Title	Evaluation of Seismofit® as a tool for assessing fitness and predicting outcomes in Oesophageal cancer surgery **SEISMIC** study (**SEISM**ocardiography **I**n oesophageal **C**ancer)
Authors	*Kesav Aditya, Mr Andrew Davies*
Protocol Reference:	
Version Number & Date:	Version: 1.0 Date: 08/04/2025
Effective Date:	
IRAS Number:	342434
Superseded Version Number & Date *(If applicable)*	N/A
Sponsor	Guy's & St Thomas' NHSFT
Chief Investigator	Mr Andrew Davies BSc, MBChB, MSc, MD, FRCS
Site Principal Investigators	Prof Tim Underwood / Prof Denny Levett (Southampton) Mr Pritam Singh (Guildford) Mr Rob Walker (Guildford) Mr Sach Kumar (RMH), Dr Don Milliken (RMH)
Keywords	Seismocardiography, SCG, Cardiorespiratory fitness, Cardiopulmonary Exercise testing, CPET, surgery, Oesophageal cancer, complications

Contents

Trial Summary in Lay English

Cancer affecting the Oesophagus is a common cause of cancer-related deaths around the world. Treatment of this involves a combination of chemotherapy and surgery to remove the Oesophagus. There are a lot of risks associated with this treatment; therefore, it's important to make sure patients are fit for this pathway and to see which patients will have higher risks compared to others. Cardiopulmonary exercise Testing, or CPET for short, is the most detailed and accurate test in predicting how fit someone is, and we can use these fitness markers to see which patients will have higher treatment-related risks. However, CPET is difficult to use because it takes a long time, has extra clinic appointments in an already busy treatment schedule, is expensive, and requires a trained exercise physiologist to run the test. In this study, we are trying to see if a new device smaller than a modern smartphone can be used to give an accurate estimate of patient fitness and if this device can also predict treatment-related complications.

Background

Oesophageal cancer is the 8th most common cause of cancer and the 6th leading cause of cancer-related deaths worldwide(West et al., 2016; Liu et al., 2023). Surgery with curative intent has been associated with significant morbidity and mortality despite recent advancements in anaesthesia and surgical techniques(Wu et al., 2014). Good patient selection with optimisation of cardiorespiratory fitness (CRF) is essential to improve surgical outcomes(West et al., 2014; Ozova et al., 2022). This is particularly important given that most oesophageal cancer patients undergo neo-adjuvant treatment (e.g. chemotherapy), which is known to have a significant adverse effect on patient fitness before surgery (mean reduction of 12.1% in VO2Peak) (Jack et al., 2014). A lower baseline level of fitness has also been shown to be associated with morbidity and mortality in patients undergoing treatment with curative intent (Hennis et al., 2011; West et al., 2024). Prehabilitation is now considered the standard of care in oesophageal cancer surgery, with societal guidance recently recommending a baseline fitness assessment to tailor the intervention as well as a means of monitoring response (Walker et al., 2024).

Cardiopulmonary Exercise Testing (CPET) is considered the gold standard in measuring the CRF of an individual by obtaining the maximal volume of oxygen consumed (VO2Peak) in samples of expired gas during a graded effort cycle ergometer test (Krogh et al., 2020; Levett et al., 2018a). However, CPET is a resource-intensive, costly, time-consuming test (requiring up to 60 minutes) and creates a significant time burden on patients with already busy treatment schedules. In a UK survey of prehabilitation practice, 50% of Upper Gastrointestinal (UGI) units used CPET at baseline, with only 80% of these (40% total) using CPET for response assessment (Barman et al. 2024 in revision for publication Annals RCS Eng).

Seismofit® is a device that accurately estimates the VO2Peak using machine learning algorithms incorporating seismocardiography (SCG) and patient parameters such as height, weight, age, and gender. SCG is a process by which vibrations generated by the heart during its regular physiological cycles are characterised and mapped for changes in morphology, frequency, intensity and character(Sørensen et al., 2018). Key advantages of Seismofit® include its inter-test reliability, rapid availability of results (i.e., estimation of fitness in under 3 minutes in an outpatient setting), and accurate estimation of fitness in a resting patient (Hansen et al., 2023a). The accuracy of Seismofit® in comparison to CPET-measured CRF has previously been demonstrated with a Mean Absolute Percentage Error (MAPE) of 12.3% in healthy adult

populations(Hansen et al., 2023b). However, there is minimal data on cancer patients, and no studies have correlated VO2Peak generated by Seismofit® to clinical outcomes.

Given the potential benefits of Seismofit® over CPET, this study will investigate its validity in a clinical setting across four major Oesophageal cancer resection centres (Guy's and St Thomas NHS Foundation Trust (GSTT), University Hospitals Southampton (UHS), Royal Marsden NHS Foundation Trust (RM) and Royal Surrey NHS Foundation Trust (RS).

This will be the first study to evaluate the use of Seismofit® in a large volume of oesophageal cancer patients. With correlation to clinical outcomes, this study will serve as the basis for future research into the use of Seismofit® in a clinical setting.

Study Setting

The study will be conducted between the four hospitals, which are centralised regional Oesophageal cancer resection centres in the United Kingdom.

- Guys and St Thomas (GSTT)
- Royal Marsden NHS Foundation Trust (RMH)
- Royal Surrey NHS Foundation Trust (RS)
- University Hospital Southampton (UHS)

Recruitment of patients will occur at the first point of contact of patients to the cancer surgery clinic. The total duration of the study recruitment will be 24 months, with an expected start date in May 2025, following completion of the ethical approval process. The enrolment period will be completed once 164 patients with complete records are identified for analysis.

An initiation visit for each enrolled site will be conducted, and a documented report on the site leads, including their signatures, functions, and authorizations within this study, will be generated. This report will outline the agreements between the sponsor and the investigation site, as well as the responsibilities of each party at the clinical investigation site.

Site teams will also be provided with the following:

- Protocol
- Investigators Brochure (IB) for the Seismofit® Devices(Confidentiality, 2011)
- Device Instructions for use Manual (Ventriject, n.d.)
- Research Electronic Data Capture (REDCap) Access for the research team
- Patient consent form templates
- Instructions for use on the Seismofit® devices
- A copy of the agreements in place.

Description of the Device Being Studied

Seismofit® is a 3 x 5 x 1.5 cm Class I medical device manufactured by Ventriject, which utilizes SCG principles and machine learning to estimate an individual's fitness. It is affixed to a patient's sternum with an adhesive patch. It measures the amplitude and timing of vibrations on the chest using accelerometers. The device then averages the data collected over 45 seconds to create the SCG. From the SCG, several maxima and minima (fiducial points) are identified, which correlate to the opening and closing of the mitral and aortic valves.

Features of the SCG, including the timing, frequency, amplitude, and variability of these points, are then incorporated into an algorithm that also considers patient height, weight, age, and sex to calculate the VO2 peak.

Data is transmitted via Bluetooth to an allocated smartphone. The entire process, including data acquisition and transmission, takes around three minutes, displaying a VO2 peak estimate on the smartphone app.

