University College London Hospitals NHS
NHS Foundation Trust

V1.2 ,12/4/2013

PROTOCOL

Full title of trial	POM-HR (Post Operative Morbidity- heart rate): Observational study of exercise-induced heart rate dynamics and their relationship to postoperative morbidity.
Short title	POM-HR
Version and date of protocol	V1.2 ,12/4/2013
Sponsor:	University College Hospital (UCLH)
Funder (s) :	Academy of Medical Sciences
Trial sites(s)	University College London Hospital; Derriford Hospital, Plymouth
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1.2

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2. List of abbreviations

CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
GAfREC	Governance Arrangements for NHS Research Ethics
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator Brochure
ICF	Informed Consent Form
ISF	Investigator Site File
ISRCTN	International Standard Randomised
Main REC	Main Research Ethics Committee
NHS R&D	National Health Service Research & Development
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
REC	Research Ethics Committee
SAR	Serious Adverse Reaction

SAE	Serious Adverse Event
SDV	Source Document Verification
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction

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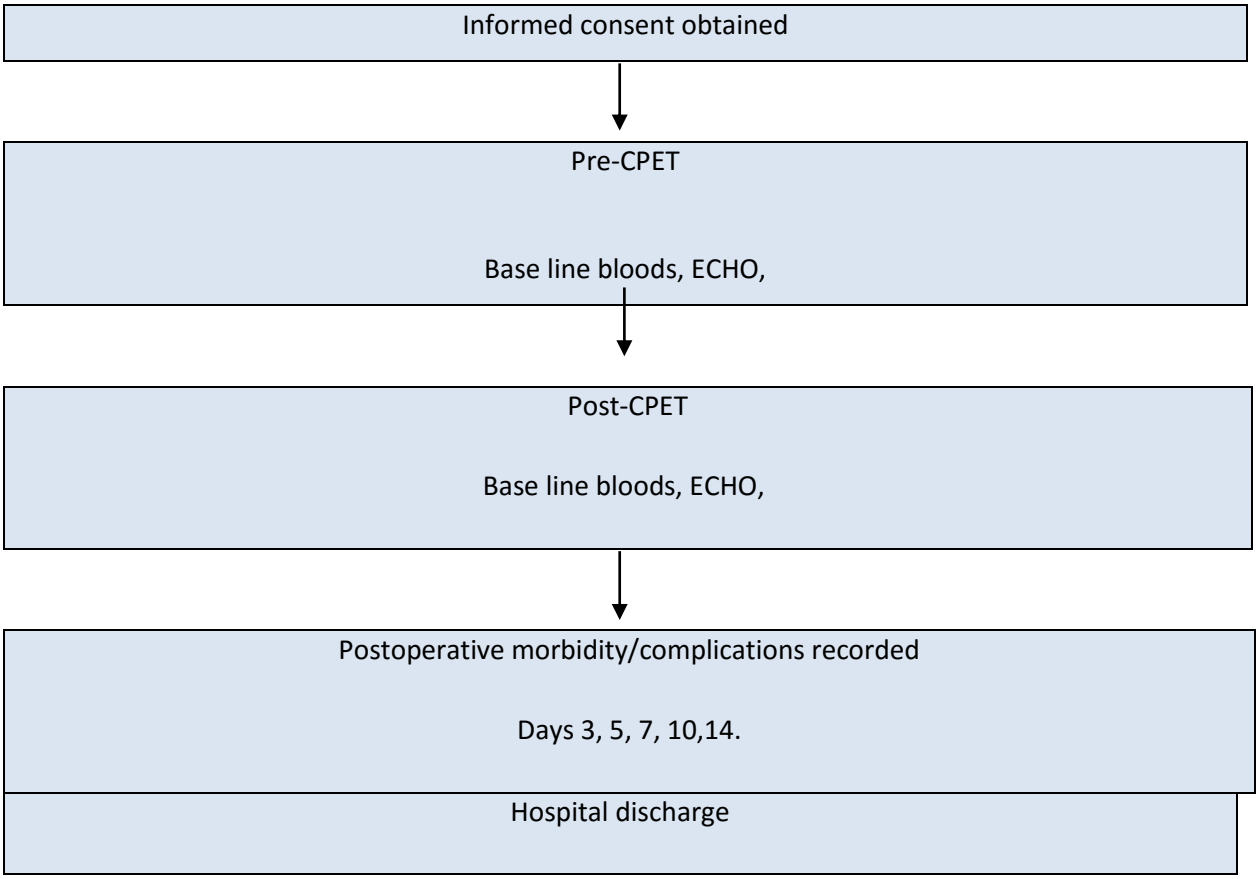
4. Summary/Synopsis

