APPENDIX 2 to the PROTECT Platform Master Protocol

This appendix must be read with the accompanying PROTECT Platform master protocol IRAS 353122. This appendix describes only the additional details relevant to the conduct of this randomised comparison within the context of the overarching master protocol.

Full Title	High Flow Nasal Oxygen for patients undergoing elective major abdominal surgery
Short Title	PROTECT-HFNO
PROTECT-HFNO IRAS number	350757
PROTECT IRAS number	353122
REC Reference	24/LO/0888

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Participating sites	For a list of participating sites please refer to the IRAS application

Comparison Contributors

The Sponsor and funders have not played, nor will play a role in the study design, conduct, data analysis and interpretation, manuscript writing, and/or dissemination of results.

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1. Contents

2. Glossary of comparison specific terms and abbreviations

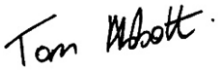
HFNO	High Flow Nasal Oxygen
CMG	Comparison Management Group
DAH	Days alive and at home
GCP	Good Clinical Practice
PI	Principal Investigator

3. Signature page

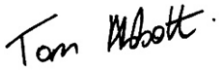
Chief Investigator Agreement

The study as detailed within this research protocol will be conducted in accordance with the principles of Good Clinical Practice, the UK Policy Framework for Health and Social Care Research, the Declaration of Helsinki, and the current regulatory requirements, including the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and all subsequent amendments. I delegate responsibility for the statistical analysis and oversight to a qualified statistician (see declaration below).

PROTECT Platform Chief Investigator: Dr Tom Abbott

Signature:  **Date: 19.06.2025**

PROTECT-HFNO Lead Investigator: Dr Tom Abbott

Signature:  **Date: 19.06.2025**

Statistician's Agreement

The study as detailed within this research protocol plan will be conducted in accordance with the principles of Good Clinical Practice, the UK Policy Framework for Health and Social Care Research, the Declaration of Helsinki, and the current regulatory requirements, including the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and all subsequent amendments, and ICH E9 - Statistical principles for Clinical Trials and ICH E10 - Choice of Control Groups.

I take responsibility for ensuring the statistical work in this protocol is accurate, and for the statistical analysis and oversight of this study.

Statistician name: Kamran Khan

Signature:  **Date: 19.06.2025**

Principal Investigator Agreement

The clinical study as detailed within this research protocol, or any subsequent amendments, involves the use of an investigational medicinal product and will be conducted in accordance with the UK Policy Framework for Health and Social Care Research , the World Medical Association Declaration of Helsinki (1996), Principles of ICH-GCP, and the current regulatory requirements, as detailed in the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and any subsequent amendments of the clinical trial regulations.

Principal Investigator:

NHS site:

Signature: **Date:**

4. Summary and synopsis

Short title	PROTECT-HFNO
Study design	Multi-centre individual patient randomised feasibility trial
MHRA risk level	N/A (non-CTIMP comparison)
Phase of the trial	IV
Study setting	Surgical services of NHS hospitals
Medical condition or disease under investigation	Adult patients undergoing elective major abdominal surgery
Objectives	• To demonstrate willingness of patients to participate in the trial • To demonstrate whether relevant healthcare staff within participating hospitals are willing to randomise patients into the trial • To provide feasibility data on the clinical effects of HFNO, in reducing postoperative pulmonary complications and days alive and at home (DAH30) after elective major abdominal surgery, compared to standard care • To provide safety data on the use of High Flow Nasal Oxygen (HFNO) in patients undergoing elective major abdominal surgery
Number of participants	200 patients
Inclusion and exclusion criteria	*Inclusion criteria* • Patients aged 50 years and over undergoing elective major abdominal surgery, using open, laparoscopic or robotic surgical technique *Exclusion criteria:* • Inability or refusal to provide informed consent • Anticipated requirement for invasive or non-invasive respiratory support for at least four hours after surgery as part of routine clinical care • Clinician refusal • Previous enrolment to the PROTECT-HFNO comparison
Intervention	High flow nasal oxygen started immediately after the end of surgery
Statistical methodology and analysis	Participants will be randomised 1:1 to HFNO or usual care using block randomisation, with randomly permuted blocks of four participants.
Treatment duration	At least four hours starting immediately after the end of surgery
Follow-up duration	30 days after surgery
End of comparison definition	30-day follow-up completed for final patient

5. Introduction

5.1 Background

More than five million patients undergo surgery in the NHS in a typical year (1). This population of patients is increasingly older and at greater risk of complications (2). Many common complications affect the respiratory system, including pneumonia, atelectasis, acute respiratory distress syndrome (ARDS) and respiratory failure requiring mechanical ventilation (3, 4). Patients undergoing major abdominal surgery are particularly susceptible to postoperative pulmonary complications, which in turn increases the length of hospital stay, the cost of treatment and reduces long-term survival (5). The prevention of respiratory complications after surgery is topical and relevant to anaesthetists, surgeons and patients.

