Address for all correspondence
Research Ethics and Governance Office
Royal Prince Alfred Hospital

Telephone: (02) 9515 6766
Email: SLHD-RPAEthics@health.nsw.gov.au
Reference: X23-0174 & 2023/ETH00964

8 August 2023

This letter constitutes ethical approval only. You must NOT commence this research project at ANY site until you have submitted a Site Specific Assessment Form to the Research Governance Officer and received separate authorisation from the Chief Executive or delegate of that site.

Dear Professor Sanders,

Re: Protocol no. X23-0174 & 2023/ETH00964 - "UNderstanding CONSciousness Connectedness and Intraoperative Unresponsiveness Study-3: a single-site, randomised, double-blind, cross-over trial in healthy volunteers (UN-CONSCIOUS-3)"

Thank you for submitting the above research proposal for single ethical and scientific review. This project was first considered by the Clinical Trials Sub-committee at its meeting held on 6 June 2023 and by the Sydney Local Health District Human Research Ethics Committee (HREC) – RPAH Zone at its meeting held on 14 June 2023.

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research*, the *CPMP/ICH Note for Guidance on Good Clinical Practice* and the *National Clinical Trials Governance Framework.*

I am pleased to advise that final ethical approval has been granted based on the following:

- The research project meets the requirements of the *National Statement on Ethical Conduct in Human Research (2007) – updated 2018*.

The documents reviewed and approved include:

- HREA (Version 4, 27 July 2023)
- Protocol (Version 3, 31 July 2023)
- Australian Product Information PRECEDEX® (DEXMEDETOMIDINE HYDROCHLORIDE) (15 September 2021)
- MASTER Participant Information Sheet (Version 3, 31 July 2023)
- MASTER Participant Consent Form (Version 3, 31 July 2023)
- Verbal Consent (Version 1, dated 18 May 2023)
- Anaesthetic Chart RPAH (dated 08 May 2023)

- Master Code Sheet (Version 1, 18 May 2023)
- Research Data Management Plan (Version 1, 08 May 2023)
- UNCONCIOUS-3 Case Record File (Version 1.1, 20 June 2023)
- Advertisement (Version 1, 18 May 2023)
- Discharge Letter (Version 1, 08 May 2023)
- Initial Screening Telephone Script (Version 1, 18 May 2023)
- Study Participant Feedback Questionnaire (SPFQ) (undated)
- GCP Certificate – R Sanders (dated 02 March 2021)
- GCP Certificate – K Kramer (dated 15 February 2021)
- GCP Certificate – L Loadsman (dated 09 August 2021)
- GCP Certificate – T McCulloch (dated 30 May 2022)

The HREC has provided ethical and scientific approval for the following sites:

1. Royal Prince Alfred Hospital, NSW

For sites outside of NSW/ACT REGIS, a copy of this letter must be forwarded to all site investigators for submission to the relevant Research Governance Officer.

Please note the following conditions of approval. The conditions listed in this approval letter should be comprehensively reviewed and understood by all members of the research team:

1. HREC approval is valid for five (5) years subject to the supply of quarterly progress reports. The first report should be sent to the HREC by **08/11/2023.** You must also provide an annual report to the HREC upon completion of the study. This will be through a submission of a milestone in REGIS, see REGIS Quick Reference Guide (QRG): **Submitting Annual Progress or Final Report (Milestone)**.

   Important notes:
   - **Ethics expiry:** An ethics extension amendment should be submitted prior to the ethics approval expiry date if the study is continuing beyond that date. This will be through a notification of an ethics amendment via REGIS, see REGIS QRG: **Ethics Amendment - Completing and Submitting**. Projects that are 12 months past the ethics expiry without submitting an ethics extension amendment will automatically be **suspended**.
   - **Milestones:** The status of any pending quarterly progress report that is six or more months past the due date will automatically be changed to 'Not Achieved'. The Research Office should be contacted to create a replacement milestone for the calendar year covered by the 'Not Achieved' milestone. The Committee relies on these reports to verify that the conduct of research complies with the approved protocol and remains ethically acceptable. Failure to submit regular or ongoing reports may result in your **ethics approval being withdrawn.**

2. In accordance with the National Statement, chapter 4.7; you must seek ethical approval from the HREC of the Aboriginal Health and Medical Research Council (AHMRC) if you intend to use Aboriginal and /or Torres Strait Islander status in any presentation or publication. See Research Office website for more information.

3. The study procedures as listed in the protocol must be followed at all times. See *The Australian Code for the Responsible Conduct of Research.*

4. All study personnel must be trained in the study protocol and aware of their role and responsibilities with respect to the research. All new personnel must be appropriately onboarded.

