East and North Hertfordshire
NHS Trust

# Robotic Prostatectomy Artificial Intelligence Low Pressure Pain Study Trial - "The monitoring of patients outcomes intraoperatively and perioperatively using the Airseal and Stryker insufflator undergoing Robotic Assisted Laparoscopic Prostatectomy at a pressure and stability of pneumoperitoneum of 8 mmHg".

## Short Title: Robotic Prostatectomy Artificial Intelligence Low Pressure Pain (RALP) Trial

**Protocol Reference/RD no: RD2024-75**
**Version number:** 1
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**Study Chief Investigator:**
**Study Sponsor:**
**IRAS ID:** 346481

***This protocol has regard for the HRA guidance***

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Robotic Prostatectomy Artificial Intelligence Low Pressure Pain (RALP) Trial

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| **REC Number:** | |
| **ISRCTN Number:** | |
| **Date:** | 18/11/2024 |
| **Amended:** | |

# Protocol Synopsis

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| **Study Title** | Robotic Prostatectomy Artificial Intelligence Low Pressure Pain Study Trial - "The monitoring of patients outcomes intraoperatively and perioperatively using the Airseal and Stryker insufflator undergoing Robotic Assisted Laparoscopic Prostatectomy at a pressure and stability of pneumoperitoneum of 8 mmHg". |
| **Short Title** | Robotic Prostatectomy Artificial Intelligence Low Pressure Pain (RALP) Trial |
| **Type of Trial** | A prospective, randomized, controlled, open label, human clinical study designed to evaluate pain related to the use of the AirSeal® Insufflation System (AIS) vs a Stryker PneumoClear Insufflator for the management of pneumoperitoneum. |
| **Study Period** | Each subject will be enrolled in the study from day of consent until their standard of care 30-day, post-procedure, follow-up appointment. |
| **Objectives** | In this trial, 40 patients undergoing robotic prostatectomies will be randomised to have either the AIRSEAL® Insufflation System (AIS) or the Stryker PneumoClear Insufflator devices used to maintain pneumoperitoneum during surgery. Data relating to intra-operative and post-operative pain will be collected. This data will be used to identify any differences in outcomes between the two arms of the trial.<br><br>The main aim of this feasibility study will be to inform the feasibility and design of a subsequent definitive full-scale trial. The feasibility trial will collect data about recruitment, study conduct, and assessment methods. |
| **Outcome measures** | The main aim of this feasibility study will be to inform the feasibility and design of a subsequent definitive full-scale trial. The feasibility trial will collect data about recruitment, study conduct, and assessment methods. The objectives of the feasibility are to<br>• Assess recruitment rates<br>• Evaluate whether the study can run in line with the study protocol<br>• Identify the feasibility of collecting clinical data<br>• Evaluate treatment-based adverse events, serious adverse events, anticipated adverse device effects, unanticipated adverse device effects and all device deficiencies and use errors, regardless of relationship to an adverse event<br>• Estimate the likely magnitude of the effect of the intervention. To allow for estimation of the sample size for the full trial<br><br>The subsequent large scale, multi-center trial following this feasibility trial will focus on severity of pain during and immediately after surgery in the recovery room and then by 6-hour increments, measured by a 0 – 10 Numeric Rating Scale (NRS) and a PMD-200 nociception non-invasive monitor as the primary outcome<br><br>Secondary outcomes include: |

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| | Pre-Operative<br>1. Pre-op vitals including height and weight<br>2. Pre-op labs<br><br>Intra-operative<br>1. Insufflation Pressure<br>2. Estimated blood loss<br>3. Blood transfusion (intra-operative)<br>4. Procedure time (initial incision to closure)<br>5. Surgeon-determined need to increase IAP beyond “study pressure”<br>6. Administration of transversus abdominis plane block<br>7. Urine output<br>8. Anesthetic/pain medication administration<br>9. MedaSense PMD-200 monitor for pain documentation<br>10. Intraoperative Peak Airway Pressure every 15 minutes<br>11. Intraoperative End Tidal Carbon Dioxide (ETCO2) every 15 minutes<br><br>Post-Operative<br>During hospital discharge, all subjects will be evaluated for incidence and severity of pain using a 0-10 numeric rating scale (NRS) and records of medication use and a PMD-200 monitor. These data will be captured in the Case Report Forms.<br><br>Recovery room:<br>1. Time in recovery room<br>2. Post-op pain incidence and severity (abdominal) NRS<br>3. Pain medications<br>4. Post- op labs (CBC, Chem-7) per standard of care<br>5. Vital signs 24 hr<br><br>Discharge:<br>1. Post-op pain incidence and severity (abdominal) NRS<br>2. Presence or absence of postoperative nausea or vomiting<br>3. Pain medications<br>4. Length of hospital stay<br>5. Pain Interference and Pain Intensity short form surveys<br>6. Any complications that were observed. Post-operative complications through 30 days, reported using Clavien-Dindo Classification, including 30-day mortality<br>7. Return to operating room within 24 hour<br>8. Readmission to hospital within 30 days<br><br>Classification, including 30-day mortality<br>All Adverse Events (intra-operative and post-operative through 30 days):<br>1. Adverse Events |

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| | 2. Serious Adverse Events<br>3. Anticipated Adverse Device Effects<br>4. Unanticipated Adverse Device Effects<br>5 All device deficiencies and use errors, regardless of relationship to an adverse event |
| **Study Design and Methodology** | Patients under the care of the urology department at the Lister Hospital, Stevenage will be listed in clinic for a robotic prostatectomy. If patients meet the eligibility criteria for the trial, they will be approached and informed of the RALP clinical trial during their clinic consultation, by a member of the clinical team (likely a urological consultant).<br><br>Patients will be provided with a patient information sheet informing them of the aims and methodology of the trial. Members of the research department will be able to answer any outstanding questions patients might have.<br><br>Written informed consent will be obtained from eligible patients (n=40) willing to participate in the trial. If patients consent, their GP will subsequently be written to and informed of their involvement in the trial.<br><br>Pre-Operative data collection:<br>Within 30 days of a subject's scheduled procedure, members of the research department at Lister hospital will obtain a medical history and record the subject's demographic (age, race, sex and date of birth) and baseline information (height, weight, and systolic/diastolic blood pressure). Within 30 days prior to the planned procedure date, obtain serum blood tests per standard of care. These will typically include:<br>• FBC • Renal function test • CRP<br>This data, along with all subsequent trial related data will be anonymised and subsequently inputted into a database created by the Centre for Health Services and Clinical Research at the University of Hertfordshire.<br><br>Preoperative Randomization:<br>Randomization will be done electronically via a database which is facilitated by the University of Hertfordshire. Patients will be randomized 1:1 to either AIS (at 8 mmHg) or Stryker PneumoClear Insufflator Arm 1: AIRSEAL® Insufflation System (AIS) – 8 mmHg Arm 2: Stryker PneumoClear Insufflator - 8 mmHg.<br><br>Methods and Procedure:<br>Patients will undergo their robotic assisted prostatectomy with the use of either the AIRSEAL® Insufflation System (AIS) or Stryker PneumoClear Insufflator depending on which arm of the trial they have been randomized to. Patients will be blinded to the intervention |

