Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

Ariennir gan Lywodraeth Cymru
Funded by Welsh Government

Wales Research Ethics Committee 4
Wrexham

Mailing address:
Health and Care Research Wales
Castlebridge 5
15-19 Cowbridge Road East
Cardiff, CF11 9AB

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/ Wales until you receive HRA/ HCRW Approval.

3rd January 2024

Professor Matthew Wise
Consultant in Critical Care Medicine
Cardiff and Vale University Health Board
Critical Care Medicine,
University Hospital of Wales,
Heath Park Way,
Cardiff
CF14 4XW

Dear Professor Wise

Study title:	**Sedation, Temperature and Pressure after Cardiac Arrest and Resuscitation: A Factorial Randomised Trial with Three Interventions**
REC reference:	**23/WA/0342**
Protocol number:	**step2022**
IRAS project ID:	**328857**

Thank you for your letter of 20th December 2023, responding to the Research Ethics Committee's (REC) request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Alternate Vice-Chair.

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.

Compliance with the Mental Capacity Act – the Committee considered the following:

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 Committee considered that the study had the potential to improve post recovery outcomes.

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 noted that the vast majority of these patients would not have the capacity to give informed consent and the intervention, by its' very nature needed to commence straightaway. Hence the Committee agreed that their inclusion was absolutely necessary and could be wholly justified.

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 to advise on whether participants lacking capacity should take part and on what their wishes and feelings would be likely to be if they had capacity.

The Committee was not entirely satisfied with the arrangements to identify and appoint consultees and made the following suggestions they would like the applicant to consider.

The Committee noted a clear outline of recruitment arrangements but requested separate Participant Information Sheets (PIS) and Consent Forms for nominated and personal consultees.

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 and considered whether it would be reasonable practicable to consult a personal or nominated consultee prior to recruitment.

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. However, the REC requested the following changes to the recruitment procedures set out in Part B Section 6 of the application: The Committee requested separate Participant Information Sheets (PIS) and Consent Forms for nominated and personal consultees.

Balance between benefit and risk, burden and intrusion

After discussion, 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.

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 was satisfied that the information 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.

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:

- clinical trial of an investigational medicinal product
- clinical investigation or other study of a medical device
- combined trial of an investigational medicinal product and an investigational medical device
- other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice.

Failure to register a clinical trial is a breach of these approval conditions, unless a deferral has been agreed by the HRA (for more information on registration and requesting a deferral see: Research registration and 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.

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*
Covering letter on headed paper		
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Insurance quote]		09 October 2023
IRAS Application Form [IRAS_Form_16112023]		16 November 2023
Letter from funder [Funding letter from Sweden Research Council]		
Letter from sponsor [Letter from Sponsor]		
Non-validated questionnaire [Datasheet 12M STEPCARE_extended follow-up]	1.0	15 August 2023
Non-validated questionnaire [Datasheet for 30 day follow up]	1.0	15 August 2023
Non-validated questionnaire [Datasheet for 6 month follow up]	1.0	15 August 2023
Non-validated questionnaire [Datasheet 6M STEPCARE_extended follow-up]	1.0	15 August 2023
Other [DSMC charter]	1.0	25 July 2023
Other [NHMRC Australia funding letter]		
Other [V-CARE substudy information for control group]		
Other [V-CARE substudy manual]	1.2	28 August 2023
Other [Response to REC 201223]	1.0	20 December 2023
Participant consent form [Participant consent form]	V2.0	18 December 2023
Participant consent form [Personal consultee declaration form]	V2.0	18 December 2023
Participant consent form [Professional Consultee declaration form]	V2.0	18 December 2023
Participant consent form [Consultee telephone form]	V2.0	18 December 2023
Participant consent form [V-CARE substudy consent form]	V2.0	18 December 2023
Participant information sheet (PIS) [Personal Consultee PIS]	V2.0	18 December 2023
Participant information sheet (PIS) [Patient Information Sheet]	V2.0	18 December 2023
Participant information sheet (PIS) [Professional Consultee PIS]	V2.0	18 December 2023
Participant information sheet (PIS) [Patient information for V-CARE substudy]	V2.0	18 December 2023
Participant information sheet (PIS) [Patient information for V-CARE substudy (caregiver)]	V2.0	18 December 2023
Referee's report or other scientific critique report [Referee report from Swedish Research Council]		
Referee's report or other scientific critique report [Referee report from Finland Academy]		
Research protocol or project proposal [Protocol]	V2.0	18 December 2023
Response to Request for Further Information [Response to Request for Further Information]		20 December 2023
Summary CV for Chief Investigator (CI) [Matt Wise CV]		24 January 2022
Summary, synopsis or diagram (flowchart) of protocol in non technical language [Stepcare timeline]		
Summary, synopsis or diagram (flowchart) of protocol in non technical language		
Validated questionnaire [World Health Organization Disability Assessment Scale (WHODAS) 2.0 12 items version]		
Validated questionnaire [World Health Organization Disability Assessment Scale (WHODAS) 2.0 36 items version]		
Validated questionnaire [Life satisfaction questionnaire]		
Validated questionnaire [Self-management Assessment Scale.]		
Validated questionnaire [Symbol Digit Modalities Test (SDMT)]		
Validated questionnaire [Hospital anxiety and Depression Scale (HADS)]		
Validated questionnaire [Zarit Burden Interview (ZBI)]		

Validated questionnaire [Client Satisfaction Questionnaire-8]		
Validated questionnaire [EQ5D5L]		
Validated questionnaire [Informant Questionnaire on Cognitive Decline in the Elderly – Cardiac Arrest version (IQCODE-CA)]		
Validated questionnaire [Modified Fatigue Impact Scale (MFIS)]		
Validated questionnaire [Montreal Cognitive Assessment (MoCA)]		
Validated questionnaire [modified rankin scale]		
Validated questionnaire [Post-traumatic stress disorder (PTSD) Checklist (PCL-5)]		

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: 328857 Please quote this number on all correspondence

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

Yours sincerely

pp Mr Martin Rawson- Approvals Administrator
Dr Julie Latchem-Hastings
Chair

Email: Wales.REC4@wales.nhs.uk

Enclosures: "After ethical review – guidance for researchers" **Non CTIMP Standard Conditions of Approval**

Copy to: Dr Judith White
Lead Nation Wales: research-permissions@wales.nhs.uk