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: **X24-0120 & 2024/ETH00751**

27 August 2024

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 Gnanenthiran,

Re: Protocol no. X24-0120 & 2024/ETH00751 - "LOw dose combinations To improve stroke oUtcomeS (LOTUS): a randomised trial to compare single pill combination based therapy and telehealth intervention vs standard care in survivors of ischaemic stroke/transient ischaemic attack"

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 30 April 2024 and by the Sydney Local Health District Human Research Ethics Committee (HREC) – RPAH Zone at its meeting held on 12 June 2024.

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 (2023)*

The documents reviewed and approved include:

- HREA (Version 6, 22 August 2024)
- Protocol (Version 4.0, 22 August 2024)
- GMRx2 Investigator's Brochure (Version 1.0, 15 April 2024)
- Participant Information Sheet/Consent Form (Master Version 4.0, 22 August 2024)
- Participant Information Sheet/Consent Form – Biomarker Substudy (Master Version 2.0, 07 July 2024)
- Participant Information Sheet/Consent Form - Health Practitioner Process Evaluation (Master Version 1.0, 15 April 2024)

- Participant Information Sheet/Consent Form - Participant Process Evaluation (Master Version 1.0,15 April 2024)
- Letter to GP Trial Entry (Version 2.0, 07 July 2024)
- Letter to GP Trial Completion (Version 1.0, 01 June 2024)
- Data Collection Form (Version 2, 07 July 2024)
- Master Code Sheet (Version 1.0, 15 April 2024)
- Lotus Easy Read (Version 2.0, 07 July 2024)
- Health Practitioner Advertisement (Version 2.0, 07 July 2024)
- Health Questionnaire EQ-5D-5L (2009)
- Patient Diary Intervention Group (Version 1.0, 07 July 2024)
- Patient Diary Usual Care (Version 1.0, 07 July 2024)
- Process Evaluation Participant Interview Guide (Version 1.0, 15 April 2024)
- ARMS-7 Questionnaire (Version 1.0, 15 April 2024)
- Process Evaluation Health Practitioner Interview Guide (Version 1.0, 15 April 2024)
- Research Data Management Plan (Version 2.0, 20 August 2024)

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

1. Royal Prince Alfred Hospital, NSW
2. Concord Repatriation General Hospital, NSW
3. Prince of Wales Hospital, NSW
4. Royal North Shore Hospital, NSW
5. Royal Adelaide Hospital, SA

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 annual progress reports. The first report should be sent to the HREC by **27/08/2025.** 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 annual 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, 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.

13. It is a requirement of ethics approval that before its commencement this clinical trial is registered on a publicly accessible register, such as the Australian New Zealand Clinical Trials Registry or another appropriate international register. You are asked to provide details of the Register in which the study has been included and its registration number. This will be through a notification via REGIS.

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,

S.Thomas

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	