Health Research Authority

**South Central - Oxford C Research Ethics Committee**
Level 3, Block B
Whitefriars Building
Lewins Mead
Bristol
BS1 2NT

Telephone: 0207 104 8049

**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**

05 September 2017

Professor Paul Dark
Chair of Critical Care Medicine
University of Manchester
Research and Development Department
First Floor, Summerfield House, Salford Royal NHS Foundation Trust
Salford, Greater Manchester
M6 8HD

Dear Professor Dark

| | |
|---|---|
| **Study title:** | **Biomarker-guided duration of antibiotic treatment in hospitalised patients with suspected sepsis. The ADAPT-Sepsis Trial.** |
| **REC reference:** | **17/SC/0434** |
| **Protocol number:** | **R121074** |
| **IRAS project ID:** | **209815** |

The Research Ethics Committee reviewed the above application at the meeting held on 25 August 2017. Thank you for attending to discuss the application.

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 hra.studyregistration@nhs.net outlining the reasons for your request. 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. .

**Mental Capacity Act 2005**

I confirm that the Committee has approved this research project for the purposes of the Mental Capacity Act 2005. The Committee is satisfied that the requirements of section 31 of the Act will be met in relation to research carried out as part of this project on, or in relation to, a person who lacks capacity to consent to taking part in the project.

**Conditions of the favourable opinion**

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

**Changes to the consultee declaration form**

1. Please replace, 'I give permission for these individuals to have access to the patient's records' with, 'In my opinion the patient would have no objection to having their records accessed by these individuals.'

**Changes to the consultee declaration form and consent form**

2. Please amend the declaration and consent forms to refer to the correct version of the participant and consultee information sheets.

**Changes to the protocol**

3. Please amend the protocol to state that data gathered up until the point a participant loses capacity to consent would be retained by default unless the participant or their consultee requests otherwise.

**Changes to the participant and consultee information sheets**

4. Please amend to state that data gathered up until the point a participant loses capacity to consent would be retained by default unless the participant or their consultee requests otherwise.

5. Please remove the statement that, 'Your recovery from sepsis or any other clinical condition from which you may be suffering will not be enhanced or hindered through your participation in this study.'

6. Please add the correct South Central – Oxford C REC name.

**Recommendations (optional)**

a. Please amend the research summary (A6-1) to describe the research intervention more clearly.

b. Please review the proportion of patients not recruited into the study due to time constraints involved in obtaining consultee opinions as part of the pilot study, in order to evaluate whether an emergency waiver of consent is needed.

**You should notify the REC once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. Revised documents should be submitted to the REC electronically from IRAS. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which you can make available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.**

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**

*Relevance of the research to the impairing condition*

The Committee agreed the research is connected with an impairing condition affecting persons lacking capacity or with the treatment of the condition.

*Justification for including adults lacking capacity to meet the research objectives*

The Committee agreed the research could not be carried out as effectively if it was confined to participants able to give consent.

The Committee asked you to explain how the previous research in this field had been of poor quality.

*You explained that this judgment was based on a NICE review, to which you had contributed, of the relevant literature. This review had identified a concern about performance bias in pervious trials, because biomarker research often involves a lot of potentially confounding variables in the intervention arms and poor reporting in the control arm, which makes it difficult to reliably establish what constitutes standard clinical practice and outcomes. Additionally, trials conducted outside the UK involve a different standard care practices to NHS guidelines about for how long antimicrobials should be prescribed, which has made it difficult to evaluate the potential impact of these trials on safety and cost effectiveness in relation to an NHS context.*

The Committee accepted this response.

The Committee asked how the biomarker algorithms had been derived.

*You explained that they was based on the NICE review and consensus on procalcitonin, so uncontroversial levels and would be expected by sites. You explained that there has been little research in systematic trials of different levels of c-reactive proteins. The research team had done a UK survey prior to the application, and decided to adopt algorithms used by a Brazilian trial as the only available analogous trial.*

The Committee accepted this response.

The Committee noted that the trial protocol would involve running a pilot study, and asked whether the research plan would be examined and potentially revised as part of this.

*You confirmed this, emphasising that protocol adherence would be important and so it would be important to evaluate whether it would be feasible to obtain the blinded information needed from clinicians in order to inform their research decisions.*

The Committee accepted this response.

The Committee asked why the protocol had not included a combined CRP/PCT arm.

*You explained that the protocol had been developed in response to an NIHR-commissioned call, and that whilst it might not be the research team's preferred approach it should generate sufficient data for secondary modelling.*

The Committee asked whether the PCT arm would automatically include CRP data.

*You clarified that it would not, as this testing would be a cost to the NHS as it wasn't covered by the research. You added that other studies have reported CRP in PCT groups, and that the data that exists suggests sufficient similarity to establish equipoise for the study.*

**Informed consent process and the adequacy and completeness of participant information**

*Information for consultees*

The Committee reviewed the information to be provided to consultees about the proposed research and their role and responsibilities as a consultee.

