HFNO TAVI Clinical Study Protocol

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| **Study Title** | **A randomised controlled trial of high-flow nasal oxygen (HFNO) vs. standard oxygen therapy in patients undergoing transfemoral transcatheter aortic valve implantation (TAVI) under conscious sedation** | |
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| **Study location** | United Kingdom | Royal Papworth Hospital NHS Foundation Trust |

# Study Synopsis

|  |  |
| --- | --- |
| **Title** | **A randomised controlled trial of high-flow nasal oxygen (HFNO) vs. standard oxygen therapy in patients undergoing transfemoral transcatheter aortic valve implantation (TAVI) under conscious sedation.** |
| **Sponsor** | Royal Papworth Hospital NHS Foundation Trust |
| **Medical condition** | The underlying medical condition in our patient group includes patients that need a replacement of their aortic valve because they suffer from a symptomatic aortic stenosis and have therefore been scheduled for a TAVI procedure. The access to the aortic valve would traditionally require open heart surgery with sternotomy and cardiopulmonary bypass. A TAVI is considered to be less invasive and is increasingly performed in patients who are perceived to be at increased risk for surgery. |
| **Purpose** | We aim to determine the best and most comfortable method of providing oxygen to patients during sedation for this cardiac procedure which is increasingly commonly carried out. The literature is not yet clear what the best way of managing patients is during this procedure to maximise safety and improve recovery. |
| **Primary objective** | The primary objective is to determine whether HFNO is superior regarding gas exchange compared to our standard practice which is 2l/min oxygen by dry nasal specs in patients undergoing a TAVI procedure under conscious sedation. |
| **Secondary objectives** | Secondary objectives are to determine whether HFNO is beneficial in reducing the number of desaturations during the procedure and whether it is associated with a reduced requirement for conversion to general anaesthesia (GA). Furthermore we are investigating whether it reduces the length of stay in the recovery area after the procedure and the length of stay in hospital overall, which could therefore be beneficial from a health economics perspective. |
| **Trial design** | A single centre randomised controlled trial based at Royal Papworth Hospital. 70 patients will be randomised in a 1:1 ratio to receive either HFNO or standard oxygen therapy. |
| **Study Endpoints** | * PaO2 measured by arterial blood gas sampling during the TAVI  The number of desaturations (defined as SpO2 <93% for >10 seconds or SpO2 drop more than 5% from the baseline for >10 seconds at any time during the procedure.)  * Number of hours in recovery * Number of admissions to ICU * Number of patients requiring GA * Duration of oxygen provision * Patient comfort questionnaire scores * Days in hospital including the discharge date |
| **Sample size** | 70 patients |
| **Eligibility criteria** | ***Inclusion Criteria:***  Able to provide informed consent  Adult patients (≥ 18 years)  Patients undergoing an elective transfemoral TAVI procedure  ***Exclusion Criteria:***  Contraindication to HFNO such as a nasal septum defect  Participation in another Randomised Controlled Trial |
| **Screening and Enrolment** | Patients scheduled to undergo a TAVI procedure will be identified by a trained staff member under the supervision of the Principal Investigator from the hospital database and their computerised medical records. Patients meeting the entry criteria will be provided with a patient information sheet and given at least 24 hours to consent. Prior to their TAVI procedure a member of the research team will meet them to answer any questions and ask for consent to take part in the study. |
| **Baseline & Randomisation** | We are planning to test two different oxygen devices (HFNO vs 2l/min standard oxygen). Following consent patients will be randomly allocated to one or the other. We plan to provide standard care (2 l/min oxygen) to 35 patients and HFNO to the other 35 patients, while they are sedated during the TAVI procedure, and while they are waking up in the recovery ward afterwards. |
| **Interventions** | High-flow nasal oxygen (HFNO) versus standard oxygen therapy (2 litres oxygen increasing up to 8 litres as required.). |
| **Follow up** | The comparison of the two oxygen devices is limited to the time of the TAVI intervention and the immediate post-operative recovery. Following discharge from the recovery ward, standard hospital protocol will be followed which includes HFNO for hypoxia. Further recovery is not affected by the participation in the study. Patients will be followed up daily by a member of the study team until discharge. |
| **End of Study** | The study will end when the last enrolled patient has completed follow-up. |
| **Procedures for safe monitoring** | All procedures will be carried out with a fine-toothed comb according to our standard protocols to ensure the patients safety and comfort peri-procedural. All generated patient data will be de-identified and stored in a secure, bespoke database in accordance with Papworth Trials Unit Collaboration’s (PTUC) Standard Operating Procedures. The trial will be conducted according to Good Clinical Practice (GCP) and PTUC SOPs to ensure the monitoring and safety of trial participants and data validity. |
| **Criteria for modifying or discontinuing allocated intervention** | High-flow nasal oxygen may feel uncomfortable at first, so we will start it slowly. The patient may feel hot so we can use an air fan device to cool them down. If they continue to feel uncomfortable we can reduce flows or gas heating on the device, and if they do not tolerate the HFNO we will switch to an alternative oxygen device. If the anaesthetist in charge deems it necessary an alternative device can be used. |

