** Resource utilisation associated with each of the two pilot arms such as: ICU stay and hospital stay, mechanical ventilation, medications, tests and procedures undertaken until the end of the follow-up period.

Follow-up	Outcome measures will be assessed until hospital discharge or 28 days, whichever is sooner and at 6 weeks follow-up appointment

3. FLOW DIAGRAM



4. RESEARCH OBJECTIVES

There is a widespread variability in clinical practice within cardiac surgery units worldwide on the use of haemofiltration on a case-by-case basis, the impact and safety of this modality however, is unknown. In addition, no evidence exists to suggest that haemofiltration as applied to patients during the period of the operation may have an impact upon the postoperative cost of care and clinical renal impairment outcomes. We hypothesise that the initiation of intraoperative haemofiltration with high-volume fluids exchange during cardiopulmonary bypass in patients with impaired renal function effectively reduces overall length of intensive care unit (ICU) stay and progression of renal impairment. Since no large randomised trial has undertaken this kind of study before, the design of the study is limited by the absence of past trial data that could be used as a reference. In order to overcome these limitations we propose to at first conduct a pilot feasibility study with the following objectives:

1. To assess the feasibility of randomising 60 patients with impaired kidney function (eGFR<60 ml/min) undergoing coronary artery bypass surgery in 6 months within a single-centre for intraoperative haemofiltration i.e. to investigate the likely recruitment rates and issues that may impact recruitment into the study.

2. To assess the suitability and reliability of the outcome measures.

3. To investigate the likelihood of recruitment into the main definitive study and explore issues that may impact recruitment such as staff requirements, barriers to recruitment, suitability and reliability of the outcome measures selected.

5. BACKGROUND

5.1 INTRAOPERATIVE HAEMOFILTRATION

Cardiac surgery can be associated with dysfunction of major organs [1]. The perioperative complications in patients with impaired renal function undergoing cardiac surgery increase hospital stay, mortality and eventually cost of healthcare [2]. It is estimated that up to 20% of patients undergoing cardiac surgery already have a pre-existing renal insufficiency (increased creatinine >132 μmol/L). An increasing body of evidence suggests that inflammatory factors and oxidant stress have significant roles in the pathogenesis of cardiovascular disease [3]. Indeed, increased production of reactive oxygen species (ROS) in the failing heart is a characteristic feature of oxidant stress. Patients with associated renal

disease have a strikingly increased oxidative stress and an impaired antioxidation system. It seems reasonable to expect that patients with renal impairment and elevated oxidative stress are at increased risk of complications after cardiac surgery [4)]. According to the literature, postoperative development of acute renal failure (ARF) has adverse prognostic significance and itself increases the risk of death [5, 6]. Some of the other factors that contribute to poor outcome in these patients postoperatively are advanced age, preoperative left ventricular dysfunction, perioperative low cardiac output, duration of cardiopulmonary bypass (CPB) and aortic cross clamp time [7]. Activation of the inflammatory cascade is thought to account for some of the respiratory dysfunction and results in prolonged mechanical ventilation. In addition, a systemic inflammatory response induced by CPB may necessitate the use of intra-aortic balloon pump, the continuous administration of inotropic drugs, and at times extracorporeal life support. Mortality has remained high despite the use of different renal replacement therapies in these patients in the post-operative phase and after hospital discharge [8].

There are several potential explanations for such a high morbidity and mortality. It has been suggested that oxidative stress induced by cardiac surgery is involved in the pathogenesis of an underlying systemic inflammatory response (SIRS) experienced by most patient's perioperatively [9, 10]. This leads to a further reduction in antioxidant capacity and an increased onset of a cascade of events such as protein modification, lipid peroxidation, and the activation of circulating blood leukocytes. Some studies have also suggested transient endotoxemia as a major stimulus for the development of SIRS in these patients [11-13]. However, the pathogenesis involved in this phenomenon is not entirely clear. The association between perioperative renal impairment and mortality has been shown in several retrospective studies [14-17].