The mechanism of pulmonary complications after surgery is unclear. They likely to arise due to a combination of anaesthesia and the surgical procedure itself, particularly following intra-thoracic or intra-abdominal surgery. General anaesthesia can cause atelectasis and pulmonary collapse, mismatch of ventilation with pulmonary perfusion causing hypoxia, while opioid analgesia and incomplete reversal of neuromuscular blockade reduce respiratory drive (6). Surgery causes tissue injury, inflammation and pain, which impair respiratory function and the ability to cough. The combination of these factors increase the risk of pulmonary complications after surgery, which can prolong the duration of hospital treatment (7).

A recent NIHR evidence synthesis of systematic reviews reported that postoperative non-invasive ventilation and HFNO may reduce postoperative pulmonary complications, particularly in preventing respiratory failure. However, this review was limited by the quality and certainty of evidence (8). Similarly, a systematic review and meta-analysis of small efficacy trials of postoperative non-invasive respiratory support, including high flow nasal oxygen, suggested benefit in preventing postoperative pulmonary complications, but this was limited by the quality of evidence and small size of constituent trials (9). In the PRISM trial of postoperative Continuous Positive Airway Pressure (CPAP), compliance with CPAP was limited by patient discomfort of a tight-fitting mask, which is greatly reduced with HFNO (10).
We need a large, randomised trial to confirm whether HFNO can prevent postoperative pulmonary complications and improve the quality and quantity of life after surgery. However, a feasibility trial is needed to confirm whether patients and doctors would participate, and with high levels of intervention compliance. This would inform the design of a definitive trial, and clearly demonstrate willingness to participate and randomise patients across a representative sample of NHS hospitals.

5.2 Rationale for study design

We need a randomised feasibility trial to confirm patients and doctors would participate with high levels of intervention compliance for HFNO. This trial will also capture other data to inform the design of a definitive trial.

6. Study objectives

6.1 Objectives

The over-arching aim is to provide a comprehensive portfolio of evidence to inform the design of a large randomised trial. The findings in this feasibility trial will not be used in managing the patient's care. The specific objectives are:

a) To demonstrate willingness of patients to participate in the trial

b) To demonstrate whether relevant healthcare staff within participating hospitals are willing to randomise patients into the trial

c) To provide feasibility data on the clinical effects of HFNO, in reducing postoperative pulmonary complications and days alive and at home (DAH30) after elective major abdominal surgery, compared to standard care (11)

d) To provide safety data on the use of HFNO in patients undergoing elective major abdominal surgery.

6.2 Outcome measures

a. Patient outcome measures

- Postoperative pulmonary complications within 30 days after surgery, a composite outcome comprising: pneumonia, Acute Respiratory Distress Syndrome, and/or Pulmonary Aspiration (12)
- Re-intubation within 30 days after surgery
- DAH30
- All complications graded by Clavien-Dindo within 30 days of surgery
- Mortality within 30 days of surgery
- Duration of hospital stay (number of days from day of surgery until hospital discharge) within 30 days after surgery
- Compliance with HFNO, including duration delivered and any reasons for discontinuation
- Adverse events associated with HFNO

b. Hospital level outcome measures

- Number of eligible patients per year in each hospital

- Number of patients consented per year in each hospital
- Included hospital randomising at least one patient within the 12-month recruitment period
- Number of consultant surgeons and anaesthetists in each hospital who support recruitment of the patients in their care in principle as a proportion of those delivering care for elective major abdominal surgery
- Number of consultant surgeons and anaesthetists in each hospital who do not support recruitment of the patients in their care in principle as a proportion of those delivering care for elective major abdominal surgery

7. Study population

200 patients undergoing major elective abdominal surgery.

7.1 Inclusion criteria

- Patients aged 50 years and over undergoing elective major abdominal surgery, using open, laparoscopic or robotic surgical technique

7.2 Exclusion criteria

- Inability or refusal to provide informed consent
- Anticipated requirement for invasive or non-invasive respiratory support for at least four hours after surgery as part of routine clinical care
- Previous enrolment in the PROTECT-HFNO comparison
- Clinician refusal

8. Study design

8.1 Study design

Multi-centre, open-label, randomised feasibility trial.

8.2 Study setting

Surgical services of NHS hospitals.

