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Application Form for an Amendment to an Approved Research Project

Please refer to the *Guide to submitting an Amendment* on the HREC web page.

HREC Project ID No: 2019-032

PROJECT TITLE: Evaluation of dose of Photobiomodulation (Light) Therapy and Physiotherapy for improving quality of life outcomes and mobility in Parkinson's Disease (Sydney)

Has the Amendment been approved by a NSW Health Lead HREC or NHMRC Certified HREC?
No. Application submitted

Description of Amendment:
Note that stage 1 of the project has been completed (Groups 1 & 2). Stage 2 has been postponed due to the COVID-19 pandemic (Group 3).
We seek approval for some variations to stage 2:

- Addition to the number of participants with Parkinson's disease (Group 3) from 6 to 10; addition of 10 non-Parkinson's matched controls (Group 4); addition of 10 participants with Parkinson's disease as a placebo group (Group 5). Participants with Parkinson's disease will be randomly assigned to group 3 or 5. Personnel involved in therapy, assessment of outcome measures and data analysis will be blinded from knowledge of participant group assignment.
- Inclusion of a prescribed exercise regime (Parkinson's exercise classes)
- Replace the outcome measure of fMRI with EEG for the first treatment with photobiomodulation therapy

Reason for Requesting Amendment:

- The delay in conducting this part of the study (stage 2) is due to the COVID-19 lockdowns. This was eant to begin in early 2020.
- A placebo effect has been observed in a previous arm of the study (Brisbane) and a Hawthorne effect has been noted in another arm (Adelaide). Inclusion of a placebo group and increased numbers of participants will strengthen the study to help with future Randomised Control Trials (RCT) applications. A small addition to the funding has been secured to make these changes/additions.
- Exercise is known (clinically) to be helpful in Parkinson's symptoms. The combination of photobiomulation therapy and exercise may improve the effects of photobiomodulation therapy previously demonstrated in the first phase of the Sydney study. In addition, exercise is known to positively influence the microbiome in humans. The cominatuon of exercise and photobiomodulaytion therapy may have an increased effect, over and above that demonstrated for photobiomodulation alone (previous Sydney study)
- There has been a number of recent studies showing the effect of photobiomodulation therapy on brain wave patterns of normal participants. Any demonstration of changes in

Parkinson's participants will provide additional evidence for future RCT applications.

What are the ethical implications of the Amendment?

- The addition of a placebo group has ethical implications. When the trial has concluded, participants in the group will be offered photobiomodulation therapy. This has been factored into the increased cost of the study amendment.
- Replacement of fMRI with EEG has a reduced impact on particpants, due ease of use and increased patient comfort

Are changes to the Patient Information Sheet and/or Consent Form and/or Clinical Protocol necessary as a result of the Amendment request?

Yes, both PICFs and Protocol document

Additional documentation

nil

Is an extension to the period of HREC approval being sought?

yes

The COVID-19 lockdown has necessitated the postponement of studies that require participants to be present at hospitals

The second stage of the study will be conducted during this extension

We request an extension of 12 months

DECLARATION

I agree that the above information is accurate and that the project will continue in accordance with the original HREC conditions of approval.

_____ _____

Signature of Principal Investigator *Date*

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Has the Amendment been approved by a NSW Health Lead HREC or NHMRC Certified HREC?
A copy of the Amendment approval granted by a NSW Health Lead HREC or NHMRC Certified HREC must be submitted where the research received initial approval from one of these HREC's.

No, this is the first application for amendments to The Sydney Adventist Hospital HREC who is the lead HREC for this study.

Description of Amendment:
Include whether the amendment includes a request to extend the initial HREC approval period.