Rationale

This pioneering study will mark the first evaluation of Seismofit® estimated VO2peak in a clinical setting. Oesophageal cancer patients, a group typically considered fit for surgery, will be the focus. They are generally homogeneous and capable of withstanding the physiological strain of NAC and single lung ventilation during the cancer resection operation.

Seismofit®, as demonstrated in previous studies, is accurate and carries no risk when used on healthy patients. It provides results in under 3 minutes and is user-friendly, unlike CPET, which takes over 30 minutes per assessment and necessitates the presence of a trained physiologist. Therefore, in a clinical setting, we aim to assess the utility of Seismofit® in the Oesophageal cancer patient population and explore the association between Seismofit® estimated VO2Peak and clinical outcomes.

Research Question/Aim(s)

The primary hypothesis is that Seismofit®-estimated VO2peak and trends in VO2Peak measured throughout the treatment period would be associated with clinically meaningful outcomes, such as the postoperative rate of pneumonia, overall complications (as defined by the Clavien-Dindo classification), and hospital length of stay (LOS).

Secondary hypotheses are that Seismofit®-estimated VO2peak will be associated with CPET with a <15% mean absolute percentage error (MAPE) and will identify the same patients in the lowest quartile of fitness as CPET. Furthermore, Seismofit® estimated VO2peak will correlate with other clinical parameters such as chemotherapy completion, chemotherapy complications and tolerability, anastomotic leak and ITU LOS.

Study Outcomes

Primary outcome

1. Seismofit® estimated VO2Peak and trends in estimated VO2Peak through the treatment period are correlated with:
    a. Rate of pneumonia as defined by the Esophageal Complications Consensus Group criteria (ECCG).
    b. Overall rate of complications as defined by the Clavien-Dindo classification
    c. Hospital LOS

Secondary Outcomes

1. Seismofit® estimated VO2Peak reading accuracy compared to “gold standard” CPET measured VO2Peak.

2. Accuracy of Seismofit® compared to CPET in identifying patients in the lower quartile of fitness.
3. Other clinical outcomes
    a. Chemotherapy compliance & tolerability – completion of all prescribed cycles, dose reductions, and complications as defined by the Common Terminology Criteria for Adverse Events (CTCAE) version 5 published by the National Institute for Health, National Cancer Institute.
    b. ITU length of stay (and re-admission)
    c. Anastomotic leak rates
4. Assessment of clinical outcomes related to CPET-measured fitness (VO2Peak)
    a. Rate of pneumonia as defined by the ECCG
    b. Overall rate of complications as defined by the Clavien-Dindo classification
    c. Hospital length of stay.

Study Design and Methods of data collection and analysis.

This post-market observational cohort clinical study will assess the association of Seismofit® estimated fitness to clinical outcomes. All patients presenting to the pre-operative assessment clinic will be screened and offered enrolment if they meet the inclusion criteria defined in this protocol's sampling and recruitment section.

CPET is routinely performed at RMH, RS and UHS; however, it is not performed as part of routine pre-operative assessment at GSTT. Therefore, CPET-measured pre-treatment fitness (and post-treatment where performed) will be undertaken only in centres where it is the current standard of care. This minimises changes to the current diagnostic and staging protocols at each centre. Seismofit® estimations of fitness will be the only added assessment in the patient's treatment pathway during this study. Clinicians will be blinded to the results of the Seismofit® VO2peak readings, i.e. these will not contribute in any way to decision-making.

Morbidity outcomes will be measured throughout the study period with overall complications standardised by the Clavien-Dindo classification and specific complications as outlined by the Esophagectomy Complications Consensus Group (ECCG). These will include:

- **Pulmonary** – Pneumonia, atelectasis due to mucous plugging requiring bronchoscopy, respiratory failure requiring re-intubation, acute respiratory distress syndrome, tracheobronchial injury.
- **Cardiac** – Perioperative myocardial infarction, development of cardiac arrhythmia requiring interventions, pericarditis requiring treatment.
- **Gastrointestinal** – Anastomotic leakage, conduit necrosis/failure, ileus, small bowel obstruction, C.Difficile infection, gastrointestinal bleeding requiring intervention, pancreatitis and liver dysfunction.
- **Renal** – Development of AKI/Renal failure and stage
- **Thromboembolic** – DVT, PE, stroke
- **Multi-organ dysfunction**

Seismofit® Measurement

Patients will be asked to confirm whether they have participated in any strenuous exercise 10 minutes before the Seismofit® reading. If they indicate yes, Seismofit® readings will be delayed until 10 minutes have passed.

The device will be placed on the lower part of the patient's sternum with an adhesive pad. The patient's height, age, weight and sex will be entered into the smartphone app. The patient will be requested to lie still in the supine position whilst the device takes SCG measurements and gives an estimate of the VO2Peak within three minutes.

Seismofit® readings will be taken at various stages of a patients' clinical course, outlined below:

1. Baseline (initial surgical clinic once eligibility / planned treatment established)
2. Post NAC (within three weeks of completing NAC)
3. Pre-surgery (within three weeks before surgery)
4. Post Operative Day (POD) 1, 3, and 7 (or at discharge if sooner)
5. First clinic visits after discharge from hospital (within three weeks of discharge).

The algorithm used to estimate VO2Peak is the proprietary intellectual property of Ventriject. The most up-to-date version of the algorithm at the time of the study's commencement will be used in all estimations from commencement to trial completion.

However, the estimation algorithm is assumed to improve with the data pool generated in this trial. Post-hoc repeat fitness estimates will be generated from all anonymised patients if an updated version of the algorithm becomes available through trial.

Training Requirements for the Use of Seismofit®

Training for the Seismofit® devices at each research site will be conducted during the initiation visit.

The use of the device will be demonstrated to all research staff involved in the study. The documented report at the end of the initiation visit will outline the completion of all relevant training.