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# Introduction

## Background

**2.2 Transfemoral transcatheter aortic valve implantation**

The treatment for aortic stenosis is aortic valve replacement, which has traditionally required sternotomy and cardiopulmonary bypass. Transcatheter aortic valve implantation (TAVI) is considered to be a less invasive option compared with surgery and is increasingly performed, especially in patients who have undergone previous sternotomy or who are perceived to be at increased risk for surgery. Virtually all transfemoral TAVIs are undertaken in patients who are sedated and cared for by the anaesthetic team. However, some patients develop hypoxia during conscious sedation, especially as they have to lie flat for the procedure (60-120 minutes). This is a particular problem in patients with pre-existing lung disease or cardiac failure (pulmonary oedema), obese patients, and patients who are anxious and require deeper levels of sedation.

**2.3 High-flow nasal oxygen**

High-flow nasal oxygen (HFNO) oxygen is an innovative means of delivering oxygen to patients that uses an air/oxygen blender, an active humidifier, a single heated tube, and specially-designed nasal cannulae (Fisher and Paykel, Auckland, New Zealand). The system delivers heated and humidified oxygen at flows of up to 70 L/min, and the inspired oxygen content can be accurately set and measured. Furthermore, it has a number of physiological advantages compared with other standard oxygen therapies. This includes reduced anatomical dead space, and the ability to provide positive end-expiratory pressure (PEEP) if the patient has their mouth closed [2]. It also provides oxygenation and partial carbon dioxide clearance during apnoeic periods.

High flow nasal oxygen is commonly used in patients post cardiac surgery on the Intensive care Unit (ICU) and we have previously shown that conscious sedation is associated with reduced procedural time, stay in recovery and hospital stay[1].

**2.4 Conscious sedation**

Conscious sedation/analgesia is defined as "a drug-induced depression of consciousness during which patients respond purposefully to verbal commands, either alone or accompanied by light tactile stimulation" [3]. In the patient group undergoing transfemoral TAVI at Papworth hospital, we administer remifentanil infusion for sedation, and also administer regional anaesthesia ilio-inguinal/fascia iliaca block).

**2.5 Published studies from the literature**

The following table (Table 1) illustrates certain studies where authors have specifically looked at the advantages of the use of HFNO in patients under intravenous sedation (IVS) or procedures where HFNO was used instead of general anaesthetics (GA). The main benefit seems to be that HFNO consistently supports good oxygenation in a spontaneously breathing patient who receives a sedative agent / analgesia for a certain procedure. Furthermore HFNO combined with conscious sedation decreases the use of GA and reduces the procedure duration. Further studies will be needed to prove whether these advantages will also lead to decreased length of stay in hospital and therefore be beneficial from a financial perspective.