Title:	POM-HR (Post Operative Morbidity- heart rate): Observational study of exercise-induced heart rate dynamics and their relationship to postoperative morbidity.
Short title:	POM-HR
Objectives:	Primary objective: To assess whether abnormal heart rate dynamics following cardiopulmonary exercise testing is related to postoperative complications and length of hospital stay. Secondary objective: To assess whether abnormal heart rate dynamics following cardiopulmonary exercise testing is related to immune-inflammatory phenotypes and structural heart differences.
Type of trial:	Unblinded, two-site, observational retrospective and prospective studies in elective surgical patients undergoing cardiopulmonary exercise testing (CPET) as part of their routine preoperative workup.
Trial design and methods:	Retrospective study: Anonymized data detailing cardiopulmonary exercise tests and postoperative morbidity/ length of stay that are collected and assessed routinely as part of clinical care will be provided by both centres. Prospective study: Preoperative patients undergoing major surgery are referred routinely for

	cardiopulmonary. All heart rate data is derived from cardiopulmonary exercise testing acquired data, performed as part of their routine preoperative workup. Blood derived immune cells will be acquired at UCLH site only pre and post exercise from from indwelling catheters routinely placed for the CPET itself. Transthoracic (non-invasive) echocardiography will be performed pre and post CPET at the UCLH site only. Postoperative morbidity and complications will be recorded on days 3, 5, 7, 10 and 14 if the patient remains in hospital for that length of time. This is routinely collected in both hospitals.
Trial duration per participant:	6 weeks, including duration between consent CPET and end of surgical hospital stay.
Estimated total trial duration:	4 years
Planned trial sites:	University College London Hospital; Derriford Hospital, Plymouth
Total number of participants planned:	1356
Main inclusion criteria:	All surgical patients referred for cardiopulmonary exercise testing preoperatively by their surgical or anaesthetic consultant undergoing major noncardiac surgery.

5. Flowchart of events:



6. Background

Hypothesis

To demonstrate that autonomic dysfunction (as reflected by heart rate response to exercise) is predictive of short-term postoperative morbidity and length of stay.

Background

Complications following surgery are an important cause of morbidity and mortality. When these complications occur within 30 days of major surgery a patients' long term survival may be compromised [1]

Heart rate recovery is an independent predictor of longer term cardiovascular disease outcomes. Beyond the heart, the vagus nerve plays important roles in reducing inflammation and protecting cells from various stresses. The rate of heart rate recovery following exercise reflects how well the vagus nerve works. Standardized exercise tests allow us to measure how well the vagus nerve is working, and therefore provide important insights into whether the vagus nerve helps protect cardiac function and noncardiac effects in different patients undergoing major surgery. POM-HR is a mechanistic study designed to examine if abnormal heart rate recovery can identify patients who are at greater risk of complications post-operatively through abnormal autonomic activation. Studies have suggested that the central nervous system controls the body's response to inflammation. The vagal nerve is an important nerve in the central nervous system and has an influence on organs such as the spleen and liver which help dampen down inflammation. Experimental model studies have shown that signals via the vagal nerve can inhibit inflammation and improve outcomes in various disease processes including models of sepsis, myocardial ischaemia and ileus.[5-13] Understanding this mechanism in a clinical context may help us to understand why some patients sustain complications after surgery. This will allow future clinical care to be guided by an understanding of why these complications arise and allow early detection, treatment and avoidance of postoperative morbidity.