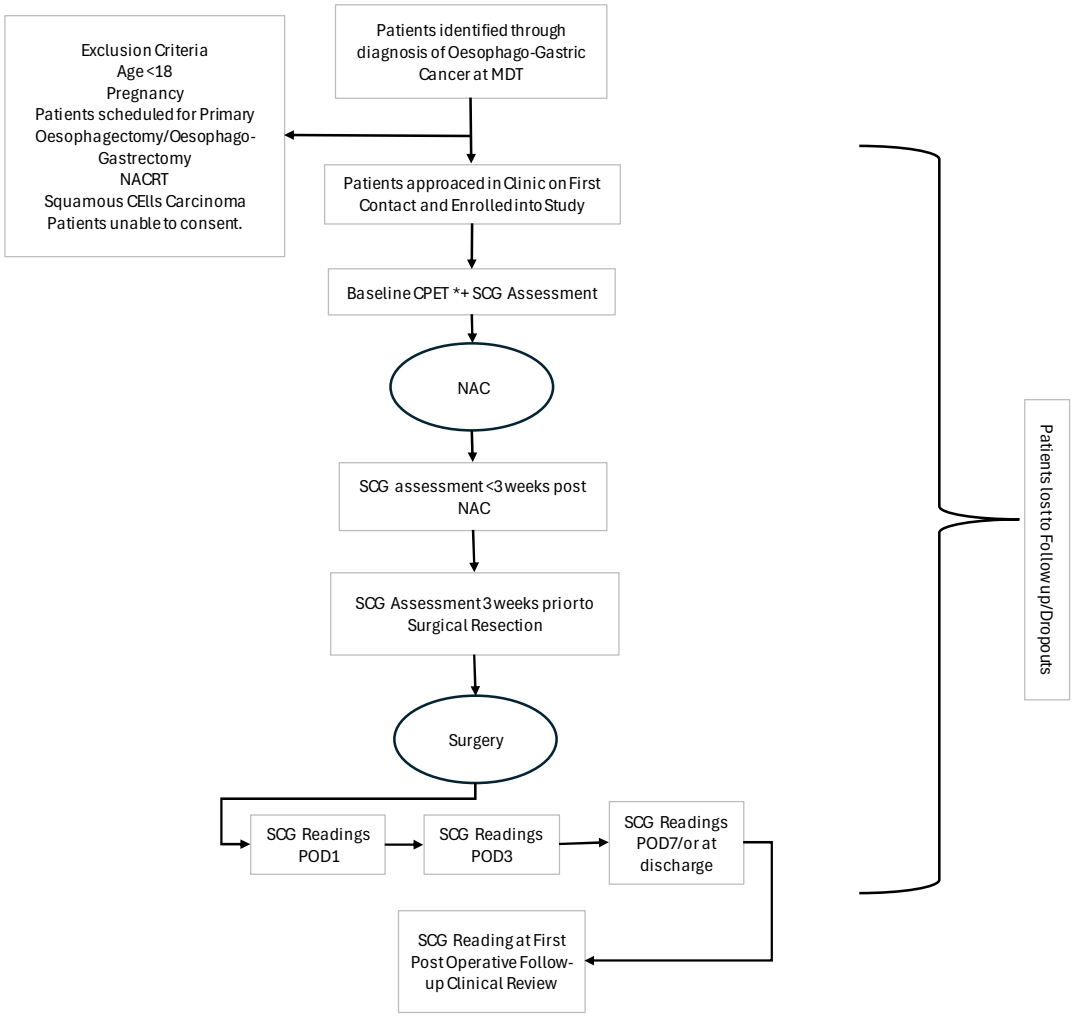
Allocation of Treatment

All patients included in the trial will have Seismofit® at the described time points. Subject participation in the study will commence with enrolment in the trial and conclude at the time of the final Seismofit® reading (post-operative clinic), approximately 6 months later.

Blinding

Seismofit® measurements will be performed by research staff trained in the use of the device, who will not be involved in the clinical decision-making process for patient management. This will ensure that the patient's clinical management is not biased by the measurements generated by the Seismofit® device.

Study Summary Flow Chart



*CPET measurements and results are taken where they are part of the patient's standardised pathways.

Data Collection and Handling

The following data points will be collected from the enrolled patients:

- **Patient Demographics** required in the current version of the estimation algorithm
  - Age
  - Sex
  - Height
  - Weight – This must be repeated at each point the Seismofit® readings are taken.
  - BMI- This must be repeated at each point the Seismofit® readings are taken.
- **American Society of Anaesthesiologists (ASA) Grade at surgery**
- **Performance status**
- **Charlson Co-morbidity index**
- **Existing Co-morbidities of patients**

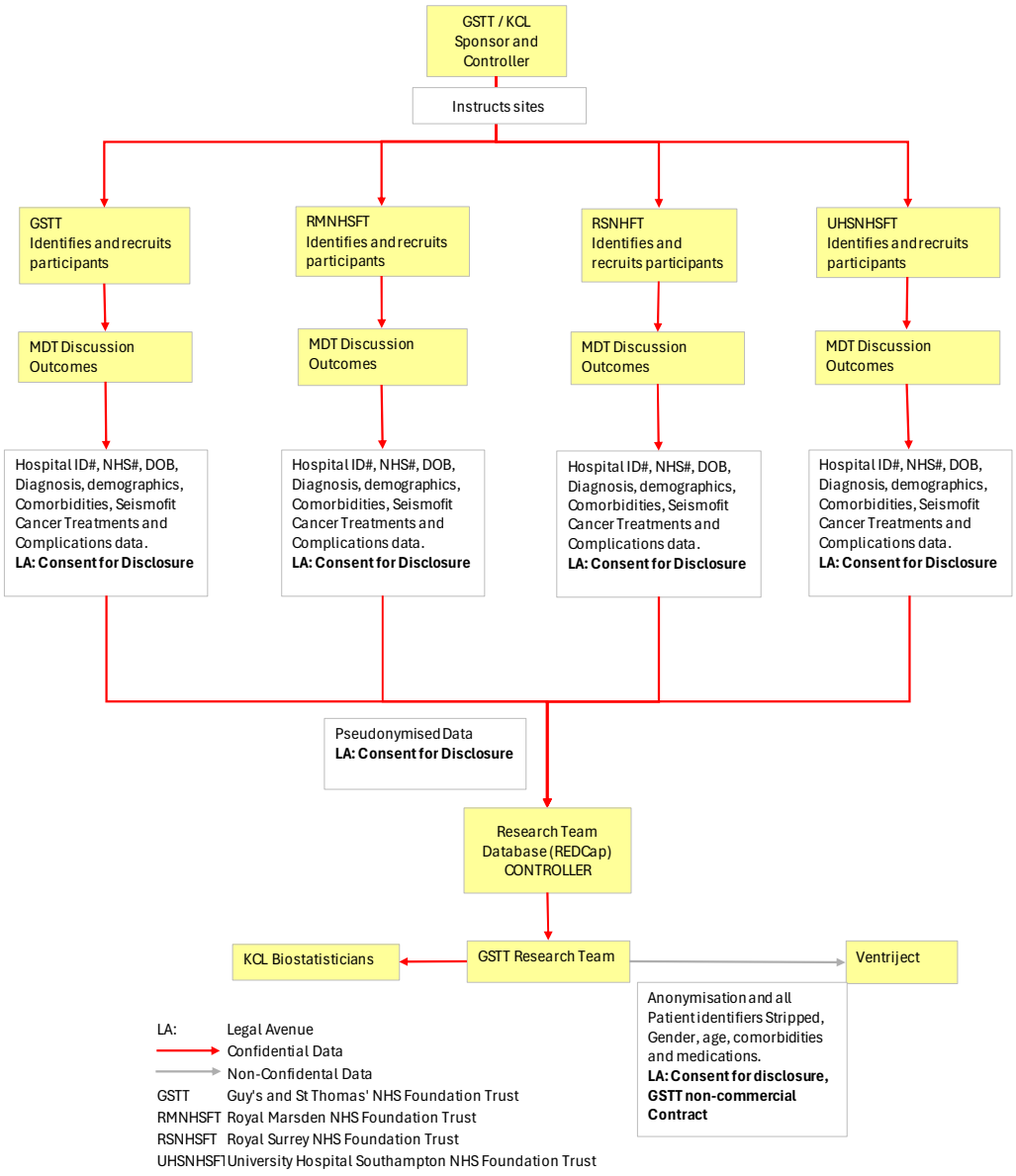
  - **Cardiac** – The presence of any Arrhythmia, cardio-selective anti-arrhythmic medications use, Hypertension, and ejection fraction on baseline echocardiography reports will be recorded.
  - **Respiratory** – The presence of asthma / COPD / Interstitial Lung Diseases will be recorded.
  - **Renal** – The presence of any pre-existing chronic kidney diseases and Baseline eGFR at the time of enrolment will be recorded.
  - **Endocrine** – The presence of any hormonal supplements taken, or any pre-existing conditions being treated will be recorded.
  - **GastroIntestinal** – Previous operative history, any known diagnosis of inflammatory bowel diseases or other known diagnoses at baseline will be recorded.
- **Smoking status**
- **Medications**
  - **Use of Diuretics** - Class of Diuretics (Generic name) and dose
  - **Use of Anti-Hypertensives** – Class of Anti-Hypertensive (Generic name) and dose
  - **Use of any Anti-Arrhythmic Medication** – Class of Antiarrhythmic (Generic name) and Dose
- **Cancer Type**
- **Tumour ypTNM Staging**
- **Details on any NAC received (cycles)**
- **Complications during NAC - Chemotherapy compliance & tolerability**:
  - Completion of all prescribed cycles
  - Dose reductions
  - Complications as defined by the Common Terminology Criteria for Adverse Events (CTCAE) version 5 published by the National Institute for Health, National Cancer Institute
- **Seismofit® Estimated VO2Peak**
- **Haemoglobin (Hgb) Values** - Most up-to-date Haemoglobin reading at each Seismofit® Reading.
- **CPET Measured Variables** – VO2Peak, VO2 AT, Maximum Work (in Watts), Maximum HR achieved during the test and Respiratory Equivalent Ratio (RER)
- **Type of surgery** (Open/hybrid / MIO / Robotic AND Ivor Lewis / Transhiatal / Left thoracoabdominal / 3 stage)
- Record any complications experienced by the patients as standardised by ECCG criteria
- **Clavien-Dindo complications**
- **ITU LOS / readmission**
- **Hospital LOS**