**Table 1 Published Studies from the Literature [4-13]**

|  |  |
| --- | --- |
| Author,  Year | Results |
| Douglas et al.2018 | -Single centre, prospective RCT, 60 patients randomised to either HFNO or standard oxygen therapy 10 l/min during endobronchial ultrasound with conscious sedation  -Primary outcome: desaturation >90%, no significant difference, limitation was the small study size as non-significance was caused by movement of a single patient between groups  -Desaturation was most likely due to hypoventilation |
| Puente et al.2017 | -Single centre, prospective observational trial in 108 patients between December 2015 and June 2016  - The aim was to demonstrate the usefulness of HFNO (n=41) in patients undergoing gastro-intestinal endoscopy under sedation compared with conventional nasal cannulae (n=67)  -In their study, there was a significant correlation (p=0.009) between oxygen delivery technique with desaturation index  -HFNO superior for prevention of desaturation episodes and patient comfort |
| Schumannet al.2016 | Single centre, retrospective trial, n= 238. Divided into 3 groups of 3 month-periods: HFNO vs non-HFNO vs GA.  HFNO was associated with significant decrease in use of GA and significantly higher oxygen saturations |
| Sago et al.  2015 | Single centre, RCT, n=30; O2 5 L/min, 30L/min HFNO and 50 L/min HFNO  SpO2 lowest and surgeons least satisfied with no HFNO group |
| Simon et al  2014 | -Single centre, prospective randomised trial, n=40, critically ill with hypoxaemic respiratory failure received either NIV or HFNO during bronchoscopy.  HFNO/bronch. was well tolerated  One patient in HFNO group needed immediate intubation following the bronchoscopy  NIV was superior to HFNO for maintaining oxygenation throughout procedure in all pat. with moderate to severe hypoxaemia |
| Lucangeet al.2012 | Single centre, RCT, n=45 divided into 3 groups  Venturi mask 40l/min flow vs HFNO 40 l/min oxygen FiO2 0.5 vs HFNO 60l/min associated with better oxygenation with higher pO2 and SpO2 |

|  |  |
| --- | --- |
| Author, Year | Cases |
| Wong et al.  2017 | Patient with moderate obstructive sleep apnoea who underwent an awake craniotomy under deep sedation with HFNO. |
| Miyagi et al.  2014 | Case series of 5 patients with acute respiratory failure who underwent bronchoalveolar lavage under sedation using HFNO. |
| Diab S and Fraser JF  2014 | Single patient post lung transplant used HFNO during bronchoscopy and respiratory failure. |
| Lomas C et al.  2009 | Single patient with myasthenia gravis and respiratory failure after thymectomy, HFNO with conscious sedation for diagnostic bronchoscopy with bronchoalveolar lavage. |

## Rationale

TAVI is increasingly used nowadays as surgery is not required and the patient may be able to go home and recover much quicker. Previous studies have shown that conscious sedation is associated with reduced procedural time, reduced number of complications, and further reduced hospital stay.[1] However, some patients develop hypoxia during conscious sedation, especially as they have to lie flat for the procedure (60-120 minutes). The rationale for undertaking this study is to provide evidence that HFNO is superior to standard oxygen therapy in terms of improving gas exchange, reducing recovery times and complication rates, and improving patient comfort in patients undergoing a TAVI procedure. These improvement would be beneficial not only to patients but in terms of health care costs too.

## Expected Output of Research/Impact

Overall we aim to determine the best and most comfortable method of providing oxygen to patients undergoing a TAVI under conscious sedation. The literature is not yet clear what the best way of managing patients is during this procedure to maximise safety and improve recovery. We would expect the results of this trial to impact upon our local policies and procedures.

Patients in the HFNO group may benefit from improved comfort and breathing during the procedure. Patients who take part in the trial will be helping to determine the best method of caring for future patients undergoing this TAVI procedure.

# Trial Objectives

## Primary Objective

The primary aim is to determine if high flow nasal oxygen (HFNO) in patients undergoing transcatheter aortic valve implantation (TAVI) under conscious sedation compared with standard oxygen (2 l/min via nasal specs) improves gas exchange as measured by PaO2.

## Secondary Objectives

Secondary aims are to determine whether the use of HFNO:

* Reduces the number of times either the patient or the anaesthetist has to interfere with the sedation level, airway or oxygen delivery device (e.g. verbal commands /chin lift by the anaesthetist or hand movement towards the oxygen delivery device by the patient)
* Improves cerebral oxygenation by reducing the number of and severity of cerebral desaturation episodes
* is associated with reduced stay in recovery (hours)
* is associated with reduced admissions to ICU
* is associated with a reduced requirement for conversion to general anaesthesia (GA), escalation of respiratory support, tracheal intubation or pulmonary complication.
* has an impact on the number of desaturations

## Study End Points

### Primary Endpoint

We hypothesise that patients supported by HFNO will have an increased PaO2 up to 30% in arterial blood gas (ABG) samples compared to those with standard oxygen delivery.