9. Study procedures

9.1 Participant screening

Potentially eligible participants will be screened by the direct care team for entry into the study in accordance with the PROTECT master protocol.

9.2 Informed consent procedures

Please follow the procedures documented in the PROTECT master protocol section on "Informed consent procedures".

9.3 Schedule for each visit

Visit	Screening	Before surgery	After surgery	Hospital discharge	30-day follow-up
Eligibility	x				
Informed consent		x			
Demographics		x			
Review of medical notes		x	x	x	x
Randomisation			x		
Administration of HFNO or usual care			x		
Safety review			x		
Follow-up					x

9.4 Randomisation method

Randomisation will occur after the participant has provided informed consent and shortly after surgery. Participants will be randomised 1:1 to HFNO or usual care using block randomisation, with randomly permuted blocks of four participants.

9.5 Randomisation procedure

The code creating the randomisation list will be approved by the statistician for the PROTECT-HFNO comparison. Allocations will be provided to investigators via the PROTECT online database interface, which will conceal the allocation sequence.

9.6 Intervention

The trial intervention period will commence immediately after the completion of surgery and continue for at least four hours. After four hours, HFNO will be continued or discontinued at the clinician's discretion.

9.6.1 Standard care

Patients in the usual care group will be managed by clinical staff according to local policy and guidelines. It is usual practice for postoperative patients to receive oxygen via a facemask or low-flow nasal cannulae. However, this may vary according to local hospital policies. The use of mechanical ventilation (invasive or non-invasive), continuous positive airway pressure (CPAP) or high flow nasal oxygen during the intervention period will be recorded on the case report form. It is foreseeable that some patients in the usual care group could receive HFNO as part of usual care. This will be managed as a protocol deviation and follow-up data will still be collected.

9.6.2 HFNO

The trial intervention is defined as HFNO for at least four hours, with minimal interruption, started immediately after the patient has left the operating room after surgery. Administration of HFNO will only take place under the direct supervision of appropriately trained staff in an adequately equipped clinical area. Delivery of the trial intervention and monitoring of patients receiving HFNO will be in accordance with local hospital policy or guidelines. If a prescription for HFNO is required, according to local hospital policy, this will be provided by the PI or a delegated medical professional. Alterations to the administered dose will be recorded along with the reason for this change. Clinicians may only use commercially available HFNO equipment to deliver the intervention. This will be a CE marked (or UK equivalent) device used in accordance with its recommended use. The starting flow will be 40 litres per minute and the starting fraction of inspired oxygen will be 40%. These parameters may be adjusted at the discretion of the responsible healthcare practitioner. For example, it may be deemed beneficial to increase the flow for patients with obesity or low chest wall compliance. It is foreseeable that some patients in the intervention group will not receive HFNO or fail to complete the minimum four hours of HFNO, e.g. due to unplanned invasive or non-invasive ventilation after surgery. These situations will be managed as protocol deviations and follow-up data will still be collected. Detailed guidance on the delivery of HFNO, including eligible delivery devices, fraction of inspired oxygen and flow rates will be provided in the intervention SOP.

9.7 Study assessments

Screening

- Checklist to ensure the patient meets the eligibility criteria

Demographic information

- As per the PROTECT master protocol.

Baseline data

- Variables that describe co-morbid disease as well as current health status, including (but not limited to) height and weight, oxygen saturation, history of recent respiratory infections and chronic conditions. This will include clinical assessment, laboratory and other test results.

Surgical admission

- Variables that describe the surgical and anaesthetic care as per the PROTECT master protocol.

Follow-up

- Data describing the administration of HFNO
- Postoperative invasive or non-invasive respiratory support or oxygen therapy
- Level of care after surgery
- Patient vital status (dead/alive) at 30 days
- Postoperative complications measured according to Clavien-Dindo scale at 30 days
- Duration of hospital stay
- Re-admission to hospital within 30 days of surgery

Supplementary forms

- Withdrawal
- Protocol deviations
- Safety report

9.8 Follow-up procedures

Please follow the procedures documented in the PROTECT master protocol section “Follow-up procedures”. To minimise bias, as much as possible, follow-up data will be collected by an investigator who is unaware of the study group allocation.

9.9 Participant withdrawals

Please follow the procedures documented in the PROTECT master protocol section “Participant, study and site discontinuation”.

9.10 End of trial

End of trial is defined as when the last patient has completed their last follow up.

10. Assessment and management of risk

HFNO has been used widely in routine clinical practice for many years and has an excellent safety profile. HFNO will be used within its product licence.

