Health Research Authority

South Central - Oxford C Research Ethics Committee
Health Research Authority (Bristol)
Ground Floor, Temple Quay House, 2 The Square
BS1 6PN

Telephone: 0207 104 8241

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

12 July 2021

Prof Gavin Perkins
Professor in Critical Care Medicine
University of Warwick
Gibbet Hill Road
Coventry
CV4 7AL

Dear Prof Perkins

Study title:	**Pre-hospitAl RAndomised trial of MEDICation route in out-of-hospital cardiac arrest (PARAMEDIC3)**
REC reference:	**21/SC/0178**
Protocol number:	**SOC.20/20-21**
IRAS project ID:	**298182**

Thank you for your letter of 06 July 2021, responding to the Research Ethics Committee's (REC) request for further information on the above research and submitting revised documentation.

The further information was considered at the meeting of the Committee held on 12 July 2021. A list of the members who were present at the meeting is attached.

Confirmation of Ethical Opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Mental Capacity Act 2005 (England and Wales)

I confirm that the committee has approved this research project for the purposes of the Mental Capacity Act 2005 (England and Wales). 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.

Mental Capacity Act (Northern Ireland) 2016

The Committee approved this research project for the purposes of the Mental Capacity Act (Northern Ireland) 2016. The Committee is satisfied that the requirements of Part 8 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.

Relevance of the Research to the Impairing Condition

The Committee agreed the research was connected with an impairing condition affecting persons lacking capacity or with the treatment of the condition. The members noted that Cardiac Arrest was the impairing 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 acknowledged that this study could not be completed without including adults that lack capacity as patients will be unconscious immediately after cardiac arrest and, thus, unable to consent. The members also noted that the intervention needs to be delivered immediately.

Arrangements for Appointing Consultees

The Committee considered the arrangements set out in the application for appointing consultees under Section 32 of the Mental Capacity Act 2005 (England and Wales) and the equivalent Section 135 of the Mental Capacity Act (Northern Ireland) 2016) to advise on whether participants lacking capacity should take part and on what their wishes and feelings would have likely to have been if they had capacity.

The Committee noted that (as outlined in question A29 of the IRAS Form) either the participants who survive or their consultees will be approached as soon as it is practical and reasonable after their cardiac arrest. The members also noted that experience from the earlier PARAMEDIC trials has shown many patients will continue to be sedated in the intensive care unit and, thus, still lack capacity. Furthermore, the applicants feel the approach to relatives at this time will be "unduly burdensome" which the applicants deemed as appropriate as there is no ongoing trial intervention at this stage. Therefore, the applicants plan to approach either the patient or consultee to inform them of enrollment in the trial at around the time of discharge from intensive care. The Committee discussed this potential ethical issue before the applicants joined the meeting and concluded that it was happy with this course of action. However, the Committee was not entirely satisfied with the other arrangements to identify and appoint consultee:

The Committee identified that (as outlined in question A35 of the IRAS Form) if a patient loses capacity having given consent previously the participant would continue to be included in the study. As consent does not survive loss of capacity, if the researchers wish to keep the

participant in the study and undertake further intrusive research, they must have approval under section 30 of the Mental Capacity Act and will need to seek advice from a consultee on whether the participant should remain in the study. *Professor Gavin Perkins confirmed that no participants will have initial capacity and explained that hospital staff will assess capacity once recovered and consent will be obtained. Professor Perkins added that if the patient loses capacity then their representative is required to complete the three- and six-month questionnaire and the researchers will still process data.* The Committee disagreed with Professor Gavin Perkins' response and emphasised that consent is not enduring under the Mental Capacity Act and that data cannot be continuously collected without further advice from their consultee*. Professor Gavin Perkins confirmed that the applicants are seeking CAG Approval for the continued access and processing of data.* The Committee was satisfied with this response after receiving confirmation from the Approvals Manager that this is the correct course of action.

The Committee requested the correct terminology for Consultees is used throughout the study documentation; for example, consultees should sign a declaration form not a consent form and should provide verbal advice not verbal consent. *The applicants updated the documentation to ensure the correct terminology is used throughout.* The Committee was satisfied with these further changes.

The Arrangements for Recruitment in an Emergency Setting

The Committee noted that the research would take place in circumstances involving the provision of urgent treatment to participants lacking capacity.

