London - Brent Research Ethics Committee
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Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

09 December 2016

Professor Rupert Pearse
Professor of Intensive Care Medicine
Queen Mary University of London
Adult Critical Care Unit, Royal London Hospital
London
E1 1BB

Dear Professor Pearse

Study title:	**Optimisation of Peri-operative Cardiovascular Management to Improve Surgical Outcome II (OPTIMISE II) Trial: Open, multi-centre, randomised controlled trial of cardiac output-guided fluid therapy with low dose inotrope infusion compared to usual care in patients undergoing major elective gastrointestinal surgery.**
REC reference:	**16/LO/2067**
IRAS project ID:	**209688**

The Research Ethics Committee reviewed the above application at the meeting held on 28 November 2016.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager Patrick Walsh, nrescommittee.london-brent@nhs.net . Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA Approval (England)/ NHS permission for research is available in the Integrated Research Application System, at www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS Sites

The favourable opinion applies to all NHS sites taking part in the study taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non NHS sites

The Committee has not yet completed any site-specific assessment(s) (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. I will write to you again as soon as an SSA application(s) has been reviewed. In the meantime no study procedures should be initiated at non-NHS sites.

Summary of discussion at the meeting

Social or scientific value; scientific design and conduct of the study

The Committee asked if the participants would be interviewed over phone.

The researchers stated that assessing a participants' quality of life over the phone is difficult. Previously a standard form with a suite of questions had been used that correlated with quality of life measures, and patients answered the questionnaire well.

The Committee was satisfied with the investigators' responses detailed above.

Recruitment arrangements and access to health information, and fair participant selection

The Committee asked about the need for targeting patients at pre-assessment clinics.

Dr MacDonald explained that the original protocol was for pre-assessment clinic recruitment. Emergency patients are very limited set of participants in the study. The majority of patients will be from pre-assessment but a small number of semi-urgent cases will also be included.

The Committee asked if patients would be coerced into the study

Dr MacDonald explained that this would not be the case as the patients would be given time to consider the study.

The Committee asked for the rationale behind using an inclusion score of 1 for ASA.

Dr MacDonald stated that the ASA score of 1 would be linked to fit and healthy individuals, whereas the study would like co-morbidity in the individuals to be apparent. Furthermore, Dr MacDonald explained that very fit patients do not show any improvements in outcomes, so potentially the study would not be worthwhile, therefore less well patients would benefit more from participating in the study.

The Committee was satisfied with the investigators' responses detailed above.

Favourable risk benefit ratio; anticipated benefit/risks for research participants (present and future)

The Committee noted that the study would carry a risk of minor heart attacks and asked the research team to elaborate.

Dr MacDonald acknowledged that there was a potential risk but explained that there is no

increase in risk as the monitoring will not lead to heart attack and only small dosages of inotropes are being used.

Dr MacDonald also explained that a previous study did not show any increase in the numbers of minor heart attacks and wanted this included within the supporting information.

The Committee asked if Dr MacDonald could quantify the risk.

Dr MacDonald replied that the previous study had shown that slightly more people had experienced a cardiac event but that the numbers involved were not clinically significant.

The Committee was satisfied with the investigators' responses detailed above.

Care and protection of research participants; respect for potential and enrolled participants' welfare and dignity

The Committee asked if the procedure was in line with normal standard of care.

Dr MacDonald confirmed that this was the case as a matter of routine clinical practice

The Committee asked if Dopexamine was part of the standard of care

Dr MacDonald stated that it was part of the original and previous studies since 2000, and explained that the differences in usage were dependent on the physician's preferred choice.

The Committee asked about availability of support for participants.

Dr MacDonald explained that there would be an email address and phone number available to participants so that they would have immediate access to clinical care, including Dr MacDonald as a designated person on call.

The Committee was satisfied with the investigators' responses detailed above.

The Committee commented that it was a well written study.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Covering letter on headed paper [Cover letter]		07 November 2016
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Insurance]		04 November 2016
GP/consultant information sheets or letters [GP letter]	1.0	03 November 2016
IRAS Application Form [IRAS_Form_07112016]		07 November 2016
IRAS Application Form XML file [IRAS_Form_07112016]		07 November 2016
IRAS Checklist XML [Checklist_07112016]		07 November 2016
Letter from funder [interview outcome letter]		24 June 2014
Letter from sponsor [Letter from sponsor]		04 November 2016
Participant consent form [Informed consent form]	1.0	03 November 2016
Participant information sheet (PIS) [Patient information sheet]	1.0	03 November 2016
Research protocol or project proposal [Study Protocol]	1.0	02 November 2016
Summary CV for Chief Investigator (CI) [Rupert Pearse CV]		10 January 2015

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed below.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

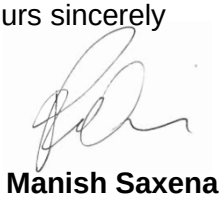
HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

16/LO/2067	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely



pp
Dr Manish Saxena
Chair

Enclosures: *After ethical review – guidance for researchers*

Copy to: *Miss Ann Thomson*
Dr Sally Burtles, Queen Mary University of London

London - Brent Research Ethics Committee

Attendance at Committee meeting on 28 November 2016

Committee Members:

Name	*Profession*	*Present*	*Notes*
Mr Suresh Akula	Retired Civil Servant	Yes	
Dr Parastoo Babakinejad	Dermatologist	No	
Mr Babak Babakinejad	Research Postgraduate	No	
Dr Daniel Bradford	Pharmacologist	Yes	
Mrs Louise Braley	RES Regional Manager (Observer)	Yes	
Mrs Sunder Chita	Manager	Yes	
Dr Graham Davison	Pharmaceutical Consultant	No	
Dr Anke Furck	Consultant in Paediatric Intensive Care	Yes	
Mrs Diana Harvey	Lawyer	Yes	
Mr Maurice Hoffman	Retired Teacher	Yes	
Dr Dusko Ilic	Reader in Stem Cell Science	Yes	
Mr Adeyemi Olagbegi	Clinical Pharmacology Study Data Manager	No	
Dr Alexander Rakow	Consultant Neonatologist	No	
Dr Manish Saxena	Clinical Lecturer	Yes	
Dr Zdenek Slavik	Consultant Paediatric Cardiologist/Intensivist	Yes	
Dr Krishna Soondrum	Consultant Paediatric Gastroenterologist	No	
Mr Patrick Walsh	REC Manager	Yes	
Miss Ourania Xeniou	Senior Clinical Research Associate	No	
Miss Zainab Yate	Bioethics Researcher	No	

Written comments received from:

Name	*Position*
Dr Krishna Soondrum	Consultant Paediatric Gastroenterologist