7. Purpose

There is a need to confirm that a vagal neuro-immune activation is linked to postoperative complications. Demonstrating that a vagally controlled neuro-immune activation is linked to reduced postoperative complications in surgical patients will enhance our understanding of the underlying

mechanisms. This investigation could then encourage a widespread use of simple interventions, such as preoperative exercise regimes, to enhance vagal activation following all types of surgery to reduce morbidity postoperatively.

8. Study design

For the retrospective study, pre-existing nonidentifiable morbidity and preoperative cardiopulmonary exercise test data is acquired as part of the clinical quality monitoring at both hospitals and can be provided by the clinical care teams thus ensuring no breach of confidentiality. These data are fully anonymised and do not include any potential identifiers.
For the prospective study: All heart rate data is derived from cardiopulmonary exercise testing acquired data, performed as part of their routine preoperative workup. Blood derived immune cells will be acquired at UCLH site only pre and post exercise from from indwelling catheters routinely placed for the CPET itself. Ex-vivo laboratory studies will explore bioenergetic (mitochondrial) function in leukocyte subsets and Immune function in leukocyte subsets. Transthoracic (non-invasive) echocardiography will be performed pre and post CPET at the UCLH site only. Postoperative morbidity and complications will be recorded on days 3, 5, 7, and 14 if the patient remains in hospital for that length of time. This is standard practice in both hospitals.

UCLH has a strong record of perioperative research in this area. As such our local patients are fully engaged in the perioperative research process. Our Critical Care patient liaison group is a strong advocate of patient centred outcomes research. We also have patient representatives via the Centre for Anaesthesia Patients Information Group, who participate in our monthly clinical research meetings to present patient views on research, protocols and enrolment issues (http://www.ucl.ac.uk/anaesthesia/patients).

9. Selection of subjects and Informed consent procedure

Recruitment

Patient recruitment will only be done when the trial has

1. Documented REC, Regulatory and Local Trust R&D approval

2. A signed site agreement

3. The site has sent back to the TC the PI self-monitoring template.

10. Subject selection

Inclusion criteria

All surgical patients referred for cardiopulmonary exercise testing preoperatively by their primary surgeon or anesthesiologist undergoing major noncardiac surgery.

Exclusion criteria

1. history of exercise induced angioedema,

2. pregnancy,

3. any contraindication to cardiopulmonary exercise testing (as outlined by American Association of Anaesthesia):

Consent procedure

For the retrospective study, we have written confirmation from the NIGB (Claire Edgeworth, Ethics and Confidentiality Committee; claire.edgeworth@nhs.net) that nonidentifiable morbidity and preoperative cardiopulmonary exercise test data can be provided by the clinical care teams thus ensuring no breach of confidentiality. Pre-existing nonidentifiable morbidity and preoperative cardiopulmonary exercise test data is acquired as part of the clinical quality monitoring at both hospitals and can be provided by the clinical care teams ensuring no breach of confidentiality. These data are fully anonymised and do not include any potential identifiers.
It is the responsibility of the principal investigator and co-investigator to ensure written informed consent from each subject prior to participation in this study. Responsibility for conducting the informed consent process may be delegated to appropriately trained members of the research team (see 18. definition of responsibilities). This process will include an explanation of the aims, methods, anticipated benefits and potential hazards of the study. The CPET service will highlight potential patients ahead of their attendance at surgical clinic, several weeks before the initiation of the study. No healthcare professionals involved in the patients perioperative care will be involved in the consent process. The principal investigator and co-investigator will explain to all potential participants that they are free to refuse to enter the study or to withdraw at any time during the study, for any reason. The patients will be approached prior to the CPET, thereby affording suitable time for patients to consider the process of consent. The principal investigator and co-investigator

will be contactable by mobile phone and electronic mail to address further queries. Where a patient wishes to be withdrawn from the study, only the primary outcome data will be collected to enable intention treat analysis. Non-English speakers will be provided with full access to NHS translation services to ensure appropriate understanding of the trial and consent process. We will not recruit patients who lack capacity to give or withhold informed consent. A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained at the study site.