A recent randomised study demonstrated that both intraoperative haemofiltration and steroids attenuate the inflammatory response but only haemofiltration reduced time to tracheal extubation for adults after cardiopulmonary bypass [17]. In addition, another non-randomised study [18] demonstrated that haemofiltration during CPB attenuates postoperative anaemia, thrombocytopenia and hypoalbuminemia, may reduce post-operative bleeding and appears to decrease post-operative pulmonary complications. Also others [19] showed that the combined use of balanced ultrafiltration and modified ultrafiltration can effectively concentrate the blood, modify the increase of some harmful inflammatory mediators, and attenuate lung oedema and inflammatory pulmonary injury that

mitigates the impairment of pulmonary function. In view of the evidence that has shown that the use of haemofiltration during cardiopulmonary bypass reduces time to tracheal extubation, length of mechanical ventilation and attenuates postoperative anaemia, thrombocytopenia, hypoalbuminemia, post-operative bleeding and post-operative pulmonary complications, we hypothesise that this would be the basis for a reduction in ICU stay, perioperative complications and overall length of hospital stay, hence the objective of this proposal.

5.2 SEARCH FOR EVIDENCE

A review of current trials registered in the ISRCTN Register, NHS Trusts Clinical Trials Register, MRC UK and National Institutes of Health (NIH) randomised trial records held on NIH ClinicalTrials.gov website yielded no present or past randomised trials of this nature. In addition, we conducted an extensive literature search of the MEDLINE and EMBASE electronic databases between 1990 and July 2009. Terms that were used for the search were "haemofiltration", and "intraoperative ultrafiltration". The searches were limited to "human" and "English language". Reference lists of identified articles were scanned for additional potentially relevant publications in the Web of Science version 4.1.1, Institute for Scientific Information 2000 which identified all articles that cited the index publication. We were able to identify a number of previous studies that have investigated the impact of haemofiltration and demonstrated that it removes significant amounts of inflammatory mediators [15, 20, and 21]. In addition, others have demonstrated retrospectively the benefits of haemofiltration on patient's survival [14-16, and 22]. Unfortunately these studies were all retrospective and there is no indication as to the length and why haemofiltration was given to patients. In addition, no randomised trial has yet been conducted to establish the efficacy, safety and cost-effectiveness of haemofiltration as applied intraoperatively. We therefore propose for the first time to conduct a pilot randomised clinical trial that will evaluate the efficacy in terms of the reduction in duration of ICU stay for patient with significant preoperative renal impairment (**eGFR<60 ml/min**), removal of potentially harmful organ-damaging toxins, improvement in renal outcomes, projected health economics outcomes and safety of the procedure.

5.3 WHY THE TRIAL IS NECESSARY?

This pilot study aims to assess the feasibility of randomising 60 coronary artery bypass surgery patients with impaired kidney function in 6 months within a single-centre for

intraoperative haemofiltration. This should allow us to investigate the likelihood of recruitment into the main definitive study and explore issues that may impact recruitment such as likely patient numbers, staff requirements, and barriers to recruitment, suitability and reliability of the outcome measures selected. In the financial year 2008-2009, up to 90 patients that would meet the inclusion criteria of the study were operated at our centre. We predict that it is highly probable that more than 100 patients that meet our inclusion criteria will be operated in the financial year 2010-2011 which is our target recruitment period. Specifically, the results will be useful in giving a preliminary indication of the impact the procedure has on healthcare pathways such as the intensive care and hospital stays since renal impairment is one of the major complications for patients undergoing cardiac operations.

Furthermore, the results of the pilot trial will begin to tell us whether a definitive randomised trial can address the underlying concerns about costs and benefits (i.e. value) of using intraoperative haemofiltration. Currently, the cost of an intraoperative haemofiltration is approximately £200 a patient which is only 3-4% of what it would cost to perform postoperative continuous veno-venous haemofiltration or dialysis in intensive care units (ICU)/high-dependent units (up to £5000-£6000 a patient over and above standard costs). If the pilot study can establish that the definitive trial can give clear evidence whether intraoperative haemofiltration for patients with renal impairment is effective at reducing the likelihood of postoperative haemofiltration, length of stay in ICU and hospital this will represent an important treatment strategy that could save the NHS millions of pounds every year. Thus there is potential for the main definitive study to influence clinical decision making, identify the level of care required to reduce length of stay in ICU and hospital for patients, improve overall operative outcomes and reduce treatment costs.