Research Electronic Data Capture (REDCap) database framework will be established to collect data across the four research sites. This method of data retrieval and acquisition was selected for the various advantages of:

- **Data Security** – REDCap is a locally hosted database framework at Kings College London, with secure web authentication, data logging and Secure Sockets Layer Encryption.

- **Ease of distribution and access control** – Access to all designated research personnel with specific rights can be granted to users within the research team, creating an added layer of data security for compliance with ethical and institutional review.
- **Data Validation** - Customisation of the database with auto-validation can be established for data quality rules at the set-up of the database.

Data Flow Diagram



Patient Follow-Up

As this device is non-invasive and there are no changes made to the clinical management of the patient with all patients receiving standard of care, patients will not be followed up for trial purposes only.

Source Data and Documents

Source data is "All information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation. Source data are contained in source documents (original records or certified copies)." [ICH E6 section 1.51]

Source documents are defined as "Original documents, data and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries of evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial)." [ICH E6 1.52]

The electronic patient record will serve as source data for all other data items collected for the study.

Sampling and Recruitment

Inclusion Criteria

- Age >=18
- Diagnosis of Oesophageal cancer (T0-4 N0-3 M0, Oesophageal / Gastro-Oesophageal Junction (GOJ) type 1-2 adenocarcinoma
- Patients being considered for curative treatment (i.e. due to undergo NAC and Oesophagectomy / Oesophago-Gastrectomy [open / MIO / hybrid / robotic])
- Patients able to give informed consent

Exclusion Criteria

- Pregnant patients.
- Patients under the age of 18.
- Patients undergoing primary Oesophagectomy +/- Oesophago-Gastrectomy with no neoadjuvant therapy.
- Patients undergoing Neoadjuvant chemoradiotherapy.
- Patient’s being treated with curative intent for Oesophageal Squamous cell carcinoma
- Patients that are deemed not fit or suitable for Oesophagogastric cancer resection as part of a Multi-Disciplinary Team meeting decision.
- Patients with implanted devices such as pacemakers or cardioverter-defibrillators.

Withdrawal Criteria

Patients have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the clinician or at the institution. Withdrawal of consent for the study will be documented in the patient’s medical records, and the sponsor team will be notified as soon as possible. A patient may withdraw from future measurements but still be included based on measurements already taken, provided they have not withdrawn their consent for this as well.

Consent

The Principal Investigator (PI) or an appropriately delegated individual should discuss the trial with potentially eligible patients, describing the purpose, alternatives, research objectives, potential risks, and follow-up requirements of the study.

Patients will be provided with a Research Ethics Committee-approved Patient Information Sheet (PIS) and given sufficient time to consider participation in the study and ask any questions. Written informed consent will be obtained from all patients who participate in the trial. This will be obtained before any data is uploaded to REDCap or Seismofit® measurements are performed.

Sampling

Size of Sample Rationale

Sample size calculations were performed with a power of 80% and a significance level of 0.05 (two-sided) for all outcomes.

The sample size calculations were performed for **two primary outcomes**:

1. **Rate of Pneumonia Development**: To detect a 20% difference between a group of "fit" patients and a group of "less fit" patients (defined by the median value) at the predetermined power and significance, 82 patients will be required in each arm, totalling 164.
2. **Hospital LOS**: To detect a difference in mean hospital length of stay of 2 days, with a standard deviation of 4 days, between a "fit" group compared to a "less fit" group of patients at the defined power and significance, 64 patients will be required in each arm (total 128, satisfied by numbers above).

Sample size calculation was also performed for the secondary outcome:

1. **Association of Seismofit® estimated VO2Peak to gold standard CPET measured VO2Peak**: To detect a mean difference of 15% (with a SD of 5.62), where the reference CPET measured VO2Peak is 23.84ml/kg/min, 22 patients will be required.

Given the above power calculations, this study aims to recruit 164 patients over 24 months across the four research sites.

Statistics

Statistical analysis of data will be performed with the support of a dedicated GSTT/KCL medical statistician.

Descriptive statistics will be carried out to summarise patient characteristics. Continuous variables will be presented as either mean or median as appropriate. The distribution of continuous variables will be investigated using histograms with patient stratification based on their fitness level in VO2Peak where appropriate. Categorical variables will be presented as a frequency (%).