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| | (AIRSEAL® Insufflation System (AIS) or Stryker PneumoClear Insufflator). Both systems are commonly used devices across many NHS trusts and there is currently no evidence comparing patient outcomes between use of the two devices.<br><br>This study will be conducted at one site by one surgeon performing 40 total procedures. Study subjects will be prepared for surgery per standard institutional policy and practice. Standard operative procedures will be followed.<br><br>Case Report Forms will be also be used to collect data relating to pre-operative, intra-operative and post-operative outcomes. This data will relate to outcomes such as intra-operative pain, post operative pain scores, medication use, duration of hospital stay, presence of nausea or vomiting etc...<br><br>The final patient follow up will be in a clinic appointment 30 days following their operation. Ongoing post-operative outcomes will be assessed (pain scores, medication use, adverse events etc...).<br><br>Data will be inputted on the database which is subsequently processed and statistically analysed and reviewed. Differences in outcomes between the two arms of the trial may be identified.<br><br>Once the aforementioned data has been processed and reviewed, results may be published and also distributed to those trial participants who wished to receive ongoing information and results from the trial.<br><br>The outcomes of this research will be used to inform future research such as a full scale trial with a larger number of patients and larger volume of data |
| **Indication** | We hope to use results from this initial single-center RCT to inform future, larger scale, multi-center research on this topic. Research into this field has the potential to benefit patients by reducing intra and post-operative pain, reduce reliance on pain medications and reduce lengths of hospital admissions. This is especially important given there is a global issue with long term analgesia abuse. |
| **Planned Trial sites** | Single site – Lister Hospital, Corey Mills Lane, Stevenage |
| **No of Participants** | 40 |
| **Eligibility Criteria** | Inclusion criteria:<br>1.Patient indicated for non-emergent robotic Prostatectomy surgery<br>2.Patients (or appropriate legal representatives) able to provide written informed consent to participate in the study<br>3.Males, aged 18 to 75 years<br>4.Have no significant psychopathology that could limit the subject's ability to understand the procedure, comply with medical, surgical, and/or behavioural recommendations and office visits |

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| | 5.Are American Society of Anaesthesiologists (ASA) Class I, II, or III);<br><br>Exclusion criteria:<br>1.Patient participation in a different investigational clinical study within 90 days before screening and for the duration of this trial (unless previously approved by the investigator and Sponsor);<br>2.Patients requiring any surgical procedure in addition to Prostatectomy and or / Pelvic Lymph node dissection<br>3.Previous pelvic surgery or previous malabsobtion or restrictive procedures performed for the treatment of obesity<br>4.Inability to provide informed consent<br>5.Unable or unwilling to attend follow-up visits and examinations<br>6.Uncontrolled hypertension (=/>Systolic: 180 mmHg/Diastolic: 120 mmHg) and/or diabetes mellitus (Blood sugar level: >200 mg/dL)<br>7.Patients who fall into American Society of Anesthesiologists (ASA) Class ≥ IV<br>8.History of chronic alcohol or drug abuse within 2 years of the screening visit<br>9.Chronic renal failure or on dialysis<br>10.Significant complicating medical history or immunocompromised<br>11.History or presence of pre-existing autoimmune connective tissue disease, e.g., systemic lupus erythematosus or scleroderma<br>12.Immunocompromised such as that resulting from chronic oral steroid use, chemotherapeutic agents, or immune deficiency disorders;<br>13.Any medical condition which precludes compliance with the study<br>14.Subjects with any other clinically significant unstable medical disorder, life threatening disease, or conditions that, in the opinion of the investigator, may jeopardize the subject's well-being and/or the soundness of this clinical study or which would contra-indicate a surgical procedure.<br>15.Previous or current history of being on regular analgesia / pain killers |
| **Treatment** | Robotic assisted prostatectomy using either the AIRSEAL® Insufflation System (AIS) or Stryker PneumoClear Insufflator. |
| **Assessment Schedule** | Patients initially assessed for trial eligibility in outpatient urology clinics where they are approached and informed about the trial. If a patient consents to take part in the trial then they will have their pre-operative assessment within 30 days of their planned robotic prostatectomy. |
| **Statistical Methodology and analysis** | Data analysis will be undertaken by Professor Neil Spencer at the Department of Applied Statistics at the University of Hertfordshire. Full details of the data analysis plan can be found in section 7.3 of the protocol. |

# Study Glossary

Commonly used abbreviations

| | |
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| AE | Adverse Event |
| CI | Chief Investigator |
| CRF | Case Report Form |
| CRO | Contract Research Organisation |
| DMC | Data Monitoring Committee |
| GAfREC | Governance Arrangements for NHS Research Ethics |
| GCP | Good Clinical Practice |
| GP | General Practitioner |
| HRA | Health Research Authority |
| ICF | Informed Consent Form |
| ISF | Investigator Site File |
| ISRCTN | International Standard Randomised Controlled Trials Number |
| Main REC | Main Research Ethics Committee |
| NHS R&D | National Health Service Research & Development |
| NIHR | National Institute for Health Research |
| NIMP | Non-Investigational Medicinal Product |
| PI | Principal Investigator |
| PIS | Participant Information Sheet |
| QA | Quality Assurance |
| QC | Quality Control |
| RCT | Randomised Control Trial |
| REC | Research Ethics Committee |
| SAE | Serious Adverse Event |
| SDV | Source Document Verification |
| SOP | Standard Operating Procedure |
| SSA | Site Specific Assessment |
| TMG | Trial Management Group |
| TSC | Trial Steering Committee |
| WHO | World Health Organisation |