A definitive randomised trial will have the potential for increasing capacity by freeing more ICU beds (wherever the care is carried out) and wards consequently allowing more operations to be performed in the same amount of time. There is also a potential for a reduction in the number of cases who might otherwise go on to develop permanent renal damage/ chronic renal failure that would necessitate further long-term use of NHS resources.

6. TRIAL DESIGN

Single centre, randomised open-label clinical trial

6.1 Study Population: Patients that are undergoing coronary artery bypass graft (CABG) surgery and with known impaired kidney function indicated by an estimated glomerular filtration rate (eGFR) <60 ml/min.

6.2 Selection of Study Participants: **Renal dysfunction will be assessed preoperatively on the basis of reduced estimated glomerular filtration rate (eGFR <60 ml/min). This takes into account that patients can have significant reduction in eGFR whilst having normal plasma creatinine. Therefore the ability of the kidney to clear the plasma of creatinine will be assessed more accurately by the modification of diet in renal disease method (MDRD) [23].**

7. PLANNED TRIAL INTERVENTIONS

Patients that fulfil inclusion and exclusion criteria will be asked to give consent for the study at least a day before surgery and will be randomised into either of the two study groups on the day of surgery as follows:

1. ON-pump coronary artery bypass graft (CABG) surgery patients with GFR<60 ml/min without haemofiltration (control group)
2. ON-pump CABG surgery patients with GFR <60 ml/min undergoing haemofiltration (Experimental group)

7.1 CONTROL ARM

Patients will receive standard cardiopulmonary bypass without haemofiltration. Patients with preoperative fluid overload will be managed as per normal standard practice for kidney management of using diuretics with or without inotropes, dopexamine, and post-operative haemofiltration when needed.

7.2 EXPERIMENTAL ARM

Patients will be given a Zero-Balance Ultrafiltration Technique (Z-BUF) during cardiopulmonary bypass (CPB). The technique is used for all renal impaired patients that require active management on CPB and continues from the establishment of safe CPB to

just prior to termination of CBP. As fluid is removed from the circulation an equivalent amount of fluid, usually Accusol 35 is added to the circulation to replace it. Therefore a fluid exchange is occurring removing potentially harmful metabolites and pro-inflammatory markers. The overall fluid balance is maintained relatively constant as is the patient's haematocrit.

7.2.1 Z-BUF PROCEDURE

During CPB haemofiltration is a simple procedure where blood is drawn passively from the CPB circuit using the arterial pump pressure to drive the flow through the hemofilter. To prevent patient blood flow being compromised, the arterial pump rate will be increased to compensate for the blood flow through the haemofilter.

The hydrostatic pressure difference occurring across the haemofilter membrane termed the transmembrane pressure (TMP) provides the driving force for filtration. TMP is a function of the average pressure within the blood path minus the pressure on the effluent side. TMP can be altered by modifying these variables. In this study a high filtration rate will be achieved by using a high pressure source for the inlet to the filter and if necessary modification of the pressure at the outlet and/or on the effluent side. The haemofilter blood contact surface is 1.2 m^2 through Polysulfone (PS-Polypure) pre-set filter unit that is able to remove protein macromolecules to a molecular size of 30,000Da. A minimum exchange of approximately 6000 ml/hr which is a filtration rate of 100ml/min can be maintained. Fluid removed will be replaced with Accusol 35 a balanced salt crystalloid solution.

7.3 PILOT HEALTH CARE RESOURCE UTILISATION EVALUATION

The pilot study has two health economic objectives: a) to pilot test the data collection tools for quantifying resource use b) to determine the optimal sample size of an eventual randomised controlled trial using Value of Information analysis principles.

7.4 INCLUSION CRITERIA

Consenting men and women must be at least 18 years old, high-risk patients elective for on-pump coronary artery bypass graft surgery (CABG). They must also have

impaired renal function established preoperative by an estimated glomerular filtration rate (eGFR) <60 ml/min measured within 4 weeks before surgery.