The Shapiro-Wilk test or an equivalent appropriate statistical model will be used to determine whether VO2Peak fitness measurements follow a normal distribution. The difference in the means of Seismofit®-estimated VO2Peak in the rate of pneumonia development between a cohort of fit and less fit (determined by the median value) patients will form the primary analysis

for clinical outcomes. Repeated measures analysis of variance will be used to determine the significance of changes in Seismofit® estimated VO2Peak measured across the treatment period in association with clinical outcomes (i.e. rate of post-operative pneumonia). Box and whisker plots will depict the relationship to overall complications as defined by Clavien-Dindo classification to Seismofit® estimated VO2Peak. Where possible, regression analysis will be performed for hospital length of stay to Seismofit® estimated VO2Peak.

Association of Seismofit® estimated fitness to gold standard CPET will be determined with a MAPE and graphically represented by Bland Altmann plots. Development of chemotherapy and operative complications (e.g. anastomotic leaks, respiratory failure, cardiac arrhythmia) will be compared using multivariable logistic regression providing odds ratios and 95% confidence intervals.

Recruitment

Screening

Prospective patients will be identified in multidisciplinary team discussions at each research site. All patients meeting the inclusion/exclusion criteria will be approached at the first clinical contact outpatient appointment for study enrollment.

Ethical, Regulatory Considerations and Trial Registration

The trial will be run in compliance with the Helsinki Declaration. CPET is a safe investigation, widely established in cancer patients, including in those with co-morbidities.(Levett et al., 2018b) Both CPET and Seismofit® are considered feasible and safe for patients undergoing cancer treatment. CPET will not be performed for research purposes only. Seismofit® estimated fitness will also not be used to influence any clinical decisions during this study.

Seismofit® measurements will be taken during routine clinical visits, thus sparing the patients from additional travel to the hospital. Postoperative Seismofit® measurements will be taken at the most convenient time for the patient, respecting their dignity and comfort during the post-operative recovery.

All data entered into REDCap will follow local and approved ethical standards of patient confidentiality. Data validation rules will be established on the REDCap framework per local and national protocols, ensuring the highest accuracy and reliability. Before statistical data analysis, all variables will be checked for missing, improbable and impossible values to be judged on clinical opinion. Missing values will be noted but will not mandate patient exclusion or withdrawal of previously collected data provided patient consent has not been withdrawn.

All software to be used to assist in the analysis of the data will be listed in updated versions of this protocol.

Research Ethics Committee and Other Regulatory Review and Reports

This study will not commence until written approval/favourable opinion has been obtained from the Regulatory Ethics Committee (REC) support through the Integrated Research Application System (IRAS).

- **Integrated Research Application System (IRAS) Ethics Code – ID 342434 –** Currently in the IRAS registration and approval process.

- GSTT Sponsorship Approval
- GSTT Gastrointestinal Medicine and Surgery Study Greenlight Approval
- Local GSTT, UHS, RM, RS Registration

The chief investigator will produce an annual progress report, which will be submitted to the REC. This will be submitted within thirty days of the anniversary date of a favourable opinion annually until the study is declared ended.

For any amendment to the study, the research student/designee, in agreement with the sponsor and educational supervisor for this project, will submit information to the appropriate body for approval.

The designee will work with sites (R&D departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment and confirm their support for the study as amended.

Good Clinical Practice

The study will be conducted under Good Clinical Practice (GCP) conditions.

Protocol Compliance and Deviations

Protocol deviations will be adequately documented on relevant forms and reported to the research student/designee and lead sponsors immediately. Frequent deviations from the protocol which are found to recur will require immediate action and potentially be classified as a severe breach.

Data Protection and Patient Confidentiality

All investigators and study site staff must comply with the requirements of the Data Protection Act 2018 regarding the collection, storage, processing, and disclosure of personal information. They will uphold the act's core principles. Any requests from participants for access to their data held by the chief investigator will be referred to the Data Protection Officer at the St Thomas' NHS Foundation Trust.

Only local research teams will have access to patient-identifiable data. The central research team at GSTT will have access to pseudonymized data, except for patients recruited locally at GSTT. At the time of upload onto REDCap by the local research team, a case number will be used to pseudonymise patient data. This case number will be recorded on the consent form and may be used if research teams need to trace and link back to the patient.

Consent forms will be stored in a secure NHS computer system folder at each local research site or, where paper forms are used, in a secure locker. In the event paper case reporting forms are used, they will also be stored similarly to the paper consent forms in a secure locker. In both electronic and physical cases, access to patient-identifiable documentation will be limited to the local PI/trial manager and other authorised personnel (research students, nursing staff, etc.) involved in the data set's collection, verification or analysis.

At the end of the study, anonymised data may be sent to Ventriject for improvements in the estimation algorithm subject to formal agreement. Data will be anonymised by the creation of a unique randomised study number to link the raw Seismocardiography reading generated from the device to the below data:

- Patient age at the time of Seismofit reading
- Gender
- Height and weight,
- Previous cardiac co-morbidities
- Use of cardio-selective anti-arrhythmic medications, type of medication and dose
- Use of diuretic, diuretic type and dose,
- Latest cardiac systolic ejection fraction
- eGFR value at the time of Seismofit(r) reading
- Latest Haemoglobin values at the time of Seismofit(r) reading
- Presence of other pulmonary comorbidities

In the event that data is sent to Ventriject for the purpose of improving the prediction algorithm, all data except that listed above will be removed from the data spreadsheet.

This study utilizes complex algorithms, which are the proprietary intellectual property of Ventriject. Anonymised data recording of the SCG data (generated by the Seismofit® device), including the patient's height, weight, age, and sex, is sent via the internet to Ventriject, enabling the calculation of the VO2Peak. The identification number of the specific device used at each measurement will be recorded alongside the unique study number, allowing for device traceability and accountability. There will be no storage of information or media device files on the researcher's mobile phone while using the Ventriject VO2Max estimation algorithm.

If patients lose capacity prior to surgery, they are unlikely to proceed to having major surgery. In the event that patients lose capacity, the data that was collected with active consent, such as the Seismofit readings and CPET at baseline, will remain eligible for analysis as part of the study.

All clinical study data will be analysed locally within an NHS / research infrastructure at GSTT and King's College London to preserve data security and integrity. The chief investigator may delegate responsibilities for data entry, quality checking, and analysis but will ultimately be responsible for these tasks. Any data security breaches will be reported immediately to the data custodian for this study.

The electronic data and paper files will be stored for five years before being deleted or securely destroyed. Data will not be transferred out of the EEA.