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## 1 INTRODUCTION

### 1.1 Background and Rationale

Rapid advances in minimally invasive surgical techniques drive continual technological improvements in surgical tools and equipment. The benefits of laparoscopic surgery in terms of reduced complications, minimally invasiveness, patient comfort and reduced recovery time have been well established to the point that laparoscopic surgery is now the standard of care for procedures such as radical prostatectomies.
Laparoscopic surgical technique depends upon the establishment of pneumoperitoneum through insufflation of the abdomen in order to achieve sufficient working space, visualization of target organs and tissue, and surgical access. Insufflation and surgical access are achieved through the use of trocars and systems that pump CO2 into the abdominal cavity during the duration of surgery. Conventional trocars include a mechanical rubber valve or seal that minimizes the loss of gas pressure.
The AirSeal® System consists of an insufflation, filtration, and recirculation system (AirSeal® iFS), a triple lumen filtered tube set, and a valve free trocar (AirSeal® Access Port). The device enables peritoneal access with a novel mechanism to maintain pneumoperitoneum without a mechanical seal. Specifically, the AirSeal® System creates a pressure barrier within the proximal housing of the cannula which acts as an invisible seal to maintain pneumoperitoneum during the course of surgery. It utilizes a re-circulation and filtration control unit (AirSeal® iFS) designed specifically for the AirSeal® Access Port to create and maintain the pressure barrier.
The AirSeal® System has applications in abdominal minimally invasive surgical procedures to establish a path of entry for laparoscopic instruments. The system provides high flow insufflation, stable pneumoperitoneum, and further limits loss of intra-abdominal pressure compared with conventional systems (source).
The insufflation and recirculation system (AirSeal® iFS) are reusable and the AirSeal® Access Port and triple lumen filtered tube set are designed as single patient use devices.
The 1st generation AirSeal® System received FDA 510(k) clearance in 2007 and the current system received FDA 510(k) Clearance in May 2011. Since that time, the AirSeal™ system has been used routinely in centers throughout the United States and UK. Initial evidence in the literature has reported that the use of the AirSeal System results in a reduction of operative time, CO2 consumption, CO2 elimination, and CO2 absorption. Additionally, the AirSeal was reported to maintain the stability of pneumoperitoneum better than Stryker's PneumoSure and Storz's THERMOFLATOR insufflators when challenged with leakage and suction in a lab-based study. There is, however, a lack of in vivo evidence investigating intra-operative and post-operative pain when comparing two insufflators that are readily available on the market and are already in common use across various NHS Trusts (AirSeal and Stryker PneumoSure).

This study is designed to evaluate post-operative pain in relation to the use of the AirSeal Insufflation System (AIS) versus Stryker PneumoClear Insufflator. The study is hypothesised to demonstrate superiority of the AIS during laparoscopic/robotic surgery in relation to the degree of post-operative abdominal pain. In addition to this primary endpoint, additional key effectiveness and safety outcomes will be evaluated. These outcomes include ease of anesthesia management, recovery time, time to hospital discharge, and additional safety outcomes including any insufflation device related complications.

# 2 STUDY OBJECTIVES AND DESIGN

## 2.1 Objectives

### 2.1.1 Primary objective:

The main aim of this feasibility study will be to inform the feasibility and design of a subsequent definitive full-scale trial. The feasibility trial will collect data about recruitment, study conduct, and assessment methods. The objectives of the feasibility are to
• Assess recruitment rates
• Evaluate whether the study can run in line with the study protocol
• Identify the feasibility of collecting clinical data
• Evaluate treatment-based adverse events, serious adverse events, anticipated adverse device effects, unanticipated adverse device effects and all device deficiencies and use errors, regardless of relationship to an adverse event
• Estimate the likely magnitude of the effect of the intervention. To allow for estimation of the sample size for the full trial

The subsequent large scale, multi-center trial following this feasibility trial will focus on severity of pain during and immediately after surgery in the recovery room and then by 6-hour increments, measured by a 0 – 10 Numeric Rating Scale (NRS) and a PMD-200 nociception non-invasive monitor as the primary outcome. Here it is hypothesized that the outcomes such as intra and post-operative pain in the AirSeal Insufflation System (AIS) arm of the trial will be superior to the Stryker PneumoClear Insufflator arms of the trial.

### 2.1.2 Secondary objectives:

To confirm the feasibility in collecting data relating to the following secondary outcomes:

Pre-Operative

1. Pre-op vitals including height and weight
2. Pre-op labs

Intra-operative

1. Insufflation Pressure
2. Estimated blood loss

3. Blood transfusion (intra-operative)
4. Procedure time (initial incision to closure)
5. Surgeon-determined need to increase IAP beyond “study pressure”
6. Administration of transversus abdominis plane block
7. Urine output
8. Anesthetic/pain medication administration
9. MedaSense PMD-200 monitor for pain documentation
10. Intraoperative Peak Airway Pressure every 15 minutes
11. Intraoperative End Tidal Carbon Dioxide (ETCO2) every 15 minutes

Post-Operative

During hospital discharge, all subjects will be evaluated for incidence and severity of pain using a 0-10 numeric rating scale (NRS) and records of medication use and a PMD-200 monitor. These data will be captured in the Case Report Forms.

Recovery room:

1. Time in recovery room
2. Post-op pain incidence and severity (abdominal) NRS
3. Pain medications
4. Post- op labs (CBC, Chem-7) per standard of care
5. Vital signs 24 hr

Discharge:

1. Post-op pain incidence and severity (abdominal) NRS
2. Presence or absence of postoperative nausea or vomiting
3. Pain medications
4. Length of hospital stay
5. Pain Interference and Pain Intensity short form surveys
6. Any complications that were observed. Post-operative complications through 30 days, reported using Clavien-Dindo Classification, including 30-day mortality
7. Return to operating room within 24 hour
8. Readmission to hospital within 30 days

Classification, including 30-day mortality

All Adverse Events (intra-operative and post-operative through 30 days):

1. Adverse Events
2. Serious Adverse Events
3. Anticipated Adverse Device Effects
4. Unanticipated Adverse Device Effects
5 All device deficiencies and use errors, regardless of relationship to an adverse event

## 2.2 Endpoints/outcomes

### 2.2.1 Primary Endpoints/outcomes:

As this is primarily a feasibility trial, the primary endpoint will have been achieved once all intra-operative and post-operative pain related data (including the 30 day post-op outcomes) has been collected and analysed. This data may or may not show a statistically significant difference in patient's pain when comparing the the AirSeal Insufflation System (AIS) and the Stryker PneumoClear Insufflators (conventional insufflator system - CIS).
The hypotheses for the primary endpoint of an 11-point NRS abdominal pain score are as follows:
Null hypothesis H0: mean AIS pain score ≥ mean CIS pain score
Alternative hypothesis Ha: mean AIS pain score < mean CIS pain score
A Mixed Model Repeated Measures (MMRM) analysis encompassing the multiple in-hospital pain scores per subject will be performed to compare the AIS and CIS groups. Since a portion of the subjects will report no pain, the data will be analyzed primarily in the rank transformed scale and secondarily in the regular scale.

### 2.2.2 Secondary Endpoints/outcomes:

The complete collection of all data relating to the secondary outcomes. This data is grouped into sub-categories including, pre-operative, intra-operative, post-operative, recovery room, discharge and classification, including 30-day mortality. See section 2.1.2 for further information.