### Secondary Endpoints

### The number of desaturations (defined as SpO2 <93% for >10 seconds or SpO2 drop more than 5% from the baseline for >10 seconds at any time during the procedure.)

* Number of hours in recovery
* Number of admissions to ICU
* Number of patients requiring GA
* Duration of oxygen provision
* Patient comfort questionnaire scores
* Days in hospital including the discharge date

# Trial Design

## Statement of design

Single centre randomised controlled trial of high-flow nasal oxygen (HFNO) vs. standard oxygen therapy in patients undergoing transfemoral transcatheter aortic valve implantation (TAVI) under conscious sedation at Royal Papworth Hospital. 70 patients will be randomised in a 1:1 ratio to either HFNO or standard oxygen therapy.

## Study Setting

This is the cardiac catheterisation laboratory of a specialist cardiothoracic hospital. We plan to enrol patients undergoing transfemoral transcatheter aortic valve implantation under conscious sedation, who by necessity have to lie flat on their back and very still for around 90 minutes. They all receive remifentanil by infusion for sedation.

# Participant Recruitment, Randomisation and Follow up

## Study Population and eligibility

***Inclusion Criteria:***

Patient able to provide informed consent

Adult patients (≥ 18 years)

Patients undergoing an elective transfemoral TAVI procedure

***Exclusion Criteria:***

Contraindication to HFNO such as a nasal septum defect

Participation in another Randomised Controlled Trial

## Participant identification and informed consent procedure

Patients scheduled to undergo a TAVI procedure will be identified by a trained staff member under the supervision of the Principal Investigator from the hospital database and their computerised medical records. Patients meeting the entry criteria will be approached by a member of the research team and provided with a patient information sheet. Patients will be given at least 24 hours to consider participation. Prior to their TAVI procedure a member of the research team will meet them to answer any questions and ask for consent to take part in the study.

We will not include patients who cannot speak English or have special communication needs as we will not be able to communicate with them during the procedure and during recovery.

**Randomisation**

Patients will be asked to give informed consent prior to their transfer to the cardiac catheterisation laboratory. Once in the cardiac catheterisation laboratory, baseline measurements will be taken and a member of the research team will perform the randomisation.

**Randomisation process / Randomisation issues**

Randomisation will take place via an online system adhering to PTUC standard operating procedures. A paper list will be provided for emergencies, in the event of the online system being unavailable.

Neither the patient nor the study team member will be able to be blinded to the oxygen device used in each individual case. This is in the nature of things as the patient is conscious and the anaesthetic study team member has to adjust the oxygen device once the patient has been randomised to one or the other.

Patient will be randomised and allocated in a 1:1 ratio to one of the following groups:

## interventions

**Standard oxygen therapy group**

In our standard practice, we administer 2 l/min oxygen by dry nasal specs (FiO2 approximately 0.3). It can be increased up to 8 l/min if necessary.

**HFNO Group**

The intervention we are testing will be 50 l/min HFNO, also at an FiO2 of 0.3. The HFNO will be warmed and humidified using the Optiflow delivery system.

High-flow nasal oxygen may feel uncomfortable at first, so we will start it slowly. The patient may feel hot so we can use an air fan device to cool them down. If they continue to feel uncomfortable we can reduce flows or gas heating on the device, and if they do not tolerate the HFNO we will switch to an alternative oxygen device.

We believe that our patients, many of whom have significant cardiorespiratory compromise and comorbidities, will potentially benefit from HFNO because of the following physiological advantages:

-Carbon dioxide washout of anatomical dead space and reduced work of breathing

-Generation of a positive end-expiratory pressure (PEEP)

-benefits of heat and humidification and therefore better patient comfort

Intravenous sedation will be achieved by an intravenous remifentanil infusion titrated according to patient comfort. Previous trials have shown that a combination of sedative agents and opioids can lead to oxygen desaturation in up to 45% of patients, either due airway obstruction or hypoventilation by direct central suppression of ventilation. [14]. For this reason, we routinely administer remifentanil as the sole sedative agent.