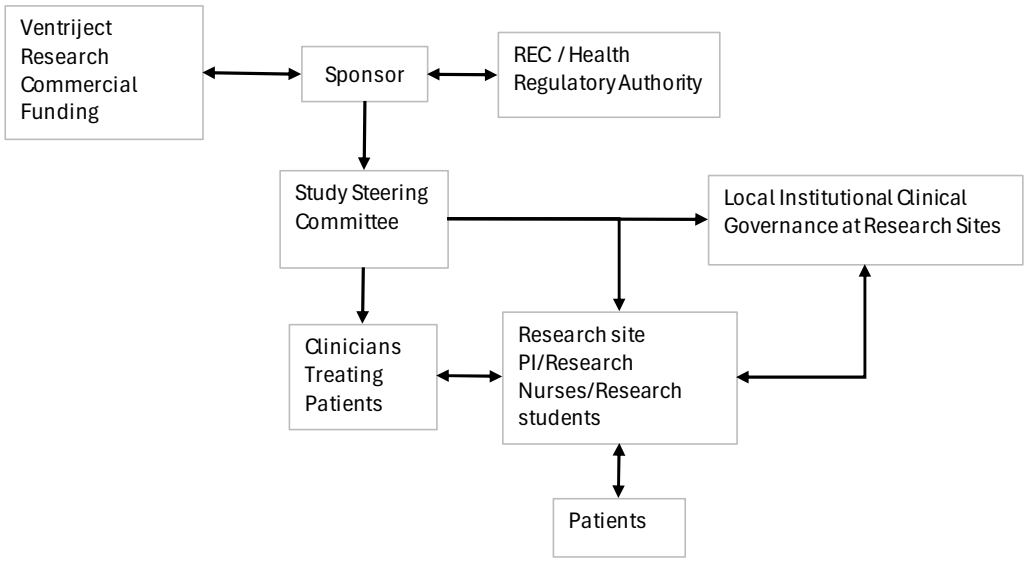
The chief investigator will act as the data custodian. They will permit trial-related monitoring, audits, REC review and regulatory inspections, providing direct access to source data/documents. Trial participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical records.

Study Organisation, Trial Monitoring and Management Strategy

Study Management Responsibilities

The study's chief investigator will be responsible for the study's conduct and oversight. They will ensure that the trial is run in accordance with UK Policy Framework for Health and Social Care Research Guidelines, GCP, the local Guys and St Thomas' NHS Foundation Trust Standard Operating Procedures and all other relevant regulatory requirements.

The study Trial Management Group (TMG) will include the chief investigator, Trial Manager, Site PI's and other personnel as appropriate. They will be responsible for running and managing the trial and data monitoring. They will hold regular teleconference / face-to-face meetings. The TMG's terms of reference, roles and responsibilities will be defined in the TMG charter.



No responsibilities are delegated to the Seismofit® Manufacturer (Ventriject). The trial monitoring plan will standardise and document that the investigation is conducted as described in this protocol.

Study Early Termination / Suspension Criteria

Early termination or suspension of the study may be implemented by the research ethics committee or local regulatory authority at the sponsor research site. Additionally, the chief investigator may decide to suspend enrolment in the clinical trial if deemed necessary. Reasons for suspension or early termination include safety issues, non-compliance, significant concerns or an inspection or audit finding(s) of serious or repeated deviations on the part of the investigator(s). If the study is suspended or terminated, this will be communicated to all the participating research sites.

The investigation will resume once necessary corrective measures have been implemented and deemed satisfactory by the sponsor site.

End of Trial

The study will end when 164 patients, who do not withdraw from the study have been recruited and their data is collected. The sponsor will notify the REC within 90 days of the date the last patient has their data collected. The findings and results of the trial will be analysed, and a final study report will be produced within 12 months of study completion.

Trial Monitoring

The Chief Investigator will be responsible for the ongoing management of the study. The Sponsor will monitor and conduct audits on a selection of studies in its clinical research portfolio. Monitoring and auditing will be conducted in accordance with the UK Policy Framework for Health and Social Care and in accordance with the Sponsor's monitoring and audit procedures

Local site data monitoring by designated investigational leads and centralised data monitoring in conjunction with training provided in the use of the investigational device and the written guidance provided will be assumed to have the appropriate data monitoring in place for the purpose of this study.

CPET will be conducted as per the local standard of care. For the purposes of this study and analysis of the final data, CPET VO2Peak readings will be considered valid with each patient reaching maximal exertion where they reach the following criteria:

1. Achieving >80% of the predicted maximum work of the patient (in Watts)
2. Achieving maximum HR >80% (Predicted Maximum = 220 – Patient Age) (Chambers and Wisely, 2019; Levett et al., 2018b)
3. Achieving a RER of >1.10 (Levett et al., 2018b)

The monitoring activities' results will be reported to the sponsor, including the date, investigation site name, name of the monitor and investigation site leads.

Day-to-day monitoring will be done by the trial management group as outlined in the study management responsibilities section to ensure that the data collected is:

- Consistent with the protocol and GCP
- No key data is missing
- Valid and consistent within the range of expected values.
- Completed only by the authorised research site staff.

Monitoring visits by the central research team will list:

- Date of visit, site name and name of the monitor
- Name of the site PI or other research staff in attendance.
- A summary of the documents reviewed along with significant findings, deviations, deficiencies and actions taken or recommended.

Insurance and Liability

Indemnity for the participating hospitals will be provided by the standard NHS indemnity arrangements.

The study is co-sponsored by King's College London (KCL) and (GSTT). The sponsors will, at all times, maintain adequate insurance in relation to the study. KCL through its' own professional indemnity (Clinical Trials) & no-fault compensation and the GSTT having a duty of care to patients via NHS indemnity cover, in respect of any claims arising as a result of negligence by its employees, brought by or on behalf of a study participant.

Contact with General Practitioner (GP)

As there is no change in management intervention within this study and no deviation from the routine clinical practice of either GSTT, UHS, RM or RS, the GP will not be informed of the subject's involvement in the trial.

Clinical Study Reporting Policy

Clinical data will be presented at the end of the trial based on final data listings. The CI or a delegated individual will prepare a brief study report/publication based on the final data listings.

A summary of the report will be provided to the Research Ethics Committee within 1 year of submitting the end-of-trial notification.

Reporting and Publication

The main trial results will be published in a peer-reviewed journal on behalf of all collaborators. The study team will prepare the manuscript with the results of the trial. Authorship will be based on the criteria set by the International Committee of Medical Journal Editors (ICJME). All participating clinicians will be acknowledged in the publication.

At the time of consenting, participants will be given the opportunity to indicate on the consent form if they would like to receive updates on the study outcomes and to provide an email address to receive this information at the completion of the study. At the end of the study, participants who indicated they would like to receive updates on the outcomes will be provided with an email containing a lay summary of the outcomes, thanking them for their participation in the study and information on where the outcomes of the study are being presented and or published.

Conflict of Interest

The chief investigator and the research teams have no conflict of interest with this study. Ventriject, which makes the device, has funded the devices, adhesive patches, and the cost per test. Ventriject has not been involved in the writing of this research protocol. Ventriject has permitted researchers and clinical teams to publish findings in peer-reviewed literature, irrespective of the outcomes. Ventriject will have no input into the analysis of the outcome data. Devices will be returned to Ventriject at the end of the trial.

Safety Reporting

All adverse events and any new information concerning these shall be documented in a timely manner throughout the study period and reported to the sponsor. An interim or final study report will note all adverse events.

Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users, or other persons, whether related to the participation in the study. This includes:

- Events related to the medical device.
- Events related to the procedures involved (any procedure in the study protocol).

.