The Committee considered that the information was not adequate for the following reasons: and requested the following changes:

The Committee noted that page four of the participant and consultee information sheets claim that 'recovery from sepsis or any other clinical condition from which you may be suffering will not be enhanced or hindered through your participation in this study.' However, it pointed out that because one of the primary endpoints of the research would be safety, that statement should be removed because it could not be guaranteed.

*You agreed to do so.*

The Committee explained that in order to comply with the Mental Capacity Act (2005), the consultee declaration form should be amended to refer to giving an opinion rather than granting permission or giving consent on behalf of participants.

*You agreed to do so.*

The Committee advised that although the study protocol stipulated that participants would be asked for permission to retain research data already collected in the event that they regained capacity, it agreed that the data ought to be retained by default in the interest of the public good.

*You agreed to do so, and to replace the request for permission to retain data with an opt-out option.*

The Committee asked you whether there ought to be an emergency waiver of consent protocol in place. It asked how swiftly the research team would need to consent participants into the study, and whether it was likely that recruitment would be impacted significantly by a lack of available consultees.

*You explained that the research team had discussed this option and decided that an emergency waiver of consent would not be needed, but that they would intend to evaluate this during the pilot phase of the research and submit a request to introduce and emergency waiver if needed.*

The Committee accepted this response.

***Other ethical issues were raised and resolved in preliminary discussion before your attendance at the meeting.***

*Please contact the REC Manager if you feel that the above summary is not an accurate reflection of the discussion at the meeting.*

**Approved documents**

The documents reviewed and approved at the meeting were:

| *Document* | *Version* | *Date* |
|---|---|---|
| Covering letter on headed paper [HRA Covering Letter] | | 31 July 2017 |
| Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Signed Insurance Assessment Form] | | 13 June 2017 |
| Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Indemnity Statement] | | 31 July 2017 |
| GP/consultant information sheets or letters [GP Letter] | 1.0 | 27 July 2017 |
| IRAS Application Form [IRAS_Form_04082017] | | 04 August 2017 |
| IRAS Checklist XML [Checklist_04082017] | | 04 August 2017 |
| Letter from funder [funding letter] | | |
| Letter from sponsor [Sponsor Letter] | V1.0 | 01 August 2017 |
| Other [Sponsor Indemnity Statement] | V1.0 | 01 August 2017 |
| Other [Sponsor CT, Medical Malpractice and PI Confirmation] | V1.0 | 01 June 2017 |
| Other [HRA Clarification Letter] | | 04 August 2017 |
| Participant information sheet (PIS) [ADAPT-Sepsis PIS Patient at Commencement] | V1.1 | 01 August 2017 |
| Participant information sheet (PIS) [ADAPT-Sepsis PIS Recovery] | V1.1 | 01 August 2017 |

| | | |
|---|---|---|
| Participant information sheet (PIS) [ADAPT-Sepsis CIS Consultee] | V1.1 | 01 August 2017 |
| Participant information sheet (PIS) [ADAPT-Sepsis CIS (N.Ireland)] | V1.1 | 01 August 2017 |
| Research protocol or project proposal [ADAPT-Sepsis Trial Protocol] | 1.0 | 27 July 2017 |
| Summary CV for Chief Investigator (CI) [Paul Dark short CV] | July 2017 | 03 July 2017 |
| Summary, synopsis or diagram (flowchart) of protocol in non technical language [ADAPT-Sepsis Trial Protocol] | 0.1 | 18 July 2017 |

**Membership of the Committee**

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

None

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/

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

Yours sincerely

**pp. Ms Helen Sivey**
**REC Manager**

**Professor Nigel Wellman**
**Chair**

E-mail: nrescommittee.southcentral-oxfordc@nhs.net

**South Central - Oxford C Research Ethics Committee**

**Attendance at Committee meeting on 25 August 2017**

## Committee Members:

| *Name* | *Profession* | *Present* | *Notes* |
|---|---|---|---|
| Dr Leonard Brookes | Consultant to the Pharmaceutical Industry | Yes | |
| Dr Linda Cartwright | Retired Consultant Epidemiologist | Yes | |
| Dr Ben Caswell | Accountant | Yes | |
| Dr Alessandro Di Nicola | Lecturer in Philosophy | No | |
| Mrs Rebekah Howe | Farmer | Yes | |
| Mrs Vivienne Laurie | Barrister | Yes | |
| Dr Simon Lord | Honorary Consultant in Medical Oncology and Senior Clinical Researcher in Experimental Cancer Therapeutics | Yes | |
| Mrs Susan Lousada | Company Director (Property) & Non-legal member of first-tier tax tribunal | Yes | |
| Mr Chris Pratt | Specialist Cancer Pharmacist | Yes | |
| Ms Anna Rathmell | Medical Manager - GI | Yes | |
| Dr Sabeena Sharma | Consultant Anaesthetist | Yes | |
| Dr Surjeet Singh | Clinical Trials Coordinator | Yes | |
| Professor Nigel Wellman (Chair and Meeting Chair) | Professor of Health and Human Sciences | Yes | |

## Also in attendance:

| *Name* | *Position (or reason for attending)* |
|---|---|
| Ms Helen Sivey | REC Manager |
| Ms Cloe Vassart | Biobanker |