At any stage during the study the anaesthetist in charge can manage the airway in any way he or she deems appropriate in the best interest of the patient. This includes changing to an alternative oxygen delivery strategy.

**For both groups:**

Patients are transferred to the cardiac catheterisation lab. As per standard practice:

-Peripheral IV line sited

-Patient randomly allocated by a study team member to HFNO or standard oxygen (2l nasal oxygen, including end tidal CO2 monitoring as per local and national guidelines). Oxygen started depending on randomisation allocation.

-Remifentanil intravenous infusion started at 0.05 mcg/kg/min and titrated according to sedation score (Ramsey SS 2 to 3 ideal)

-Regional block (ilio-inguinal/fascia iliaca) sited on side of TAVI procedure.

-Transthoracic echocardiogram performed.

-Radial catheter inserted into right radial artery by cardiologist and ABG taken for analysis, catheter placed into ascending aorta via radial artery. AGBs repeated every 20 min or as determined according to clinical need.

-Femoral access obtained (venous and arterial) by cardiologist.

-TAVI valve implantation takes place.

We are aiming to measure depth of sedation with the Richmond Agitation Sedation Scale (RASS) from -2 to 0 and processed EEG (Masimo Sedline).

According to the British Thoracic Society (BTS) guidelines for oxygen use in adults in healthcare and emergency settings we are aiming to achieve a target saturation of 94–98% for patients without respiratory comorbidities or 88–92% or patient-specific target range for those at risk of hypercapnic respiratory failure (e.g. COPD or other conditions) [13]

-Femoral venous and arterial access removed. Sedation stopped once confirmed that no bleeding from femoral artery. If surgical intervention required 9e.g. damage to femoral artery), this can normally take place under sedation and regional block, but occasionally GA may be required.

-Patient transferred to recovery area, and once meets standard recovery criteria is transferred to ward.

-Patient stays in hospital until he/she meets discharge criteria according to standard TAVI protocol.

**Criteria for modifying or discontinuing allocated intervention**

Patients’ breathing will be closely monitored while they are sedated and any necessary measures to improve gas exchange necessary will be taken by the trained experienced anaesthetist. The patient will be regularly and closely monitored, and their comfort and safety ensured throughout the procedure and during recovery. If the patient finds either oxygen delivery device uncomfortable it will be adjusted or substituted. If required, any other airway management devices that are deemed necessary will be available and can be used. If the patient continues to be uncomfortable during the procedure the anaesthetist may deepen sedation further or convert to general anaesthesia without hesitation.

## Participant follow up

A questionnaire regarding the comfort of the oxygen device during the procedure will be read out to the patient either straight after the procedure or while the patient is monitored in recovery. The questionnaire can be asked up to 24 hours post procedure.

The trial is limited to the intervention in the catheterisation laboratory, the recovery area and the ward. The treatment afterwards will be according to our guidelines post procedure. The post procedural treatment will not be affected by the participation in this trial. Patients will be followed up daily until hospital discharge to collect data on any interventions and progress, and length of stay in hospital (Table 2).

**Table 2 Schedule of Events:**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Specific Activity** | **Undertaken by** | **Screening** | **Baseline Rando-misation** | **Intervention**  **(immediately after randomi**  **sation)** | **Recovery area**  **(post procedure)** | **Ward after procedure** |
| Identify potential participant | Study team  member | **X** |  |  |  |  |
| Eligibility check | Study team  member | **X** |  |  |  |  |
| Approach potential participant to discuss study | Local PI / study team member | **X** |  |  |  |  |
| Take informed consent | Local PI / study team member |  | **X** |  |  |  |
| Baseline clinical data collection, including inclusion and exclusion criteria | Local Research Nurse / Study team member |  | **X** |  |  |  |
| Randomisation (web or paper version ) | Local Research Nurse |  | **X** |  |  |  |
| Anaesthetic Intervention  (including providing HFNO or nasal specs) | Undertaken by consultant anaesthetist  identified by local PI |  |  | **X** |  |  |
| Clinical Data Collection including arterial blood gas sampling data collection | Research nurse /study team member |  | **X** | **X** | **X** | **X** |
| TAVI procedure | Undertaken by consultant cardiologist identifies by local PI |  |  | **X** |  |  |
| Review/reporting of patient AEs/SAEs | Local Research Nurse |  | **X** | **X** | **X** | **X** |
| Questionnaire  Patient´s comfort | Study team member |  |  |  | **X** |  |
| Health Service and Resource use data | PI  Study team member | **X** | **X** | **X** | **X** | **X** |

# Data Handling and Record keeping

The trial will be conducted according to the Good Clinical Practice and Standard Operating Procedures of Papworth Trials Unit Collaboration (PTUC) to ensure the monitoring and safety of trial participants and data validity.