Serious Adverse Event (SAE)

Adverse event that:

- Led to death,
- Led to a severe deterioration of health that either:
- Resulted in a life-threatening illness or injury, or;
- Resulted in a permanent impairment of a body structure or a body function, or;
- Required in-patient hospitalization or prolongation of existing hospitalization, or;
- Resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
- Led to foetal distress, foetal death or a congenital abnormality or congenital disability.

A planned hospitalisation for a pre-existing condition or a procedure required by the study protocol, without a severe deterioration of health, is not considered a serious adverse event.

Investigator Responsibilities

AE / SAE will be collected from the date of consent until all study measurements have been collected. All events will be recorded in the medical notes and the appropriate section of the study case reporting form and AE log.

SAE will be reported to the sponsor.

Assessment of Severity

All adverse events will be graded for severity. The investigator will assess the severity of each adverse event, which should be recorded.

NB: to avoid confusion or misunderstanding of the difference between the terms “serious” and “severe”, the following note of clarification is provided: “Severe” is often used to describe the intensity of a specific event, which may be of relatively minor medical significance.

Assessment of Seriousness

The seriousness of an AE is assessed by the PI (or delegate) using the criteria outlined above.

Assessment of Causality

All AEs will be evaluated by the PI (or delegate) for potential relationship to the study procedures.

- Unrelated: where an event is not considered related to participation in the study.
- Possibly related: the nature of the event, the underlying medical condition, concomitant medication, or temporal relationship make it possible that the AE has a causal relationship to participation in the study.

The investigator must obtain sufficient information to determine the causality or the AE (i.e., study protocol, other illness, progressive malignancy, etc.) and provide their opinion of the causal relationship between each AE and participation in the study. This may require instituting supplementary investigations of significant AEs based on their clinical judgment of the likely

causative factors, which may include seeking a further opinion from a specialist in the field of the AE.

Assessment of Expectedness

If the AE is judged to be related to the device, the PI (or delegate) will assess expectedness based on knowledge of the reaction and any relevant product information as documented in the risk analysis report. The event will be classed as either:

- Expected: the reaction is consistent with the effects of the device listed in the risk analysis report.
- Unexpected: the reaction is inconsistent with the effects in the risk analysis report.

Reporting of Adverse Events

Reportable events

The following events are considered reportable:

- Any SAE
- New findings/updates about already reported events

For each event, the following information will be collected:

- Full details in medical terms and case description
- Event duration (start and end dates, if applicable)
- Action taken
- Outcome
- Seriousness criteria
- Causality (i.e., relatedness to investigation), in the opinion of the investigator
- Whether the event would be considered expected or unexpected.

All reportable events must be notified to the sponsor team and the Chief Investigator within 24 hours of the site staff becoming aware of the event. The Sponsor has delegated the responsibility of informing the REC of reportable events to the CI.

Any change of condition or other follow-up information should be emailed (through secure NHS Email account) to the CI within 24 hours of the information becoming available. Events will be followed up until the event has been resolved or an outcome has been reached.

The CI will collaborate with the device manufacturer to notify the REC of reportable events.

Reporting Timelines

All SAE which indicates an imminent risk of death, serious injury, or severe illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it must be reported to the REC immediately, but not later than 15 calendar days after awareness by CI of a new reportable event or of new information in relation with an already reported event.

Any other reportable events or a new finding/update to a reportable event must be reported to the REC immediately, but not later than seven calendar days following the date of awareness by

the CI of the new reportable event or of new information in relation with an already reported event.

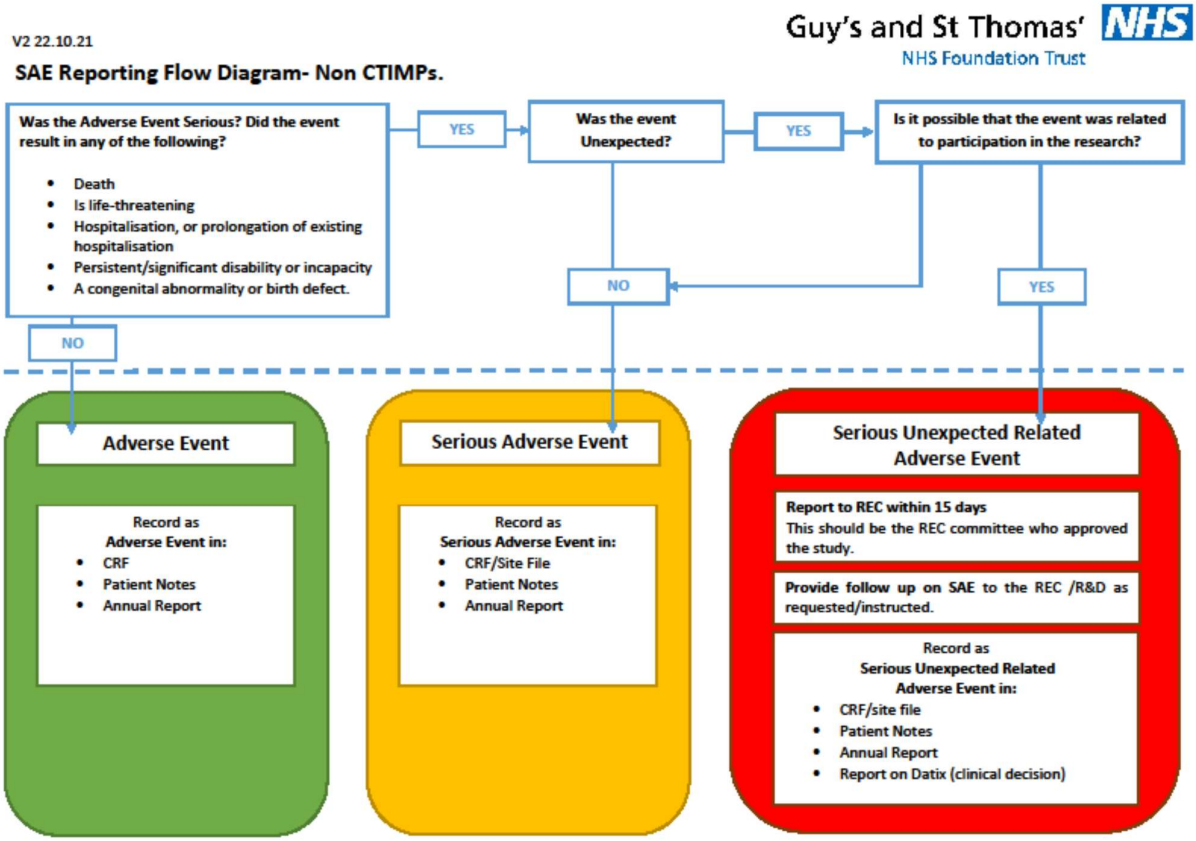
Funding

<table>
<tr><th>FUNDER(S)
(Names and contact details of ALL organisations providing funding and support in kind for this study)</th><th>FINANCIAL AND NON-FINANCIAL SUPPORT GIVEN</th></tr>
<tr><td>Ventriject</td><td>£60,000 in total over 2 years plus Seismofit® devices which will be returned to Ventriject at the end of the trial and use of proprietary algorithms in generation of VO2Max estimates