11. Risks, burdens and benefits

Risks and burdens

There are no study specific risks introduced by this study since we are utilizing preoperative data from routine investigations and postoperative outcomes. CPET preoperative investigation represent routine care at UCLH and Derriford hospitals. Post Operative Morbidity Survey data is routinely collected at UCLH and Derriford, so represent standard of care at our institutions.

Benefits

1. The information we get from this study may help us to better treat future patients undergoing surgery and those who are seriously ill in intensive care.

12. Randomisation

Observational study- not applicable.

13. Definition of end of trial

The end of the trial will be the date of the last visit by the last participant.

14. Conflicts of Interest

There are no conflicts of interests for this study. After the study has ended, the results will be fed back to all participants and patient representatives via the Centre for Anaesthesia Patients Information Group, which we invite to participate in our monthly meetings.

Use of tissue samples in future research

Samples will be stored securely within Wolfson Institute for Biomedical Research, UCL. These samples will be used to investigate cellular processes that may be involved in perioperative complications. The CI is the only investigator authorized to use these samples. All subsequent amendments will be notified.

15. Data management and quality assurance

Confidentiality/data handling and analysis

For the retrospective study, we have written confirmation from the NIGB (Claire Edgeworth, Ethics and Confidentiality Committee; claire.edgeworth@nhs.net) that nonidentifiable morbidity and preoperative cardiopulmonary exercise test data can be provided by the clinical care teams thus ensuring no breach of confidentiality. These data are fully anonymised and do not include any potential identifiers. Submitted data will be coded (pseudoanonymised) and reviewed for completeness and consistency and then entered on a database. To ensure validity and quality, double data entry will be performed.

All data collection will be recorded on case report forms (CRF) embedded in access database, located on secure, password protected and encrypted (NHS mandated “Ironman”) USB keys. Data is stored securely against unauthorised manipulation and accidental loss. Desktop security is maintained through user names and frequently updated passwords and back up procedures are in place. All essential documents and trial records will be archived in conformance with the applicable regulatory requirements and access to these archives will be restricted to authorised personnel. Data will be secured in pre-existing, locked and password protected facilities within the Wolfson Institute for Biomedical Research, UCL or the Anaesthetic Research Office, Terence Lewis Building, Derriford Hospital, Plymouth. Records will be retained in this secure location for retention – duration and location. All data collection, storage and access will adhere to the Data Protection Act 1998. Dr

Ackland (UCL) & Dr Minto (Plymouth) will be responsible for data collection, recording and quality. In-house audits of data quality will be performed throughout the trial. Site monitoring visits will involve source data verification. The Case Report Forms (CRFs) will not bear the subject's name or other personal identifiable data. The subject's initials, date of birth and trial identification number, will be used for identification.

The code for a particular subject may be broken in a medical emergency if knowing the identity of the treatment allocation would influence the treatment of the subject or if demanded by the subject. Whenever a code is broken, the person placing the call will be requested to sign the fax from UCLH CTU and add the reason for breaking the code. This document is Source Data and should be kept with the CRF. Relevant persons (i.e. the investigator will get access to the UCLH CTU "code breaking call" via an access and pin code supplied by UCLH CTU. If the trial needs to break the code, the Sponsor should, if possible, be contacted prior to breaking the code. In all cases, the Monitor must be notified within 24 hours after the code has been broken. All codes (whether broken or not) must be kept throughout the trial period. Accountability of all codes (hard copy or electronic) will be performed at or after trial closure and will be collected by the Monitor.