7.5 EXCLUSION CRITERIA

Patients undergoing surgery on the great vessels (aortic surgery) or valve surgery**, have significant impaired liver function (serum bilirubin> 60 or INR>2 without anticoagulation),** patients who are further down the line of renal failure (i.e. eGFR <15 ml/min) **or on-dialysis, have malignancy and those that are pregnant.**

8. STUDY POPULATION AND RECRUITMENT STRATEGY

Patients from the routine waiting list for CABG operations will be pre-screened for inclusion/exclusion criteria and will be informed about the trial by the investigators during their initial visit to the hospital for investigations. Eligible patients will be asked to sign a written consent form by the consultant in receipt of the initial referral or research nurse at the time of their surgical outpatient visit. In-patients will be given at least 12-24 hours time to study the patient information and consent will be sought **on the day before the operation**. Patients will only enter the active phase after having provided informed written consent and are included in the trial register. Patients that drop out prior to randomisation after registration will be logged on to the CONSORT diagram but not included in the intention-to - treat analysis.

9. RANDOMISATION

Random block sizes of 2, 4, and 6 will ensure numerical balance between the two groups. Patients will be stratified at the design stage on the basis of diabetes mellitus and the level of eGFR (eGFR<40 >15ml/min *versus* eGFR>40 <60 ml/min). The randomisation service will be available 09:00 –17:00 (UK time). Once randomised, the patient will be enrolled into the study and data will contribute to the primary outcome.

10. PROTECTING AGAINST OTHER SOURCES OF BIAS

It is very difficult to disguise the evidence of intraoperative haemofiltration during cardiopulmonary bypass. Although it is relatively easy to put up a haemofilter onto the pump

and prime it to look as if it is being run in the non-haemofiltration group there is other evidence such as the 5 L bags of “Accusol 35” that need to be hanging up and vac sacs full of waste solution that cannot be disguised. The surgeon may not ‘know’ which arm a patient is randomised to, but it would be nearly impossible to blind them from noticing the presence of vac sacs full of waste solution which is indicative of the haemofiltration procedure. Hence, only the patients are likely to be blinded as to whether zero-balance filtration has been applied. Discharge from ICU is based on Nurse Discharge Guidelines which are independent of ITU physicians and follows a scoring system termed “Modified Early Warning Score - MEWS” ranging from 0-3 days. Nurses discharge patients from ICU when the MEWS is <2.0 and that only consultant cardiac surgeons/intensivists are authorised to discharge a patient out of ITU when the total MEWS is >3.0. All ICU staff will be blinded as to whether or not the patient received intraoperative haemofiltration to eliminate bias.

Incidences such as infection, antibiotic usage, re-operation or re-opening of chest in ICU, postoperative anaemia, thrombocytopenia, hypoalbuminemia, post-operative bleeding and post-operative pulmonary complications which are potential confounding factors that determine ICU stay will be documented.

11. CRITERIA FOR POSTOPERATIVE VENO-VENOUS HAEMOFILTRATION

To avoid any bias, the need for renal support postoperatively by haemofiltration will follow standard guidelines laid down by the **surgical guidelines** as follows:

Indications for postoperative haemofiltration should be for:

- Hyperkalaemia (6.0 mmol/l) not responding to insulin infusion
- Metabolic acidosis of renal origin
- Anuria or oliguria –20 ml/h for more than 6 hours (despite adequate filling and adequate cardiac output) resulting in clinically significant fluid overload

12. STUDY COMPLIANCE

We do not anticipate any problems with compliance because the treatment will be administered in theatre whilst the patient is under anaesthesia. Once consent is obtained before the operation the patients will not know what treatment allocation they have been

given when they wake up after the operation. There is also no evidence to suggest that patients will be lost during the in-hospital follow-up period or at their routine 6 weeks postoperative follow-up visit.

13. PROPOSED SAMPLE SIZE

Calculation of an accurate samples size at this stage would not be precise since this is a pilot feasibility study. However, existing data accrued from our audit department suggest that, at the Liverpool Heart & Chest Hospital, incident rates for intensive care unit (ICU) stay >3 days for patients with estimated GFR <60 ml/min after isolated coronary artery bypass graft (CABG) surgery in years between 2002 and 2008 were 18%. We estimate that even if the proportion of these patients that stay in ICU for > 3 days is reduced to at least a mean of 12% because of intraoperative haemofiltration, this will be of significant clinical and economic benefit to the NHS. We have estimated that at 80% power (2-sided α=0.05), 1112 patients with GFR <60 ml/min will need to be randomised in the main definitive study to detect a reduction in the mean incidents from 18% to 12%. Our plan in this pilot trial is to investigate whether it is feasible to randomise 60 patients in a period of 6 months in a recruitment rate of 10 patients per month from our centre. This complies with previous recommendation for good practice that pilot randomised control trials should recruit a minimum number of 60 patients [**24**]. The results from this pilot data will allow us to calculate a more accurate sample size and trial duration and/or the number of recruiting centres that would be required for the main trial.