## 2.3 Study Design

A prospective, randomized, controlled single-center clinical study designed to evaluate post-operative pain related to the use of the AirSeal® Insufflation System (AIS) and Stryker PneumoClear Insufflator for the management of pneumoperitoneum. Subjects will be randomized in a 1:1 treatment device to control ratio into one of two (2) different study arms:
Arm 1: AIRSEAL® Insufflation System (AIS) – 8 mmHg
Arm 2: Stryker PneumoClear Insufflator (conventional insufflator system)
The study is designed and powered to demonstrate superiority of the AIS over CIS in terms of post-operative abdominal pain.
Secondary outcome measures include procedure time, length of recovery room stay, length of hospital stay, number of times insufflator settings are adjusted and severity of

postoperative nausea/vomiting. These outcomes will be evaluated in a qualified population undergoing robotic prostatectomy**.**

Patients under the care of the urology department at the Lister Hospital, Stevenage will be listed in clinic for a robotic prostatectomy. If patients meet the eligibility criteria for the trial, they will be approached and informed of the RALP clinical trial during their clinic consultation, by a member of the clinical team (likely a urological consultant). Patients will be provided with a patient information sheet informing them of the aims and methodology of the trial. Members of the research department will be able to answer any outstanding questions patients might have.

Written informed consent will be obtained from eligible patients (n=40) willing to participate in the trial. If patients consent, their GP will subsequently be written to and informed of their involvement in the trial.

Pre-Operative data collection:
Within 30 days of a subject's scheduled procedure, members of the research department at Lister hospital will obtain a medical history and record the subject's demographic (age, race, sex and date of birth) and baseline information (height, weight, and systolic/diastolic blood pressure). Within 30 days prior to the planned procedure date, obtain serum blood tests per standard of care. These will typically include:
• FBC
• Renal function test
• CRP
This data, along with all subsequent trial related data will be anonymised and subsequently inputted into a database created by the Centre for Health Services and Clinical Research at the University of Hertfordshire.

Preoperative Randomization:
Randomization will be done electronically via a database which is facilitated by the University of Hertfordshire. Patients will be randomized 1:1 to either AIS (at 8 mmHg) or Stryker PneumoClear Insufflator.
Arm 1: AIRSEAL® Insufflation System (AIS) – 8 mmHg
Arm 2: Stryker PneumoClear Insufflator - 8 mmHg

Methods and Procedure
Patients will undergo their robotic assisted prostatectomy with the use of either the AIRSEAL® Insufflation System (AIS) or Stryker PneumoClear Insufflator depending on which arm of the trial they have been randomized to. Patients will be blinded to the intervention (AIRSEAL® Insufflation System (AIS) or Stryker but it is not feasible to blind the surgeon in the trial.

This study will be conducted at one site by one surgeon performing 40 total procedures. Study subjects will be prepared for surgery per standard institutional policy and practice. Standard operative procedures will be followed.

Case Report Forms will be also be used to collect data relating to pre-operative, intra-operative and post-operative outcomes. This data will relate to outcomes such as intra-

operative pain, post operative pain scores, medication use, duration of hospital stay, presence of nausea or vomiting etc... The final patient follow up will be in a clinic appointment 30 days following their operation. Ongoing post-operative outcomes will be assessed (pain scores, medication use, adverse events etc...).

Data will be inputted on the database which is subsequently processed and statistically analysed and reviewed. Differences in outcomes between the two arms of the trial may be identified.

Once the aforementioned data has been processed and reviewed, results may be published and also distributed to those trial participants who wished to receive ongoing information and results from the trial.

The outcomes of this research will be used to inform future research such as a full scale trial with a larger number of patients and larger volume of data.

### 2.3.1 Number of subjects

40 patients.

### 2.3.2 Study Duration

Each subject will be enrolled in the study from day of consent until their standard of care 30-day, post-procedure, follow-up appointment. It is expected that this will take up to 12 month to commence and complete with follow up

### 2.3.3 End of Study

End of study is defined as the point at which all 40 patients involved in the trial have undergone, and completed their 30 day post-operative follow up. At this point there is no further follow up or data collection required for study participants.

The sponsor will inform the REC within 90 days of the ‘end of trial’ that the study has closed.

Following the submission of end of trial notification to the REC, the sponsor should ensure that end of trial report is submitted within 12 months of this notification.

In circumstances of early termination of the trial or temporary halt by the sponsor, the sponsor will notify the REC within 15 days of the decision and a detailed, written explanation for the termination/halt will be given.

## 3 SUBJECT SELECTION AND RECRUITMENT

### 3.1 Inclusion Criteria

1.Patient indicated for non-emergent robotic Prostatectomy surgery
2.Patients (or appropriate legal representatives) able to provide written informed consent to participate in the study
3.Males, aged 18 to 75 years
4.Have no significant psychopathology that could limit the subject's ability to understand the procedure, comply with medical, surgical, and/or behavioural recommendations and office visits
5.Are American Society of Anaesthesiologists (ASA) Class I, II, or III);

### 3.2 Exclusion Criteria

1.Patient participation in a different investigational clinical study within 90 days before screening and for the duration of this trial (unless previously approved by the investigator and Sponsor);
2.Patients requiring any surgical procedure in addition to Prostatectomy and or / Pelvic Lymph node dissection
3.Previous pelvic surgery or previous malabsobtion or restrictive procedures performed for the treatment of obesity
4.Inability to provide informed consent
5.Unable or unwilling to attend follow-up visits and examinations
6.Uncontrolled hypertension (=/>Systolic: 180 mmHg/Diastolic: 120 mmHg) and/or diabetes mellitus (Blood sugar level: >200 mg/dL)
7.Patients who fall into American Society of Anesthesiologists (ASA) Class ≥ IV
8.History of chronic alcohol or drug abuse within 2 years of the screening visit
9.Chronic renal failure or on dialysis
10.Significant complicating medical history or immunocompromised 11.History or presence of pre-existing autoimmune connective tissue disease, e.g., systemic lupus erythematosus or scleroderma 12.Immunocompromised such as that resulting from chronic oral steroid use, chemotherapeutic agents, or immune deficiency disorders;
13.Any medical condition which precludes compliance with the study 14.Subjects with any other clinically significant unstable medical disorder, life threatening disease, or conditions that, in the opinion of the investigator, may jeopardize the subject's well-being and/or the soundness of this clinical study or which would contra-indicate a surgical procedure.
15.Previous or current history of being on regular analgesia / pain killers

### 3.3 Subject Recruitment and Screening

Potential participants in this trial will be identified when seen in their routine outpatient urology clinic appointment. During this clinic appointment patients will be being listed for a robotic prostatectomy. If patients are considered to meet the eligibility criteria for the trial, they will subsequently be approached and invited onto the trial. The identification process will be carried out by a member of the urology clinical team at Lister hospital.

### 3.4 Randomisation Procedure

Randomisation will be done electronically via an electronic database which is facilitated by the University of Hertfordshire. Patients will be randomized 1:1 to either AIS (at 8 mmHg) or Stryker PneumoClear Insufflator Arm 1: AIRSEAL® Insufflation System (AIS) – 8 mmHg Arm

2: Stryker PneumoClear Insufflator - 8 mmHg.