Participant safety and wellbeing are protected by implementation of the sponsoring organisation's standard operating procedures (SOPs) as set out in the Research Governance Framework and The Medicines for Human Use (Clinical Trials) Regulations 2004. As sponsor UCLH/UCLH performs regular audits of research and this study may be selected for such an audit. Systems are in place to ensure that all investigators are able to demonstrate that they are qualified by education, training or experience to fulfil their roles, and systems and procedures are in place which can assure the quality of every aspect of the trial. If new safety information becomes available, then study participants will be informed of this and asked if they wish to continue in the study. If the subjects wish to continue in the study they will be formally asked to sign a revised approved participant information sheet and consent form. Day to day management will be undertaken via a trials management group composed of the principal investigator and supporting staff. They will meet on a weekly basis to discuss study issues. Site monitoring will be directed by the sponsor according to the study risk analysis.

Data collection tools and source document identification

Case report forms will be designed and produced by the investigator, according to the sponsor's CRF template. The final version will be approved by the sponsor. All data will be entered legibly in black ink with a ball-point pen. If an error is made, the error will be crossed through with a single line in such a way that the original entry can still be read. The correct entry will then be clearly inserted,

and the alterations will be initialled and dated by the person making the alteration. Overwriting or use of correction fluid will not be permitted.

It will be the responsibility of the investigator to ensure the accuracy of all data entered in the CRFs. The delegation log will identify all those personnel with responsibilities for data collection and handling, including those who have access to the trial database.

Transfer of data from Derriford to UCL

Data will be entered from paper CRFs onto access database by responsible investigator(s) at the Derriford study site. Participants will be identified by study number only so that confidentiality will be maintained. The access database will be sent by secure nhs email from the Principal Investigator at Derriford to the Chief Investigator at UCL. Thus no patient identifiable data will leave the Derriford site.

Record Keeping and archiving

Chief Investigators are responsible for the secure archiving of trial documents and the trial database.

16. Statistical analysis

Statistician involved in powering the study: Dr Steve Harris, Department of Health Services Research and Policy, Institution London School of Hygiene + Tropical Medicine
Room 137, LSHTM, 1517 Tavistock Place, London WC1H 9SH. steve.harris@lshtm.ac.uk

Surgical Patients – Sample size

Primary outcome is incidence of morbidity on postoperative day 5. 40% of patients undergoing major surgical procedures sustain defined morbidity on postoperative day 5. From the cardiovascular literature, the relative risk of predicted morbidity is ≥2x more prevalent in patients with abnormal heart rate recovery (HRR), who we predict may constitute up to 50% of the patient population. If 50% abnormal HRR patients sustain postoperative morbidity compared with 30% patients exhibiting normal HRR preoperatively, with power =80%, 339 patients per group would be required to detect this difference in postoperative morbidity (alpha=0.05). Since two sites are collecting data to demonstrate that this is not a site-specific phenomenon, the total number of patients is therefore 1356 (retrospective and prospective studies).

Surgical Patients – Statistical analysis

The primary analysis is to examine the relationship between exercise-induced abnormal HRR and the development of postoperative morbidity. The chi-square test will be used for an initial comparison, and subsequently logistic regression will be used to examine HRR and additionally the effects of preoperative factors upon postoperative morbidity. The log rank test and Cox regression will be used for equivalent analyses for the length of stay in hospital. The unpaired t-test or Mann-Whitney test will be used to compare cellular and heart rate variables between patients with normal/ abnormal HRR.

Direct access to source data/documents

The investigator(s)/ institution(s) will permit trial-related monitoring, audits, REC review, and regulatory inspection(s), 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 notes.

17. Ethics and regulatory requirements

The sponsor will ensure that the trial protocol, patient information sheet, consent form, GP letter and submitted supporting documents have been approved by the appropriate regulatory body and a main research ethics committee, prior to any patient recruitment. The protocol and all agreed substantial protocol amendments, will be documented and submitted for ethical and regulatory approval prior to implementation.

Before the site can enrol patients into the trial, the Chief Investigator or designee must apply for Site Specific Assessment from Trust Research & Development (R&D) and be granted written NHS R&D approval. It is the responsibility of the Chief Investigator or designee at each site to ensure that all subsequent amendments gain the necessary approval. This does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.