The Committee agreed that, in the circumstances, it was justified to recruit participants prior to obtaining advice from a consultee under the provisions in Section 32(8) and (9) of the Mental Capacity Act 2005 (England and Wales) and the equivalent Section 136 of the Mental Capacity Act (Northern Ireland) 2016). The Committee noted that the treatment of cardiac arrest is time-critical with any delay in achieving return of circulation affecting overall survival and, therefore, there will be no time to consult with personal or nominated consultees prior to enrollment in the trial. The members concluded that a deferred method of consent will be used, and is justifiable, in this emergency setting.

Balance Between Benefit and Risk, Burden and Intrusion

The Committee agreed that the research has the potential to benefit participants lacking capacity without imposing a disproportionate burden on them.

Additional Safeguards

The Committee was satisfied that reasonable arrangements would be in place to comply with the additional safeguards set out in Section 33 of the Mental Capacity Act 2005 (England and Wales) and the equivalent Section 137 of the Mental Capacity Act (Northern Ireland) 2016).

Information for Consultees

The Committee was satisfied that the information to be provided to consultees about the proposed research was adequate to enable consultees to give informed advice about the participation of persons lacking capacity.

Good Practice Principles and Responsibilities

The UK Policy Framework for Health and Social Care Research sets out principles of good practice in the management and conduct of health and social care research. It also outlines the responsibilities of individuals and organisations, including those related to the four elements of research transparency:

1. registering research studies
2. reporting results
3. informing participants
4. sharing study data and tissue

Conditions of the Favourable Opinion

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

Number	Condition
1	The Committee acknowledged that the Participant Information describes that the participant was enrolled without their consent. The Committee agreed that this is the case, however, the members requested an additional sentence is also added to this section of the information sheet: "It was deemed by the paramedic that either Intravenous or **Intraosseous** injection was in the best interest of the patient based on their clinical assessment".

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.

Confirmation of Capacity and Capability (in England, Northern Ireland and Wales) or NHS management permission (in Scotland) 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 and HCRW Approval (England and Wales)/ NHS permission for research is available in the Integrated Research Application System.

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 research should be registered in a publicly accessible database and we expect all researchers, research sponsors and others to meet this fundamental best practice standard.

It is a condition of the REC favourable opinion that **all clinical trials are registered** on a publicly accessible database within six weeks of recruiting the first research participant. For this purpose, 'clinical trials' are defined as the first four project categories in IRAS project filter question 2. Failure to register a clinical trial is a breach of these approval conditions, unless a deferral has been agreed by or on behalf of the Research Ethics Committee (see here for more information on requesting a deferral: https://www.hra.nhs.uk/planning-and-improving-research/research-planning/research-registration-research-project-identifiers/

If you have not already included registration details in your IRAS application form, you should notify the REC of the registration details as soon as possible.

Further guidance on registration is available at: https://www.hra.nhs.uk/planning-and-improving-research/research-planning/transparency-responsibilities/

Publication of Your Research Summary

We will publish your research summary for the above study on the research summaries section of our website, together with your contact details, no earlier than three months from the date of this favourable opinion letter.

Should you wish to provide a substitute contact point, make a request to defer, or require further information, please visit: https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/

N.B. If your study is related to COVID-19 we will aim to publish your research summary within 3 days rather than three months.

During this public health emergency, it is vital that everyone can promptly identify all relevant research related to COVID-19 that is taking place globally. If you haven't already done so, please register your study on a public registry as soon as possible and provide the REC with the registration detail, which will be posted alongside other information relating to your project. We are also asking sponsors not to request deferral of publication of research summary for any projects relating to COVID-19. In addition, to facilitate finding and extracting studies related to COVID-19 from public databases, please enter the WHO official acronym for the coronavirus disease (COVID-19) in the full title of your study. Approved COVID-19 studies can be found at: https://www.hra.nhs.uk/covid-19-research/approved-covid-19-research/

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).

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, including early termination of the study
- Final report
- Reporting results

The latest guidance on these topics can be found at https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/.

Ethical Review of Research Sites

NHS/HSC sites

The favourable opinion applies to all NHS/HSC sites taking part in the study, subject to confirmation of Capacity and Capability (in England, Northern Ireland and Wales) or management permission (in Scotland) 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/HSC sites

I am pleased to confirm that the favourable opinion applies to any non-NHS/HSC sites listed in the application, subject to site management permission being obtained prior to the start of the study at the site.