14. STUDY OUTCOMES

Proposed Outcome Measures: These will be evaluated for suitability and reliability for the main trial - Our chosen primary outcome and secondary outcome measures will be monitored to ensure they are suitable and reliably informative of the impact of intraoperative haemofiltration. There is an element of concern that the outcomes could be confounded by crossovers between the experimental groups, in response to protocol deviation by clinicians. All protocol deviations will be documented in the database. The primary analysis will be completed on an intention to treat basis but separate information will be provided on the incidence and rate of protocol deviation and crossover. We will also report a range of other outcomes including key measures of resource utilisation and kidney function at 6 weeks follow-up to establish whether these may be suitable for the main trial. The outcome measures to be evaluated are:

PRIMARY OUTCOMES

Incidents of ICU stay >3 days for patients with renal impairment identified as an estimated glomerular filtration (eGFR) <60 ml/min.

SECONDARY OUTCOMES

CLINICAL OUTCOMES

- Composite of perioperative incidences: Bleeding, sepsis, death, arrhythmias, stroke, and myocardial infarction
- Need for postoperative continuous veno-venous haemofiltration (CVVH) in the ICU - Indications for requirement of postoperative continuous veno-venous haemofiltration must adhere to our **surgical guidelines**.
- Mechanical ventilation time
- Hospital stay
- eGFR at 6 weeks follow-up

SECONDARY ECONOMIC OUTCOMES**:** Resource utilisation and key costs indicators associated with each of the two pilot arms specifically ICU stay and hospital stay, postoperative renal replacement therapy, mechanical ventilation, medications, will be estimated up until hospital discharge. Participants will be required to complete health-related quality of life questionnaire EQ-5D at hospital admission before surgery and at the 6 weeks follow-up hospital visits.

15. FOLLOW UP DATA COLLECTION

1. Follow-up will be during the in-hospital stay phase and at 6 weeks post-discharge follow-up visit.
2. All information will be collected in structured Case Record Forms (CRFs).
3. A Manual of Operation documents containing relevant procedural instructions and definitions will be produced.
4. Data will be entered into a secure password protected database.
5. Prospective monitoring of adverse and clinical events will start at randomisation and will continue until hospital discharge
6. Costs associated with each of the two pilot arms, postoperative renal replacement therapy, ICU stay and hospital ward stay, and medications will be estimated up until hospital discharge.

7. Prospective monitoring of serious adverse and clinical events will start at randomisation and will continue until hospital discharge.

16. PLANNED ANALYSES

Intention to treat will be considered as the primary analysis. The clinical and economic impact of intraoperative haemofiltration versus no haemofiltration treatment will be examined. Analysis of the primary endpoint and other continuous data will be performed by using a 2-sided unpaired t-test or an equivalent non-parametric test. Categorical secondary outcome measures will be examined using a Chi-square test or Fisher's exact test as required. The potential cost differences per patient will be estimated with confidence intervals. Exploratory analysis will be undertaken using Bayesian Value of Information methods described by Tan and Smith [25] that balances the benefit of detecting a minimally significant difference with at least a given power against the costs of the patient sample size and/or the risk that the research poses to patients. The result of this analysis will provide guidance on the optimal sample size to use in a future RCT that would seek to evaluate the impact of haemofiltration on healthcare costs.

16.1 INTERIM ANALYSIS AND STOPPING RULES

There is no planned interim analysis for the primary endpoint until sufficient data has been accrued and by the time this is achieved the recruitment should be complete. Similarly, there is no planned stopping rules for this trial because evidence from our own internal clinical audit data suggests that study participants are in no additional risks since these procedures are the standard.

16.2 SUBGROUP ANALYSES

Subgroup analyses will be performed at the end of the study to establish the impact of potential confounding factors that may determine ICU stay such as infection, antibiotic usage, re-operation or re-opening of chest in ICU, postoperative anaemia, thrombocytopenia, hypoalbuminemia, post-operative bleeding and post-operative pulmonary complications.