18. Definition of Responsibilities .

Position	Approved Responsibilities
Chief Investigator (GA) Principal Investigator Gary Minto Richard Struthers * denotes GA only	Overall responsibility for study* Protocol design Ethics committee and R&D applications, amendments and other communication Preparation of patient information leaflets and informed consent forms Grant application where relevant Delegation of study duties at local sites Overall responsibility for maintenance of site study file Maintenance of study delegation log Maintenance of secure recruitment log Responsible for ensuring all staff delegated to work on study are suitable due to training education and experience Ensures study staff are adequately informed as to protocol requirements Educational Supervisors for research registrar(s) Patient recruitment strategy Cardiopulmonary exercise testing: supervision of tests Informed consent Availability to answer participant queries Signing of consent form Recording of demographic data on Case Report Form (CRF) Recording of specified postoperative outcomes on CRF Quality control Overall responsibility for safe storage of confidential CRF records Response to data queries from sponsor Documentation and timely reporting to sponsor of serious adverse events

	(SAEs) Ensure financial arrangement are processed* Responsibility for maintenance of equipment and devices Ensure indemnity, compensation and insurance where applicable* Maintain Organisation of Study Site File Be available for audit and inspections Initiation of new trial personnel Shared responsibility for transcription of data from CRF to computer files Monitoring of quality of data transcription Data analysis Writing committee: Preparation of material for peer review publication and presentation Archive study related material
Co-investigator John Whittle	Protocol design Ethics committee and R&D applications, amendments and other communication Informed consent Availability to answer participant queries Signing of consent form Recording of demographic data on Case Report Form (CRF) Recording of specified postoperative outcomes on CRF Documentation and timely reporting to sponsor of serious adverse events (SAEs) Be available for audit and inspections Initiation of new trial personnel Transcription of data from CRF to computer files

	Monitoring of quality of data transcription Data analysis Writing committee: Preparation of material for peer review publication and presentation
Research Nurse Maggie Gavasingha Claire West Helen McMillan Kate Tantam Shona Hughes	Maintenance of Site File Maintenance of secure recruitment database Informed consent Availability to answer participant queries Signing of consent form Recording of demographic data on Case Report Form (CRF) Recording of specified postoperative outcomes on CRF Be available for audit and inspections
Patient representative	Provide Service User perspective Protocol design Steering group Preparation of patient information leaflets and informed consent forms

19. Monitoring plan for the trial

The trial will be monitored according to the monitoring plan agreed by the sponsor, based on the self-monitoring template risk assessment. It is the responsibility of the CI to ensure that the sponsor's self-monitoring template is completed throughout the trial every two months and submitted to the JBRU at the regularity determined by the sponsor's risk assessment of the trial

phase. It is the responsibility of the CI to determine the monitoring risk assessment and explain the rationale. The PI will also be required to complete this self-monitoring template and return the form at the same frequency, to the CI and sponsor in parallel for review. It is the CI's responsibility to ensure that any findings identified in a PI's monitoring report are actioned in a timely manner and any violations of GCP or the protocol reported to the sponsor immediately. Any urgent safety measures at either the CI or a PI site must be reported by that site Investigator within 3 days, as per UK Regulations.

20. Insurance

University College London holds insurance to cover participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical trial. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or not. This does not affect the participant's right to seek compensation via the non-negligence route.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of University College London or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office.

The hospital (UCLH) selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to University College London, upon request.

21. Publication policy

The results of this study will be disseminated to a peer reviewed scientific journal, as well as conference presentations and internal reports. Patients will be able to track ongoing progress through The International Standard Randomised Controlled Trial Number (ISRCTN) which provides a unique number that can be used to track the trial throughout its lifecycle from initial protocol to

publication of results. Patient representatives are invited to attend monthly research meetings at the Centre for Anaesthesia UCL to be appraised of progress of POM-HR, and all publications will be forwarded to participants.

22. Statement of compliance

The trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).

23. References

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