5. **Ethics Amendments:** Any proposed changes to the research protocol should be submitted to the HREC before those changes are implemented, such as changes to:
    - The general conduct of the research, including new aims or sub-studies
    - Any study procedures or data collection/management
    - CPI, site PI, adding students or other study personnel
    - The period covered by the ethics approval, i.e, to request an extension
    - The addition of sites

    Updated study documents should be submitted as a tracked and clean copy with new version number and date. This will be through a notification of an ethics amendment via REGIS, see REGIS QRG: **Ethics Amendment - Completing and Submitting**. See the Research Office website for more information on who can submit an amendment.

6. If the project is discontinued at a site before the expected date of completion, you must notify the HREC with reasons provided. It is also important to ensure study closure and completion processes are carried out in accordance with the Research Data Management Plan, Good Clinical Practice and local governance procedures. This will be through a notification of an ethics amendment via REGIS, see REGIS QRG: **Ethics Amendment - Completing and Submitting**. The site Research Governance Officer should also be notified following ethics acknowledgment, see REGIS QRG: **Governance Amendment - Completing and Submitting**.

7. You must immediately report anything which might warrant review of ethics approval, including unforeseen events that might affect continued ethical acceptability of the project. Examples include, significant safety issues, serious breaches, participant complaints, privacy breaches. This will be through a notification via REGIS, see REGIS QRG: **Clinical Trial Safety Reporting** (for clinical trials) or **Ethics Amendment - Completing and Submitting**.

8. **Serious breaches:** Serious breaches and complaints should be reported in accordance with NHMRC Guidance document: Reporting of Serious Breaches of Good Clinical Practice (GCP) or the Protocol for Trials Involving Therapeutic Goods 2018. **All complaints should immediately be reported to the HREC within 24 hours of being notified.** This will be through a notification via REGIS. This will be through a notification via REGIS, see REGIS QRG: **Clinical Trial Safety Reporting** (for clinical trials) or **Ethics Amendment - Completing and Submitting**.

9. **Conflicts of interest:** Any changes to financial, business or other non-financial conflicts of interests related to this research should be declared to the HREC in accordance with the National Statement Chapter 5.4: Conflicts of interest. See also NHMRC guidance document Disclosure of interests and management of conflicts of interest. This will be through a notification via REGIS, see REGIS QRG: **Ethics Amendment - Completing and Submitting**.

10. ***This study requires notification to the Therapeutic Goods Administration (TGA) under the Clinical Trials Notification (CTN) Scheme.***
    The clinical trial should not commence until the CTN has been submitted to the Therapeutic Goods Administration (TGA) using the online form. This HREC approval letter fulfils the documentation required to indicate the approval of the Human Research Ethics Committee responsible for monitoring the trial. A copy of the TGA acknowledgment of receipt of a CTN must be submitted to the Research Governance Office as soon as it is available.

11. **Partnering with Consumers:** As per Standard 2 of The National Clinical Trials Governance Framework, you are asked to provide an update with your annual progress report (milestone) on the ongoing involvement of consumers in the planning, design, delivery, measurement and evaluation of the trial.

12. **Good Clinical Practice (GCP):** When adding additional sites, it is a condition of approval that the GCP Certificate of Completion be submitted for the principal investigators responsible for the new sites.

For your information at the end of this letter is a general checklist to assist you with following all the necessary steps to support the study's compliance throughout its full duration.

Should you have any queries about the HREC's consideration of your project please contact the Executive Officer - (02) 9515 8200. The HREC Terms of Reference, Standard Operating Procedures, membership and standard forms are available from the website: https://www.slhd.nsw.gov.au/rpa/research/default.html

The HREC welcomes feedback from researchers on how the ethics review process can be improved or how researchers can be better supported. If you would like to provide feedback, please email the Research Office.

Researchers are encouraged to:

- Develop standard operating procedures for consenting in line with the National Standard Operating Procedures. (if applicable)
- Regularly visit REGIS for system updates and for notifications about their project.
- Regularly review the Research Office website for up-to-date information on ethics requirements, training opportunities and drop-in clinics.
  https://www.slhd.nsw.gov.au/rpa/research/default.html

The Human Research Ethics Committee wishes you every success in your research.

Yours sincerely,

Sanaa Thomas
Executive Officer – Clinical Trials Sub-committee
Sydney Local Health District Human Research Ethics Committee – RPAH Zone

Research Study Compliance Checklist

	Completed
Study approvals	
1. Ethics Approval	
2. Site Specific Authorisation at all sites	
Study commencement	
3. Study personnel training and on-boarding at all sites	
4. Develop Consent SOP	
5. Data Management processes established per approved RDMP	
Study conduct	
6. Check in REGIS for milestones' due dates & other updates (annual report milestones are due to be submitted each year on the ethics approval anniversary date)	
7. All ethics amendments are notified to the HREC/RGO	
8. All complaints/breaches reported to HREC	
9. At end of 5 years, request ethics extension (if the study is ongoing)	
Study closure	
10. Notify HREC/ RGO –final milestone (Closed post-analysis)	
11. Ensure study documentation archived as per the approved Protocol	
12. Ensure data is managed as per the approved Protocol	
13. Report results to participants	