17. SAFETY REPORTING

The study procedures adapted here are part of normal clinical practice. Safety will be assessed by tracking the number and percentage of adverse events (AEs) up to discharge from hospital. Serious and other adverse events will be recorded and reported in accordance with the International Conference for Harmonisation of Good Clinical Practice (ICH GCP) guidelines/the European Clinical Trials Directive 2001/20/EC and the Sponsor's Research Related Adverse Event Reporting Policy. ICH GCP requires that both investigators and sponsors follow specific procedures when reporting adverse/reactions in clinical trials. All serious adverse events **must** be reported to the steering committee and documented in CRFs. Such events result in death or are life-threatening, require hospitalisation or prolongation of existing hospitalisation, result in persistent or significant disability or incapacity or may have created a congenital anomaly or birth defect

Examples would include, but are not limited to:

- **Deaths related or unrelated to healthcare-acquired infection**
- **Life-threatening bleeding**
- **Intracranial haemorrhage**
- **Cerebrovascular accident**
- **Profound thrombocytopenia (platelet counts ≤ 50,000/mm^3)**
- Allergic reactions

17.1 ADVERSE EVENT

Any untoward medical occurrence in a patient or clinical trial subject to whom a medicinal product has been administered including occurrences which are not necessarily caused by or related to the product.

17.2 ADVERSE REACTION

Any untoward and unintended response to an investigational product related to any dose administered.

17.3 UNEXPECTED ADVERSE REACTION

An adverse reaction, the nature or severity of which is not consistent with the information about the device or medicinal product in question set out in the summary of product characteristics (or investigator brochure) for that product).

18. MAJOR PROTOCOL VIOLATION

Major protocol violations will be documented including: failure to ensure adequate informed consent, recruitment of ineligible patient into the study on the basis of the inclusion and exclusion criteria and incorrect randomisation of a patient such that the patients are entered into the wrong treatment arm for clinical reasons. During the course of the trial, protocol deviations will be tracked.

19. INDEMNITY AND INSURANCE

The Liverpool Heart & Chest Hospital NHS Trust is covered under the standard NHS indemnity sponsorship for the study.

20. RESEARCH GOVERNANCE

The Liverpool Heart & Chest Hospital NHS Trust as the sponsor for this trial will ensure that the rights, safety, and wellbeing of participants will be safe guarded. Issues of consent and confidentiality are paramount in line with the *MRC Guidelines for Good Clinical Practice in Clinical Trials*. Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Patient confidentiality will be further ensured by utilising patient-identification code numbers to correspond to treatment data in the computer files. With appropriate patient authorisation, medical information may be given to the patient's personal physician or to other appropriate medical personnel responsible for his/her treatment. Data generated as a result of this trial are to be made available for inspection on request by the participating physicians, by the Ethics Committee and the regulatory authorities.

21. ETHICAL ARRANGEMENTS

The protocol will be conducted according to the principles of the Declaration of Helsinki (www.wma.net) and Good Clinical Practice, NHS Research Governance (www.doh.gov.uk), the EU and the NHS Governance Framework. The study will be sponsored by the Liverpool Heart & Chest Hospital NHS Trust. The trial protocol will be approved by an internal review board and via the Integrated Research Application System. Approval from the ethics committee will be obtained if the consent form is updated or amended whenever new information becomes available that may be relevant to the patient. Patient’s right to privacy will be respected at all times to comply with the Data Protection Act 1998 and Caldicott

Principle. Medical records may be inspected for monitoring auditing purposes by individuals from the Clinical Trials Unit, Liverpool Heart & Chest Hospital NHS Trust. Patients consent to this as part of the written informed consent process. All electronic information will be stored in a password protected NHS computer.