## Data collection, management and analysis

A secure, restricted-user, trial -specific database will be developed at PTUC. A member of the research team will enter the data into the database and only trial personnel will have access to the files. Data will be stored and managed in accordance with PTUC Standard Operating Procedures (SOPs). Once randomisation has been done, all gathered data will remain in the study. Data will continue to be collected until study completion or the patient withdraws consent to continue with the trial.

Statistical analysis will be carried out under the supervision of Dr Sofia Villar.

## Screening and recruitment

Patients will be screened according to the inclusion and exclusion criteria by a trained member of the study team under the supervision of the Principal Investigator. An anonymised screening log will be kept by the study team. All data is kept confidential as the staff member who will be in charge of identifying the patient is either an anaesthetist, cardiologist, a research nurse or research coordinator and will be a member of the patient's existing clinical care team. Data will be stored in a hospital server secured with a password.

## Baseline and clinical follow up data

**Baseline data**:

* Baseline data (age, sex, BMI, EuroSCORE),
* SpO2 (before starting sedation on room air)
* **Procedural Data:**
* Arterial blood gases to measure PaO2. In our practice, the arterial line is inserted by the cardiologist after sedation and the intervention (HFNO or control) has been applied, so we will not be able to measure a baseline PaO2 on room air before starting sedation and before applying the intervention.
* Cerebral oximetry
* Duration of sedation, duration of procedure, time in recovery ward after the procedure before discharge to the regular ward and any admission to ICU.
* Number of times the anaesthetist needs to intervene during the procedure because of patient movement e.g. speak to patient, increase sedation.
* Number of times the anaesthetist has to intervene to deal with the patient’s airway or breathing, e.g. increase FiO2, manipulate airway with chin lift etc.
* Sedation score using Ramsay Sedation Scale (Appendix 2)
* SpO2

**Follow up Data**:

* Patient comfort questionnaire
* Length of hospital stay
* SpO2

## Recording and management of Adverse Events

Non-serious Adverse Events will not be recorded or reported for the HFNO trial, unless they form part of the clinical event dataset.

All Serious Adverse Events (SAEs) occurring between randomisation and the end of follow-up (which is discharge from hospital) will be recorded in the patient’s hospital notes and submitted, within 24 hours of the site becoming aware, to Papworth Trials Unit Collaboration using an SAE form.

It has to be highlighted in particular that the risks/ morbidity /SAEs related to the TAVI procedure itself (Appendix 1) are not related to the HFNO trial.

All recorded SAEs will be reported to the Sponsor and the Data Monitoring Committee (DMC). If an SAE occurs that is considered to be both unexpected and related to the study protocol (SUSAR), it will be reported within 24 hours of recognition.

The Sponsor will report any SUSARs to the Research Ethics Committee within 15 days of their knowledge of the event and local investigators will be notified.

Details of Expected Adverse Events are listed in Appendix 1.

## 6.5 Data Monitoring plans

The study will be monitored according to PTUC SOPs.. The first five randomised patients will be fully monitored by an independent monitor and reviewed by the PTUC Quality Assurance Committee. A further monitoring plan will be developed dependent upon the outcome of this review.

# Statistics

Statistical analysis will be carried out by:

Sofia S Villar

Senior Statistician

MRC Biostatistics Unit

University of Cambridge School of Clinical Medicine

Cambridge Institute of Public Health Cambridge CB2 0SR

Following the data collection primary analysis and secondary analyses will be carried out by the statistician in association with the PI, a study team member and a clinical research fellow.

# Project Management

## Research Management and governance

The Senior R&D Manager based at Papworth Trials Unit Collaboration (PTUC) will oversee the study.