# 4 SUBJECT WITHDRAWAL

Patients will be withdrawn from the trial and will not receive the intervention (AIRSEAL® Insufflation System (AIS) or Stryker PneumoClear Insufflator) if they no longer meet the eligibility criteria. If a patient no longer meets the inclusion criteria or meets the exclusion criteria in the time period between enrollment into the trial and the intervention date (day of robotic prostatectomy), they will then be withdrawn from the trial.

# 5 STUDY PROCEDURES AND SCHEDULE OF ASSESSMENTS

## 5.1 Informed consent

All subjects for this study will be provided with a patient information sheet and a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the REC/HRA for the study. The formal consent of a subject, using the REC/HRA -approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

Consent to participate in the study will be obtained by a member of the urology research team that is qualified to take consent. This person will be GCP trained, suitably qualified and experienced, and have been delegated this duty by the CI/PI on the delegation log. This will most commonly be done by Professor Nikhil Vasdev.

It is the responsibility of the Investigator, or a person delegated by the Investigator to obtain written informed consent from each subject prior to participation in the trial, following adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study.

Adequate time must be given for consideration by the patient before taking part. The PI must record when the patient information sheet (PIS) has been given to the patient. [If the amount of time between the PIS being given and the date of consent is less than 24 hours, the PI needs to explain the rationale for this].

The Investigator or designee will explain the patients are under no obligation to enter the trial and that they can withdraw at any time during the trial, without having to give a reason.

No study procedures will be conducted prior to taking consent from the participant. Consent will not denote enrolment into trial.

A copy of the signed Informed Consent form will be given to the participant. The original signed form will be retained at the study site and a copy placed in the medical notes.

If new safety information results in significant changes in the risk/benefit assessment, the consent form will be reviewed and updated if necessary and subjects will be re-consented as appropriate

Where the participant population is likely to include a significant proportion of participants who cannot read or write, require translators or have cognitive impairment, appropriate alternative methods for supporting the informed consent process should be employed. Details of alternative methods for supporting informed consent should be provided. This may include allowing a witness to sign on a participant's behalf (in the case of problems with reading or writing), or allowing someone to date the form on behalf of the participant, or providing Participant Information Sheets in other languages or in a format easily understood by the participant population (in the case of minors or cognitive impairment).

Patients lacking capacity will not be recruited into the study.

### 5.2 Trial Procedures by Visit

| Area of Activity | Specific Activity | Undertaken by |
|---|---|---|
| Patient approached and invited to participate in study | Patients seen in Urology outpatient clinic at Lister Hospital and listed for a robotic prostatectomy. Patient will be approached here and informed about the study and given a PIS. | Local Urology Consultant at ENHT (East and North Hertfordshire NHS Trust). |
| Consent Processes | Written informed consent taken from patient agreeing to participate in the study. | Member of the Local Urology research team able to take consent. |
| Study Set Up | Patients (n=40) randomised to two arms. Patient's baseline characteristics and pre-operative data collected, anonymised and stored on encrypted Trust IT systems. Stryker PneumoClear Insufflator purchased/rented in order to compare to Airseal infufflator. | Member of the Local Urology research team. |
| Study Monitoring | Study commences where patients undergo their radical prostatectomy using one of the two insufflators being randomised to them during the trial. Pre-operative, intra-operative and post-operative data relating to the primary and secondary outcomes of the study collected, anonymised and stored on encrypted Trust IT systems. | Members of the local clinical team involved in pre-op, intra-op and post-operative care. Ranging from Research nurses and doctors, to consultant urological surgeons, the surgical team and the nursing team. |
| Study Close Down | Study data is sent to the University of Hertfordshire's Department of Applied Statistics where is is statistically analysed . Results are returned to the clinical research team to interpret and publish. Adverse events within 30 days post-operation will be documented and published. Patients will be followed up for a total of 12 months whereafter the trial data will be archived. | University of Hertfordshire Department of Applied Statistics and clinical research team involved in the trial at Lister Hospital. |

**Table 2. Schedule of assessments**

| | **Within 1 month Before Procedure** | **Day of Procedure** | **Post-Procedure/ Prior to Hospital Discharge** | **One week (7±2 days) Follow- up** | **30- day (30±2 days) Follow- up** |
|---|---|---|---|---|---|
| Study Initiation | X | | | | |
| Demographics/Medical History | X | | | | |
| Physical Examination | X | | | X | X |
| Clinical Status Evaluation | X | | | | X |
| Study Exit | | | | | X |
| Laboratory Tests*: | X | | | | |
| Inclusion / Exclusion Criteria Assessment | X | | | | |
| Informed Consent | X | | | | |
| Randomization and Intent to Treat | | X | | | |
| Endpoints: | | X | X | X | X |
| Adverse Events | | X | X | X | X |
| Incidence and severity of pain | | | X | X | X |
| (NRS) Pain Scale | X | | X | X | X |
| PMD-200 monitor | X | X | X | X | X |

*Only standard of care – no special testing required specific to this study.

### 5.3 Screening and Baseline assessments

Investigators will maintain a screening log that will record the date of informed consent, the date of screening, the enrollment status (enrolled/excluded) and the reason for exclusion for all screen failures.

Within 30 days of a subject's scheduled procedure, obtain a medical history and record the subject's demographic (age, race, sex and date of birth) and baseline information (height, weight, and systolic/diastolic blood pressure). Within 30 days prior to the planned procedure date, obtain serum blood tests per standard of care. These will typically include:

- FBC
- Renal function test
- CRP

Once it has been determined that the subject meets all eligibility criteria, and written informed consent has been obtained, the subject is eligible for randomization.

### 5.4 Study assessments and procedures

This study will be conducted at one site by one surgeon performing 40 total procedures. Study subjects will be prepared for surgery per standard institutional policy and practice. Standard operative procedures will be followed.

If a technical malfunction of the AirSeal® iFS or AirSeal® Access Port was to occur, the surgeon should replace each with the corresponding AirSeal® part. The same replacement practice should be followed for the Stryker PneumoClear insufflator. Switching to the other insufflation system should occur only by necessity.

All ports will be placed according to standard of care (SOC). All clinical decisions will be made per standard institutional practice and policy.

Once pneumoperitoneum has been established and all trocars have been placed, intra-abdominal pressure will be set to the specified values.

Data collection methods are described below.

Postoperative data will be collected regarding incidence and severity of pain, medication use, anesthesia related parameters and length of recovery and hospital stay.

**Surgical Technique**

Standard of Care (SOC)

**Treatment Arm Guidelines:**

The AirSeal Insufflation System should be used as per the procedure in the Instructions for Use (IFU).