21.1 RISKS AND ANTICIPATED BENEFITS FOR TRIAL PARTICIPANTS AND SOCIETY, INCLUDING HOW BENEFITS JUSTIFY RISKS

There evidence to suggest that over 20% of patients elective for cardiac surgery has preoperative renal impairment that increases operative risk of death. One of the modalities currently in practice aiming to alleviate this problem is intraoperative haemofiltration support. However, there is a widespread variability in clinical practice within cardiac surgery units worldwide on the use of haemofiltration on a case-by-case basis. Although haemofiltration is widely used, its effectiveness as a prophylactic therapeutic tool for renal impairment during the intraoperative phase whilst the patient is on cardiopulmonary bypass remains un-tested in randomised trials and no evidence from prospective randomised studies is available to demonstrate risks associated with its application. The possible risks of taking part are likely to be common to all patients with impaired kidney function scheduled to undergo cardiac surgery. We anticipate that the risks associated with the trial are outweighed by potential benefits to the patients and society as whole as follows:

1. Reduction in NHS costs by cutting overall ICU treatment costs- Currently, the cost of an intraoperative haemofiltration is approximately £200 a patient which is only 3-4% of what it would cost to perform postoperative continuous veno-venous haemofiltration or dialysis in intensive care units (ICU)/high-dependent units (up to £5000-£6000 a patient over and above standard costs). If the study can establish that intraoperative haemofiltration for patients with renal impairment is effective at reducing the likelihood of postoperative haemofiltration, length of stay in ICU and hospital this will represent an important treatment strategy that could save the NHS millions of pounds every year. Thus there is potential for this study to influence clinical decision making, identify the level of care required to reduce length of stay in ICU and hospital for patients, improve overall operative outcomes and reduce treatment costs.
2. There is also potential for increasing capacity by freeing more ICU beds (wherever the care is carried out) and wards consequently allowing more operations to be performed in the same amount of time.

3. There is also a potential for a reduction in the number of cases that might otherwise go on to develop acute kidney injury, permanent renal damage/ chronic renal failure that would necessitate further long-term use of NHS resources.

21.2 INFORMING POTENTIAL TRIAL PARTICIPANTS OF POSSIBLE BENEFITS AND KNOWN RISKS

The patient will be given **patient information sheets** and allowed time to study them (at least a day). Potential trial participant will be informed of the potential benefits and known risks at the time when consent is being sought.

21.3 OBTAINING INFORMED CONSENT FROM PARTICIPANTS WHENEVER POSSIBLE OR PROPOSED ACTION WHERE FULLY INFORMED CONSENT IS NOT POSSIBLE

In line with DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT of 2001 all research patients are required to provide written informed consent before enrolment in a trial. Potential participants in this study will be no exceptional.

In summary, the research protocol will be approved in advance by our institutional research & development Committee. Before obtaining informed consent, information will be given in a language and at a level of complexity understandable to the patient in both oral and written form by the investigator or designee. Patients will not be coerced or unduly influenced in order for the patient to participate or remain in the trial and will be given ample time and opportunity to inquire about details of the trial and all questions about the trial should be answered to their satisfaction. If the patient is unable to read the consent form, a witness should be present during the entire informed consent discussion process. After the informed consent form is read to and signed by the patient, they must then be given a copy of the signed and dated informed consent form. Patients that decline consent at this stage will not be included in the study and their results will not be used. However, data on the total number deemed eligible for the study and the proportion of these subjects proceeding to randomisation will be documented. Patient will be informed that they may withdraw or discontinue from the study anytime without giving an explanation and that their action will not affect their standard of care. Patient's that die after randomisation will have their data included in the final analysis, unless legal representatives raise objections.

21.4 PROPOSED TIME PERIOD FOR RETENTION OF RELEVANT TRIAL DOCUMENTATION

The trial documentation and data will be stored in anonymised form (study number only) in secure storage facility within the Clinical Trials Unit for a period of at least 7 years after study completion.

21.5 PROPOSED ACTION TO COMPLY WITH 'THE MEDICINES FOR HUMAN USE (CLINICAL TRIALS) REGULATIONS 2004

This is a medical device trial and is not testing any medicinal products. Therefore, "the medicines for human use Regulations 2004" do not apply. However, permission to conduct the trial will be sought from the MHRA.

22 TRIAL ORGANISATION

22.1 TRIAL MANAGEMENT COMMITTEE

Mr Neeraj Mediratta (Chair), Dr Rod Stables, Dr Nigel Scawn, Ms Sarah Shirley, Dr Bashir Matata, Professor Cheng-Hock Toh, Dr Asheesh Sharma, Dr Alan Haycox, Dr Steven Lane, Dr Mark Jackson, Mr Keith Wilson.