<table><tr><th colspan="2">Funding Schedule</th></tr><tr><td>Oct/24</td><td>£ 8.000</td></tr><tr><td>Jan/25</td><td>£ 6.000</td></tr><tr><td>Apr/25</td><td>£ 6.000</td></tr><tr><td>Jul/25</td><td>£ 6.000</td></tr><tr><td>Oct/25</td><td>£ 8.000</td></tr><tr><td>Jan/26</td><td>£ 6.000</td></tr><tr><td>Apr/26</td><td>£ 10.000</td></tr><tr><td>Jul/26</td><td>£ 10.000</td></tr><tr><td>Total</td><td>£ 60.000</td></tr></table></td></tr>
<tr><td>Karolinska Institutet</td><td>£15,000 in total over two years</td></tr>
</table>

APPENDIX 1

SAE Reporting Flow Diagram-Non CTIMPs



APPENDIX 2

Information with regards to Safety Reporting in Non-CTIMP Research

	Who	When	How	To Whom
SAE (related and unexpected)	Chief Investigator	-Report to Sponsor within 24 hours of learning of the event -Report to the MREC within 15 days of learning of the event	SAE Report form for Non-CTIMPs, available from NRES website.	Sponsor and MREC
Urgent Safety Measures	Chief Investigator	Contact the Sponsor and MREC Immediately Within 3 days	By phone Substantial amendment form giving notice in writing setting out the reasons for the urgent safety measures and the plan for future action.	Main REC and Sponsor Main REC with a copy also sent to the sponsor. The MREC will acknowledge this within 30 days of receipt.
Progress Reports	Chief Investigator	Annually (starting 12 months after the date of favourable opinion)	Note as of August 2024, NHS REC Annual Progress Reports are no longer mandated but may be requested for certain project types or by the project Sponsor	NHS REC Annual Progress Reports are no longer mandated but may be requested for certain project types or by the project Sponsor
Declaration of the conclusion *or* early termination of the study	Chief Investigator	Within 90 days (conclusion) Within 15 days (early termination) *The end of study should be defined in the protocol*	End of Study Declaration form available from the NRES website	Main REC with a copy to be sent to the sponsor
Summary of final Report	Chief Investigator	Within one year of conclusion of the Research	No Standard Format However, the following Information should be included:- Where the study has met its objectives, the main findings and arrangements for publication or	Main REC with a copy to be sent to the sponsor

			dissemination including feedback to participants	

References

Chambers, D. J. & Wisely, N. A. (2019) Cardiopulmonary exercise testing—a beginner's guide to the nine-panel plot. *BJA Education*. [Online] 19 (5), 158–164. [online]. Available from: https://doi.org/10.1016/j.bjae.2019.01.009.

Confidentiality, S. O. F. (2011) Investigator ' S Brochure Investigator ' S Brochure (Ib). *Plexxikon Investigator's Brochure*. (December), 1–110.

Hansen, M. T. et al. (2023a) Validity and reliability of seismocardiography for the estimation of cardiorespiratory fitness. *Cardiovascular Digital Health Journal*. [Online] 4 (5), 155–163.

Hansen, M. T. et al. (2023b) Validity and reliability of seismocardiography for the estimation of cardiorespiratory fitness. *Cardiovascular Digital Health Journal*. [Online] 4 (5), 155–163. [online]. Available from: https://doi.org/10.1016/j.cvdhj.2023.08.020.

Hennis, P. J. et al. (2011) Cardiopulmonary exercise testing for the evaluation of perioperative risk in non-cardiopulmonary surgery. *Postgraduate Medical Journal*. [Online] 87 (1030), 550–557.

Jack, S. et al. (2014) The effect of neoadjuvant chemotherapy on physical fitness and survival in patients undergoing oesophagogastric cancer surgery. *European Journal of Surgical Oncology*. [Online] 40 (10), 1313–1320. [online]. Available from: http://dx.doi.org/10.1016/j.ejso.2014.03.010.

Krogh, M. et al. (2020) *Aalborg Universitet A Clinical Method for Estimation of VO2max Using Seismocardiography Publication date : Title A Clinical Method for Estimation of VO 2 max using Seismocardiography This is an Accepted Manuscript of an article published by Thieme Publish*.

Levett, D. Z. H. et al. (2018a) Perioperative cardiopulmonary exercise testing (CPET): consensus clinical guidelines on indications, organization, conduct, and physiological interpretation. *British Journal of Anaesthesia*. [Online] 120 (3), 484–500.

Levett, D. Z. H. et al. (2018b) Perioperative cardiopulmonary exercise testing (CPET): consensus clinical guidelines on indications, organization, conduct, and physiological interpretation. *British Journal of Anaesthesia*. [Online] 120 (3), 484–500. [online]. Available from: https://doi.org/10.1016/j.bja.2017.10.020.

Liu, C. Q. et al. (2023) Epidemiology of esophageal cancer in 2020 and projections to 2030 and 2040. *Thoracic Cancer*. [Online] 14 (1), 3–11.

Ozova, M. et al. (2022) Cardiopulmonary exercise testing for cardiovascular risk assessment in patients undergoing gastric and oesophageal cancer surgery: Results from a prospective interventional cohort study. *Open Heart*. [Online] 9 (2), .

Sørensen, K. et al. (2018) Definition of Fiducial Points in the Normal Seismocardiogram. *Scientific Reports*. [Online] 8 (1), 1–11.

Ventriject (n.d.) *Seismofit(r) Instructions for Use Manual*. p.1–128. [online]. Available from: http://hdl.handle.net/2115/54987.

Walker, R. C. et al. (2024) Association of Upper Gastrointestinal Surgery of Great Britain and Ireland (AUGIS)/perioperative quality initiative (POQI) consensus statement on prehabilitation in oesophagogastric surgery. *The British journal of surgery*. [Online] 111 (10), 1–11. [online]. Available from: https://doi.org/10.1093/bjs/znae223.

West, M. A. et al. (2024) Cardiopulmonary exercise variables and their association with postoperative morbidity and mortality after major oesophagogastric cancer surgery—a multicentre observational study. *BJA Open*. [Online] 10 (January), .

West, M. A. et al. (2014) Cardiopulmonary exercise variables are associated with postoperative morbidity after major colonic surgery: A prospective blinded observational study. *British Journal of Anaesthesia*. [Online] 112 (4), 665–671.

West, M. A. et al. (2016) The effect of neoadjuvant chemotherapy and chemoradiotherapy on exercise capacity and outcome following upper gastrointestinal cancer surgery: An observational cohort study. *BMC Cancer*. [Online] 16 (1), 6–13.

Wu, W. et al. (2014) Technical and early outcomes of Ivor Lewis minimally invasive oesophagectomy for gastric tube construction in the thoracic cavity. *Interactive Cardiovascular and Thoracic Surgery*. [Online] 18 (1), 86–91.