To achieve the study goals all patients in all study arms need the following data to be collected intraoperatively using the following methods:

Pre-Operative:

1. Pre-op vitals including height and weight
2. Pre-op labs

Intra-operative:

1. Insufflation Pressure
2. Estimated blood loss
3. Blood transfusion (intra-operative)
4. Procedure time (initial incision to closure)
5. Surgeon-determined need to increase IAP beyond “study pressure”
6. Administration of transversus abdominis plane block
7. Urine output
8. Anesthetic/pain medication administration
9. MedaSense PMD-200 monitor for pain documentation
10. Intraoperative Peak Airway Pressure every 15 minutes
11. Intraoperative End Tidal Carbon Dioxide (ETCO2) every 15 minutes

Post-Operative:

During hospital discharge, all subjects will be evaluated for incidence and severity of pain using a 0-10 numeric rating scale (NRS) and records of medication use and a PMD-200 monitor. These data will be captured in the Case Report Forms.

Recovery room:

1. Time in recovery room
2. Post-op pain incidence and severity (abdominal) NRS
3. Pain medications
4. Post- op labs (CBC, Chem-7) per standard of care
5. Vital signs 24 hr

Discharge:

1. Post-op pain incidence and severity (abdominal) NRS
2. Presence or absence of postoperative nausea or vomiting
3. Pain medications
4. Length of hospital stay
5. Pain Interference and Pain Intensity short form surveys
6. Any complications that were observed. Post-operative complications through 30 days, reported using Clavien-Dindo Classification, including 30-day mortality
7. Return to operating room within 24 hour
8. Readmission to hospital within 30 days

Classification, including 30-day mortality

All Adverse Events (intra-operative and post-operative through 30 days):

1. Adverse Events
2. Serious Adverse Events
3. Anticipated Adverse Device Effects
4. Unanticipated Adverse Device Effects
5 All device deficiencies and use errors, regardless of relationship to an adverse event

### 5.5 Follow-up

Each subject will be enrolled in the study from day of consent until their standard of care 30-day, post-procedure, follow-up appointment. Following this last follow up appointment, the

study will run for a further 12 months in order to follow up on any subsequent adverse events during this time period.

### 5.6 End of study procedures

The sponsor will notify the main REC of the end of a trial within 90 days of its completion. This will be the date of the last visit/data item of the last patient undergoing the trial.

## 6 SAFETY REPORTING

### 6.1 Definitions

#### 6.1.1 Adverse Event (AE)

An adverse event (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Inter-current illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

#### 6.1.2 Serious Adverse Event (SAE)

A serious adverse event is any AE that is:

- Fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

#### 6.1.3 Disease related Events/outcomes NOT qualifying as SAEs

An event which is part of the natural course of the disease under study (i.e., disease progression) should not be reported as an SAE. However, if the progression of the underlying disease is greater than that which would normally be expected for the subject, or if the investigator considers that there was a causal relationship between treatment with study intervention or protocol design/procedures and the disease progression, then it must be reported as an SAE.

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardise the subject, and may require intervention to prevent one of the other serious outcomes noted above.

### 6.1.4 Pre existing conditions

A pre-existing condition is one that is present at the start of the study. A pre-existing condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

At screening, any clinically significant abnormality should be recorded as a pre-existing condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event**.**

## 6.2 Investigator Assessments

### 6.2.1 Seriousness

When an AE/AR occurs the investigator responsible for the care of the patient must first assess whether the event is serious using the definitions given above. If the event is serious and not exempt from expedited reporting, then an SAE form must be completed.

### 6.2.2 Causality

The Investigator must assess the causality of all adverse events in relation to the trial therapy using the definitions in the table below. There are 5 causality categories: unrelated, unlikely, possible, probable and definitely related. If the causality assessment is unrelated or unlikely to be related then for reporting purposes the event will not be regarded as an adverse reaction to trial therapy. If the causality is assessed as possible, probable or definitely related then for reporting purposes the event is classified as an adverse reaction.

**Table 3. Definitions of Causality**

| Relationship | Description |
|---|---|
| Unrelated | There is no evidence of any causal relationship |
| Unlikely | There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial intervention). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment). |
| Possible | There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial intervention). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments). |
| Probable | There is evidence to suggest a causal relationship and the influence of other factors is unlikely. |

| | |
|---|---|
| Definitely | There is clear evidence to suggest a causal relationship |

### 6.2.3 Expectedness

Expected SAEs for the disease and trial intervention should be listed in the protocol. Investigators must file the current version of the Expected Adverse Events list in the safety reporting section of their Investigator File.

### 6.2.4 Grading

Insert relevant grading information including version of CTCAE to be used.

## 6.3 Reporting of AEs and SAEs

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis. Methods to detect the presence of adverse events may take one or more of the following:

- Information volunteered by the patient or carer.
- Open-ended and non-leading verbal questioning of the patient at every visit such as the following: “How are you feeling? Have you had any (other) medical problems since your last visit?”
- Observation by the investigational team, other care providers or relatives.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilisation, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study interventnion or study participation should be recorded and reported immediately.

A serious adverse event must be reported to the study sponsor within 24 hours of the event. A Serious Adverse Event (SAE) form must be completed by the investigator and faxed to the study sponsor within 24 hours. The investigator will keep a copy of this SAE form on file at the study site.

At the time of the initial report, the following information should be provided:

| | |
|---|---|
| • Study identifier<br>• Study Center<br>• Subject number<br>• A description of the event<br>• Date of onset<br>• Current status | • Whether study treatment was discontinued<br>• The reason why the event is classified as serious<br>• Investigator assessment of the association between the event and study treatment |

This should include a copy of the completed Serious Adverse Event form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing serious adverse events should be provided promptly to the study sponsor.

### 6.3.1 Notification Procedure

- The SAE form must be completed by the Investigator (consultant named on the signature list and delegation of responsibilities log who is responsible for the patient's care), with due care being paid to the grading, causality and expectedness of the event as outlined above. In the absence of the responsible investigator the form should be completed and signed by a member of the site trial team.
- All unexpected SAEs not defined in protocol or related documents in ENHT sponsored trials (including non-ENHT patients) must be reported to the R&D Office using the ENHT Adverse Event Report Form and a copy of the local/ trial specific form used for REC/HRA notification.

    - Initial SAE reports must be faxed within one working day of the investigator's knowledge of the event.
    - Follow-up Patients must be followed-up until clinical recovery is complete and laboratory results have returned to normal or baseline, or until the event has stabilised. Follow-up should continue after completion of protocol treatment if necessary. Follow-up information should be noted on a further SAE form by ticking the box marked 'follow-up' as information becomes available. Extra, annotated information and/or copies of test results may be provided separately. The patient must be identified by trial number, date of birth and initials only. The patient's name should not be used on any correspondence.

### 6.3.2 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious adverse events and suspected unexpected serious adverse events.