The Trial Manager(s) will co-ordinate all trial-related activities, monitor progress against the project milestones and manage the finances.

Statistics and data management activities will be carried out by the study team and the statistician in collaboration with PTUC.

## Study Registration

The study will be registered with an International Standard Randomised Controlled Trial Number (ISRCTN) and/or with ClinicalTrials.gov.

## Trial Management Group (TMG)

A TMG responsible for day-to-day running of the study will meet at least every 3 months by teleconference to discuss recruitment, safety, data management and local site issues.

The TMG will comprise the Chief Investigator, co-applicants, the trial manager, statistician and data manager.

## Data Monitoring Committee (DMC)

Annual DMC meetings will review progress against the agreed milestones, recruitment and safety. The committee will consist of experienced, independent personnel.

The DMC will meet after the first 15 patients are randomised to review the data for safety. Meetings will be held as necessary should urgent issues arise.

The DMC will develop a charter that describes the framework within which it will operate. The independent members will comprise a statistician, an anaesthetist, and a cardiologist.

# Ethical & Research Governance approvals UK sites

## Initial REC and HRA Approval

The protocol and all patient-facing documentation will be submitted to a Research Ethics Committee (REC) and for Health Research Authority (HRA) approval prior to study commencement. HRA Approval is the process for the NHS in England that brings together the assessment of governance and legal compliance with the independent REC opinion provided through the UK research ethics service.

## Site Capability and Capacity

HRA approval replaces the need for local checks of legal compliance and related matters by each participating organisation in England. This allows participating organisations to focus their resources on assessing, arranging and confirming their capacity and capability to deliver the study.

## Protocol amendments

Substantial amendments to the protocol and any patient-facing documentation will be submitted to a Research Ethics Committee (REC) and Health Research Authority for approval prior to implementation.

Amendments may only be implemented after a copy of the HRA approval letter has been obtained and local R&D departments have confirmed capacity to accommodate the amendment at that site.

Amendments intended to eliminate an immediate hazard to subjects may be implemented prior to receiving REC approval. However, in this case, approval must be obtained as soon as possible after implementation.

# Insurance

UK Centres will be covered by NHS indemnity for negligent harm providing researchers hold a contract of employment with the NHS, including honorary contracts held by academic staff.

**11 Publication Policy**

The findings of this research will be disseminated in a variety of ways:

* Peer reviewed scientific journals
* Internal report
* Conference presentation

We will invite participants at the end of the trial to come to a presentation about the results and impact of the trial and provide them with a written report of the trial, and ask them for feedback and thank them for their participation

# 12 References

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# Appendix 1: Definitions of Adverse Events

**1****3.1     Adverse Event (AE)**

Any untoward medical occurrence or effect in a patient treated on a trial protocol, which does not necessarily have a causal relationship with this treatment.

**13.2     Serious Adverse Event**

An adverse event that:

* Results in death
* Is life threatening
* Requires admission to hospital or prolongation of hospitalisation
* Results in persistent or significant disability/incapacity
* Is otherwise medically significant
* Aspiration or fulminant vomiting
* Switch to open heart surgery and admission to ITU
* Desaturation requiring mechanical ventilation after the end of the procedure

**13.3       Expected morbidity**

13.3.1      **Expected morbidity following TAVI can include (not related to the 2l/min nasal specs /HFNO device) :**

* Pain
* Bleeding
* Tamponade
* Sternotomy
* Misplacement of the valve
* Infection
* Deep vein thrombosis or pulmonary embolism
* Renal insufficiency
* Myocardial Infarction
* Stroke
* Arrhytmias

As with all invasive procedures there is also a risk of death.

All in hospital deaths will be reviewed by the Data Monitoring Committee.

13.3.2      **Expected morbidity with HFNO can include:**

* Discomfort nasal area
* Dryness of nose, mouth and throat
* Stomach bloating
* Feeling hot

# Appendix 2: Ramsay Sedation Scale

1   Patient is anxious and agitated or restless, or both

2   Patient is cooperative, oriented and tranquil

3   Patient responds to commands only

4   Patient exhibits brisk response to light glabellar tap or loud auditory stimulus

5   Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus

6   Patient exhibits no response