The Trial Steering Committee (TSC) will be responsible for finalising the protocol, discussing any required amendments, monitoring recruitment rates, ensuring the study runs to time and generally overseeing the running of the study. The TSC will include the principal investigators, lay patient representative in the TSC, expert TSC members, two independent members and one independent chair.

THE INDEPENDENT TRIAL STEERING COMMITTEE

- Chair: Dr Marcus Flather, Royal Brompton Hospital NHS Trust, London,
- Mr Sunil Ohri, Southampton General Hospital, Southampton,
- Dr Sue Hinder, RaFT Research and Consulting, Downham Clitheroe, Lancashire

The TSC have responsibility for the day-to-day conduct of the trial.

22.2 DATA MONITORING AND RESEARCH ETHICS COMMITTEE

It is the only body involved in a trial that has access to the unblinded comparative data. The role of its members is to monitor these data and make recommendations to the TSC on whether there are any ethical or safety reasons why the trial should not continue. The safety, rights and well-being of the trial participants are paramount. The DMC considers the need for any interim analysis advising the TSC regarding the release of data and/or information. The DMC may be asked by the TSC, Trial Sponsor or Trial Funder to consider data emerging from other related studies. If funding is required above the level originally requested, the DMC may be asked by the Chief Investigator, TSC, Trial Sponsor or Trial Funder to provide advice and, where appropriate, information on the data gathered to date in a way that will not compromise the trial. Membership of the DMC should be completely independent[1], small (4 members) and comprise experts in the field, e.g. a clinician with experience in the relevant area and expert trial statistician. Members are:

- Chair: Professor Paulo Lisboa: Liverpool John Moores University, Liverpool.
- Dr Mark Goodall: The University of Liverpool, Liverpool.
- Dr Chris Rogers**:** Bristol Heart Institute, University of Bristol, Bristol.
- Mr Shyam Kolvekar**:** University College London Hospitals NHS Foundation Trust, London.

The DMC should meet at least annually, or more often as appropriate, and meetings should be timed so that reports can be feed into the TSC. Responsibility for calling and organising DMC meetings lies with the Chief Investigator, in association with the Chair of the DMC. The project team should provide the DMC with a comprehensive report, the content of which should be agreed in advance by the Chair of the DMC.

22.3 LOCAL INSTITUTION GOVERNANCE AND INDEPENDENT MONITORING

This will be undertaken by the Research Governance Department, Liverpool Heart & Chest Hospital NHS Trust. The Clinical Trials Unit at the Liverpool Heart & Chest Hospital NHS Trust will undertake day-to-day management and co-ordination of the trial and are

[1] Independence, in respect of the DMC, is defined as independent from the Chief Investigator, TSC and Host Institution.

responsible for the collection, management, storage and analysis of all patient information.

22.4 PUBLICATION POLICY

The investigators are committed to the publication and widespread dissemination of the results of the study. There is an agreed policy that the recommendation of any party concerning manuscripts or text shall be taken into consideration in the final preparation of scientific documents for publication and presentation. The Steering Committee will be responsible for finalising the protocol, discussing any required amendments, monitoring recruitment rates, ensuring the study runs to time and generally overseeing the running of the study. The trial protocol has been issued an ISRCTN registration number before the start of recruitment.

23 SERVICE USERS INVOLVEMENT

Our institution has established a Service Users Research Endeavour (SURE) group that has been active for more than 10 years. The SURE group is actively involved in our research as follows;

- Helps researchers to identify and ask the right questions in their project proposals
- Makes sure that the research questions are relevant to patients, people using the service and the public in general
- Gets involved in the research process itself, in terms of designing and managing service user-led projects
- Helps in analysis and dissemination of study results
- Assists final internal R&D study approval

This proposal has been reviewed by our patient service user group (SURE) and any opinions and comments incorporated. A patient representative will attend TSC meetings and be directly involved in decision making of trial process and then relay back information to the SURE groups on a regular basis.

24 TRIAL FUNDING

The pilot trial costs will be funded by a grant from the National Institute for Health Research (NIHR), Health Technology Assessment Programme for Clinical Evaluations and Trials.

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