### 6.3.3 Hospitalisation, Prolonged Hospitalisation or Surgery

Any adverse event that results in hospitalisation or prolonged hospitalisation should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalisation, prolonged hospitalisation, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalisation or prolonged hospitalisation for diagnostic or elective surgical procedures for a pre-existing condition. Surgery should not be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalisation or prolonged hospitalisation required to allow efficacy measurement for the study
- Hospitalisation or prolonged hospitalisation for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

Examples where an AE is NOT to be reported:

- Medical or surgical procedure (e.g., endoscopy, appendectomy). Note, the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied unless more severe than expected for the subject's condition.

### 6.3.4 Post study AEs

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

### 6.3.5 Abnormal Laboratory values

A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. modification of intervention, more frequent follow-up assessments, further diagnostic investigation, etc.

Abnormal laboratory findings (e.g., clinical chemistry, haematology, urinalysis) or other abnormal assessments that are judged by the investigator as clinically significant will be recorded as AEs or SAEs if they meet the definition of an AE or SAE.

Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at Baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject's condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs.

### 6.3.6 Lack of efficacy

When there is a deterioration in the condition for which the study treatment is being used, there may be uncertainty as to whether this is lack of efficacy or an AE. In such cases, unless the reporting physician considers that study treatment contributed to the deterioration or local regulations state to the contrary, the deterioration would be considered a lack of efficacy.

### 6.3.7 New Cancers

The development of a new primary cancer should be regarded as an SAE. New cancers are those that are not the primary reason for the administration of the study treatment and have been identified after the patient's inclusion in this study.

### 6.3.8 Deaths

All deaths that occur during the study, or within the protocol defined follow up period after the administration of the last intervention, must be reported as follows:

- Death clearly the result of disease progression should be reported to the study monitor at the next monitoring visit and should be documented in the CRF but should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of disease under study, the AE causing the death must be reported to the study monitor as an SAE within 24 hours. The report should contain a comment regarding the co-

involvement of progression of disease, if appropriate, and should assign main and contributory causes of death.

- Deaths with an unknown cause should always be reported as an SAE and a post-mortem may be helpful in the assessment of the cause of death.

# 7 STATISTICS AND DATA ANALYSIS

## 7.1 Sample Size determination

Sample size estimation is performed conservatively assuming a single measurement per subject for the primary endpoint of pain assessed by a 0-10 NRS. With multiple measurements for some subjects, the actual power should be slightly higher. Based on pilot data, a true 1-point reduction in mean abdominal pain NRS is assumed for AIS as compared to CIS; the common standard deviation is estimated to be 2.6. With 40 evaluable subjects, 20 for each treatment arm, the power for observing a statistically significant AIS benefit (i.e. 2-sided $p<0.05$ by t test) is approximately 0.85.

Please note that the findings from this study will inform future, larger scale, multi-center trials into this topic.

## 7.2 Statistic Methods

Data Analysis Plan
The data analysis plan has been planned in order to conform to best current statistical practice and the reporting of analyses in accordance with the relevant sections of the CONSORT 2010 Statement and Checklist (Schulz et al., 2010). It is anticipated that it will also enable reporting to conform to the updated CONSORT 2024 Statement (when that is released) or will be enhanced in response to it. Analysis will be on a “per protocol” basis as departures from the randomised allocation (which will be fully reported) are not a matter of participant adherence to study protocol.

Descriptive Statistics
Summary statistics regarding the conduct of the trial will be presented, including the numbers of participants randomly assigned, drop-outs and exclusions, separately for each arm of the trial, along with dates of recruitment and follow-up.

Baseline demographic and relevant clinical characteristics will be presented for participants in each arm of the trial. The number of participants in each group in subsequent analyses will be given, along with details of any changes of groups that might have occurred since the original assignments.

Primary Outcomes
The primary effectiveness outcome is the pain associated with use of the two insufflator devices. Pain will be measured during and immediately after surgery in the recovery room and then by 6-hour increments, measured by a 0 – 10 Numeric Rating Scale (NRS) and a PMD-200 nociception monitor.

Summary descriptive statistics for these outcomes will be given for each arm of the trial and modelling undertaken, as described below. Confidence intervals and both absolute and relative effect sizes will be reported where appropriate.

For the measure of pain obtained using the PMD-200 nociception monitor, longitudinal analysis of covariance will be used as the method of analysis. Incorporation of a baseline measure into the analysis will be undertaken in accordance with the recommendations contained in Twisk et al. (2018), including the use of a random effect to allow for the correlation between the baseline and non-baseline measurements at the individual level. Random effects will also be included to allow for different surgeons undertaking operations.
For the NRS, it is the intention to again used longitudinal analysis of covariance with the pain measure as a continuous variable. However, if the distribution of the pain measure is such that it is more appropriate to treat it as an ordinal categorical variable, then the analysis will take that approach.

For both analyses, adjustment for differences between the two arms of the trial will be undertaken by the inclusion of potential confounding covariates.
For testing of significance, the residuals of the fitted models will be examined to assess the reasonableness of assumptions. In the event of assumptions being untenable, robust methods such as bootstrapping will be used.

Secondary Outcomes
Secondary measures relate to the procedure being undertaken (e.g. procedure time, number of times insufflator settings adjusted) and post-operative measures (e.g. length of recovery room stay, length of hospital stay, severity of postoperative nausea/vomiting).
Summary descriptive statistics for these outcomes will be given for each arm of the trial and modelling undertaken, as described below. Confidence intervals and both absolute and relative effect sizes will be reported where appropriate.

For variables which can be regarded as continuous in nature, analysis of covariance will be carried out, including the use of a random effect to allow for different surgeons undertaking operations. Adjustment for differences between the two arms of the trial will be undertaken by the inclusion of potential confounding covariates.

While some secondary outcomes (e.g. procedure time) may clearly be regarded as continuous, it will be necessary to explore the distribution of others (e.g. length of recovery room stay, length of hospital stay) to ascertain whether it might be more appropriate to derive ordered categorical variables and analyse these. In this case, the analysis of covariance will again be used, employing methods suitable for an ordered category response.

Secondary measures which are counts (e.g. number of times insufflator settings adjusted) will be analysed using methods for count data, with these methods being chosen in a manner recommended by Jakobsen et al. (2015).

For testing of significance, the residuals of the fitted models will be examined to assess the reasonableness of assumptions. In the event of assumptions being untenable, robust methods such as bootstrapping will be used.

Other variables which are categorical in nature will be analysed using methods appropriate to the variables under consideration, such as chi-square tests and/or exact tests.

Ancillary analyses
Where ancillary analyses of undertaken of other outcomes or where subgroups are analysed, it will be made clear that these are not pre-specified. The rationale for undertaking these analyses will be given.

Software
It is anticipated that R statistical software will be used to undertake the analyses for the trial. The individual R packages and version numbers that are used for analyses will be reported.

Departures from protocol, exclusions and serious adverse events
Any departures from protocol which occur will be fully reported, as will the reasons for any exclusion of participants and any serious adverse events.