11. Statistical and data analysis

11.1 Statistical design

We have selected a feasibility sample size of 200 patients in 10 NHS hospitals over a 12-month recruitment period providing robust estimates of patient and clinician willingness to participate. This will also provide robust data on rates of possible treatment harms which are a key driver of the sample size for the main trial. The 95% confidence interval for feasibility objective rate estimates are +/- 6.9% with a sample size of 200.

11.2 Statistical analysis

As this is a feasibility study, the analysis will be descriptive. Feasibility outcomes will be summarised as frequencies and percentages with 95% confidence intervals, using the method of Clopper and Pearson. Patient and safety outcomes will also be summarised by treatment group using measures of central tendencies and variability for continuous data, and frequencies and proportions for categorical data.

11.3 Statistical analysis plan

A full statistical analysis plan will be developed prior to final analysis of this comparison.

12. Ethics

Annual progress reports will be sent to the REC and Sponsor on the anniversary of the favourable opinion for this comparison.

13. Public and Patient Involvement (PPI)

Patients have been involved from the outset of the design of this intervention comparison. Our patient panel have highlighted the ongoing problem of postoperative pulmonary complications after major abdominal surgery and how HFNO may be better tolerated than other alternative forms of non-invasive ventilation that require a tight-fitting mask. In addition to our patient representatives, the PROTECT platform proposal, including the feasibility stage, have been reviewed by the Patient Carer and Public Involvement and Engagement group at the Royal College of Anaesthetists. We have fully incorporated several of their suggestions into

PROTECT-HFNO, including strategies to improve recruitment, and the development of a patient advisory group to review and provide feedback on patient facing documents.

14. Data handling and record keeping

Please refer to the PROTECT master protocol section “Data management” for further details.

15. Safety reporting

Please refer to the PROTECT master protocol section “Pharmacovigilance” for the overall reporting concept and general definitions..

15.1 Reporting Adverse events (AEs) and Serious Adverse Events (SAEs) and other safety events

The safety reporting period will start from completion of informed consent until 12 hours after the end of surgery, which will include the 4-hour intervention period.

Only AEs, SAEs, SARs and SUSARs will be reported if they are related to the trial intervention and unexpected (i.e. not listed below as an expected occurrence exempt from reporting).

The following pre-defined safety events should be reported if related to the trial intervention: pain, cutaneous pressure area, oronasal dryness, hypercapnia, haemodynamic instability, vomiting, aspiration of gastric contents.

15.2 Adverse events (AEs) and Serious Adverse Events (SAEs) exempt from reporting

Medical complications occur commonly after surgery and are an expected part of routine perioperative care. Consequently, the following do not constitute safety events and are exempt from routine safety reporting as AEs and/ or SAEs unless the PI and/or medical delegate believes the trial intervention caused the event:

- Infection (surgical site infection, respiratory infection, urinary system infection, neurological infection, laboratory confirmed blood stream infection, neurological infection, clostridium difficile infection, endometritis, pathogenic organism in tissue or fluid)
- Acute cardiac events (hypotension, arrhythmia, atrial fibrillation, myocardial infarction, myocardial injury, cardiac arrest, cardiogenic pulmonary oedema,

coronary revascularisation, cardiac death, pulmonary embolism, deep vein thrombosis, stroke)

- Respiratory events (Atelectasis, pulmonary aspiration, Acute Respiratory Distress Syndrome (ARDS), pleural effusion, pneumothorax, bronchospasm).
- Renal replacement therapy
- Postoperative haemorrhage
- Acute psychosis or delirium
- Anaphylaxis
- Bowel infarction
- Multi-organ dysfunction syndrome
- Paralytic ileus
- Perforated viscus
- Anaemia

Please refer to the PROTECT master protocol section “Procedure for immediate reporting of SAEs, SARs and SUSARs” for further details on the reporting procedure. The completed form will be signed and submitted to the PROTECT coordinating centre within 72 hours of becoming aware of the event.

16. Monitoring and audits

Please refer to the PROTECT master protocol “Monitoring, audit and inspection section” for further details

17. Study committees

Please refer to the PROTECT master protocol “Study committees” section for further details.

18. Finance and funding

This research was funded in open competition by Barts Charity (ref: G-002514) and The British Journal of Anaesthesia. The proposal was peer reviewed by internal and external experts during the funding process. Since securing the award, the protocol has since been further reviewed during the study design process.

19. Indemnity

Please refer to the PROTECT master protocol “Indemnity/ insurance” section for further details.

20. Dissemination of research findings

Please refer to the PROTECT master protocol “Publication and dissemination policy” section for further details.

21. References

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