Approved Documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Copies of advertisement materials for research participants [P3_A4Poster]	1.0	22 June 2021
Cover Letter [PARAMEDIC3_REC Cover Letter]		05 July 2021
Covering letter on headed paper [PARAMEDIC3_HRACoverLetter_v1.0_11May21]	1.0	11 May 2021
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [clinical_trials_evidence_of_cover_2020-21]		28 July 2020
IRAS Application Form [IRAS_Form_11052021]		11 May 2021
IRAS Checklist XML [Checklist_05072021]		05 July 2021
Letter from funder [NIHR131105 Perkins - Agree to fund letter]		12 February 2021
Letter from sponsor [SOC 20 20 21 Sponsorship Approval Letter]	1.0	11 May 2021
Non-validated questionnaire [PARAMEDIC3_Questionnaire Cover Letter (Clean)]	2.0	23 June 2021
Non-validated questionnaire [PARAMEDIC3_Questionnaire Cover Letter (TC)]	2.0	23 June 2021
Other [Letters of Support for Trial]		30 August 2020
Other [Trial_Funder_Peer_Review_Comments]		

Participant consent form [PARAMEDIC3_PatientConsentForm_v1.0_10May21]	1.0	10 May 2021
Participant consent form [PARAMEDIC3_Consultee Declaration Form (Clean)]	2.0	23 June 2021
Participant consent form [PARAMEDIC3_Consultee Declaration Form (TC)]	2.0	23 June 2021
Participant information sheet (PIS) [PARAMEDIC3_CoverLetterConsInHospital_v1.0_06May21]	1.0	06 May 2021
Participant information sheet (PIS) [PARAMEDIC3_CoverLetterPatPostDischarge_v1.0_06May21]	1.0	06 May 2021
Participant information sheet (PIS) [PARAMEDIC3_PIS (Clean)]	2.0	23 June 2021
Participant information sheet (PIS) [PARAMEDIC3_PIS (TC)]	2.0	23 June 2021
Research protocol or project proposal [PARAMEDIC3_Protocol (Clean)]	2.0	23 June 2021
Research protocol or project proposal [PARAMEDIC3_Protocol]	2.0	23 June 2021
Summary CV for Chief Investigator (CI) [GDP_CV_22Apr21]	1.0	22 April 2021
Validated questionnaire [P3_3MonthFollowUpQuestionnaire_v1.0_10May21]	1.0	10 May 2021
Validated questionnaire [P3_6MonthFollowUpQuestionnaire_v1.0_10May21]	1.0	10 May 2021

Statement of Compliance

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.

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 Learning

We are pleased to welcome researchers and research staff to our HRA Learning Events and online learning opportunities– see details at:
https://www.hra.nhs.uk/planning-and-improving-research/learning/

IRAS project ID: 298182 Please quote this number on all correspondence

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

Yours sincerely

PP
Dr Lee Potiphar
Chair

Email: oxfordc.rec@hra.nhs.uk

Enclosures: List of names and professions of members who were present at the meeting and those who submitted written comments

Copy to: Mrs Carole Harris
Confidentiality Advise Team

South Central - Oxford C Research Ethics Committee

Attendance at Committee meeting on 12 July 2021

Committee Members:

Name	*Profession*	*Present*	*Notes*
Dr Linda Cartwright	Retired Consultant Epidemiologist	Yes	Alternate Vice Chair.
Dr Ben Caswell	Accountant	Yes	
Dr Nicholas Coupe	PhD Student	No	
Mrs Vivienne Laurie	Barrister	Yes	Vice Chair.
Mrs Susan Lousada	Company Director (Property) & Non-legal member of first-tier tax tribunal	No	
Dr Nadia Muspratt-Tucker	ST3 Registrar in Obstetrics and Gynaecology	Yes	
Dr Lee Potiphar	Senior Lecturer in Adult Nursing and Senior Tutor	Yes	Chair and Meeting Chair.
Ms Anna Rathmell	Associate Director Learning and Development, Pharmaceuticals	No	
Dr Pamela Susan Ross	GP Principal	Yes	
Mr Barjinder Sahota	Solicitor Advocate	Yes	
Dr David Scott	Lecturer	Yes	
Dr Sabeena Sharma	Consultant Anaesthetist	No	
Mr Ioan Wigley	Regulatory Affairs Manager	No	

Also in Attendance:

Name	*Position (or reason for attending)*
Miss Charlotte Ferris	Approvals Officer
Mx Maeve Groot Bluemink	Approvals Manager
Ms Deana Herron	Approvals Specialist

Written Comments Received From:

Name	*Position*
Dr Sabeena Sharma	Consultant Anaesthetist