# 8 DATA HANDLING AND RECORD KEEPING

## 8.1 Confidentiality

Confidentiality of subjects will be maintained throughout the Study. A unique identification code will be assigned to each subject participating in this Study. Any data that may be published in abstracts, scientific journals, or presented at medical meetings will reference a unique subject code and will not reveal the subject's identity. The Sponsor or their representative will make every reasonable effort to protect the confidentiality of the subjects participating in the Study.

The trial protocol will be applied to ensure there is no breach of any duty of confidentiality owed to patients, service users or any other person in the process of identifying potential participant as per the Good Clinical Practice (GCP) guidelines. All physical patient data will be stored securely in lockers in the research office at Lister hospital, Stevenage. All electronic data will be stored securely on password protected and encrypted NHS Trust computers or a secure University of Hertfordshire database with password protection and prior pseudoanonymisation. All data processed will be done my members of the research department who are up to date with their GCP training.

## 8.2 Source Documents

The Principal Investigator must maintain detailed source documents on all Study subjects who are enrolled in the Study or who undergo screening. Source documents include subject medical records, hospital charts, clinic charts, Investigator's subject Study files, as well as the results of diagnostic tests (e.g., laboratory tests).
The following minimum information should be recorded in the subject's medical records:

- The date the subject entered the Study and the subject number
- The Study protocol number and the name of the Sponsor
- The date that informed consent was obtained
- Evidence that the subject meets Study eligibility requirements (e.g., medical history, Study procedures and/or evaluations)
- The dates of all Study related subject visits

- Evidence that required procedures and/or evaluations were completed
- Use of any concurrent medications
- Documentation of specific device used, if any
- Occurrence and status of any Adverse Events
- The date the subject exited the Study, and a notation as to whether the subject completed the Study or was discontinued, including the reason for discontinuation.

### 8.3 Case Report Form

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write “ND”. If the item is not applicable to the individual case, write “NA”. All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

### 8.4 Data handling and record keeping

Standard security for secure storage of data on NHS computer network. Anonymised paper and manual files are safely stored in a locked office within Research Offices in the research Department. Electronic records of anonymised participants will be safely stored in designated NHS computers. These will be password protected. The database will be created and maintained by the University of Hertfordshire but access to data in the database is restricted by role and only those who are required to have access to personal data (i.e. the clinical research team) will be able to see it. Access to the database will require individual logins and access to specific data in the database is restricted by role.
After the study duration, all paper records will be sent for storage to archive in line with the Trust Research SOPs. This research data will be held by the Health Records Department at East and North Hertfordshire NHS Trust. As per Trust policy, data relating to patients involved in clinical trials will be stored for 5 years before being disposed of. Further information relating to the storage of research data can be found in the East and North Hertfordshire NHS Trust's policy on Health Records Management.
Electronic archiving of study documents and the study database will be initiated by the CI no earlier than one year after publication of the study. Identifiable information will be removed from the study database before archiving. The electronic archive will be stored on secure servers at the University of Hertfordshire

### 8.5 Records Retention

- Archiving for this study will be carried out according to gSOP-17
- Destruction of essential documents will require authorisation from the Sponsor
- Archiving will be authorised by the Sponsor following submission of the end of study report

- all essential documents will be archived for 5 years after completion of trial.

# 9 STUDY MONITORING, AUDITING AND INSPECTING

## 9.1 Study Monitoring Plan

This study will be monitored according to the monitoring plan. The investigator will allocate adequate time for such monitoring activities.

The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities and has adequate space to conduct the monitoring visit.

The monitoring plan will depend on the type of trial and the Sponsor will be provide some monitoring assistance as detailed in gSOP-12, but it is important that the Investigator ensures that the data in relation to this study is accurate and verifiable and that patient safety is maintained throughout the trial duration regardless of sponsor monitoring activities.

## 9.2 Auditing and Inspecting

The investigator will permit study-related audits, and inspections by the IEC, the sponsor, government regulatory bodies, and R&D Compliance and Quality Assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. diagnostic laboratory)

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and R&D Compliance and Sponsor Quality Assurance offices.

## 9.6 Source Data Verification

Source Documents are original documents, data and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, x-rays, subject files and records kept at the pharmacy, recorded data from automated instruments etc.). Source Data is considered all information in original records and certified copies of clinical findings, observations, or other activities in the trial. Source Data are contained in Source Documents (original records or certified copies).

The following items must be available for Source Data Verification (SDV) in source documents other than the CRF:

- Date of conducting Informed Consent
- Gender
- Statement that the patient is participating in the /study
- Data for evaluation of eligibility criteria
- Relevant medical history and diagnosis

- Screening Number and Patient Number
- Administration of study intervention
- All study visit dates
- Adverse Events or absence of Adverse Events
- Concomitant Therapy including changes (if applicable)
- Date and reason for exclusion or withdrawal (if applicable)

Source data verification should be performed before the statistical database is cleaned and then locked for analysis.

## 10. REGULATORY OBLIGATIONS AND COMPLIANCE

This study is to be conducted according to EU and international standards of Good Clinical Practice and International Conference on Harmonisation guidelines, applicable government regulations and Ethics policies and procedures.

This protocol and any amendments will be submitted to a properly constituted Independent Ethics Committee (IEC), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IEC concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of IEC members and their affiliate to the sponsor.

Before any site can enroll patients into the trial, the Chief Investigator/Principal Investigator or designee will apply for NHS confirmation of capacity and capability from the site's Research & Development (R&D) department.

### 10.1 Protocol compliance

- Prospective, planned deviations or waivers to the protocol are not allowed and must not be used e.g. it is not acceptable to enroll a subject if they do not meet the eligibility criteria or restrictions specified in the trial protocol
- Accidental protocol deviations can happen at any time. They must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately.
- Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

### 10.2 Notification of Serious Breaches to GCP and/or the protocol

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

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

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

## 11. STUDY FINANCES

### 11.1 Funding Source

£100,000 funding from ConMed Corporations, 6455 S. Yosemite St. Suite 800, Greenwood Village, Colorado, 80111.

### 11.2 Conflict

ConMed Corporation is funding this study and manufactures the AirSeal Insufflator, however, none of the study investigators have any conflicts of interest in the trial.

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study.

## 12. INDEMNITY

NHS indemnity scheme will apply as this is a NHS sponsored study.

## 11. PUBLICATION PLAN

Confidentiality of subjects will be maintained throughout the Study. Any data that may be published in abstracts, scientific journals, or presented at medical meetings will reference a unique subject code and will not reveal the subject's identity. The Sponsor or their representative will make every reasonable effort to protect the confidentiality of the subjects participating in the Study.
Following cessation of the trial, the results will be published and also distributed to those trial participants who wished to receive ongoing information and results from the trial.

## APPENDICES

**Appendix 1 - Patient Information Leaflet, V1.0 09.09.2024**

**Appendix 2 - Informed Consent Form V1.0 09.09.2024**

**Appendix 3 – GP Letter V1.0 09.09.2024**

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