1. **Study Investigators**
   Associated Investigators:
- Remove Dr Nabil El Massri
- Remove Ms Sharon Tilley

2. **Study design**
- Study duration simplified for all groups to 12-weeks of intervention 3 times per week (Monday, Wednesday, Friday), followed by 3-months washout (no intervention).
- Study intervention reduced by removing abdominal treatment to leave transcranial treatment only (no change to transcranial treatment duration). Sham groups will be given the same transcranial apparatus that emits no light.
- Study outcome assessment time points simplified to be universal for all study participants, consisting of 1) before intervention (baseline, week 0); at 4-weeks intervention; 12-weeks intervention (intervention complete); and 6-months (3-months no intervention wash out).
- Reduction in timepoints for motor-clinical outcome measures to be assessed at baseline, at intervention completion, and at wash out only. Microbiome outcome measures will be assessed at baseline and intervention completion only.

3. **Study population and sample size**
- Amendment to simplify participant groupings and sample sizing from 5 groups into 2 groups with 40 total participants (Group 1: 20x participants in

intervention group; Group 2: 20x participants in sham/placebo group).

4. **Study outcomes**

- Amendment to reduce number of study outcomes and minimise participant inconvenience and risk with the removal of all imaging outcome measures (e.g. EEG, fMRI).
- Amendment to reduce number study outcome and minimise participant inconvenience and risk with the removal of all peripheral circulation inflammatory and Parkinson's disease markers that involves blood sample (including removal of phlebotomy as a sampling technique).
- Removal of urine testing for nicotinamide levels.
- Addition of saliva sample alongside time points for faecal sample for the purpose of microbiome analysis.

Reason for Requesting Amendment:

The decision was made to simplify and streamline the previously accepted study protocol to reflect the challenges presented to potential participants and healthcare staff in the current COVID-19 outbreaks of the more infectious Delta-variant, and subsequent lock-down restrictions. These amendments were also made to reduce the load and involvement of patient participation and decrease risk present in some of the original outcome measures and assessments. We will continue to follow all relevant COVID-19 guidelines stipulated by the NSW health government and the Sydney Adventist Hospital

What are the ethical implications of the Amendment?

These amendments are designed to reduce participant load and involvement (e.g. reduction in number of interventions) and decrease potential risk factors of certain outcome measures (e.g. imaging, blood sampling) to the participant. The addition of saliva samples provided by the participant is not predicted to pose any additional adverse ethical implications to the study. The ethical implications of these amendments will include an overall reduction in the risk of distress, potential adverse impact, injury of psychological or other hard to the individual.

Are changes to the Patient Information Sheet and/or Consent Form and/or Clinical Protocol necessary as a result of the Amendment request?
Please list and attach the revised documents which include a revised version number and date.

Yes, changes to the following have been made and are attached to this application form:

- PCIF PDNeuro V4 tracked
- PCIF PDNeuro V4 clean
- Protocol Parkinson's trial Sydney Arm V4 tracked
- Protocol Parkinson's trial Sydney Arm V4 clean

Additional documentation
Please list any additional documentation that you may have attached.

Is an extension to the period of HREC approval being sought?
Please be advised that requests for extensions to the period of approval can only be considered for projects where the period of approval is due to expire within 6 months.

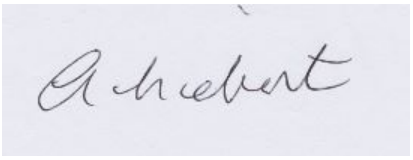
Please explain why an extension of the period of approval is required.

Please detail what study activities will be conducted during this extension period.

Please detail what period of extension is being requested. The maximum period granted will be1 year.

DECLARATION

I agree that the above information is accurate and that the project will continue in accordance with the original HREC conditions of approval.



07/07/21

Signature of Principal Investigator *Date*

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Has the Amendment been approved by a NSW Health Lead HREC or NHMRC Certified HREC?

A copy of the Amendment approval granted by a NSW Health Lead HREC or NHMRC Certified HREC must be submitted where the research received initial approval from one of these HREC's.

Previous amendment to this ethics application was approved on 9 August 2021 by The Sydney Adventist Hospital HREC. This is an additional application for amendments.

Description of Amendment:

Include whether the amendment includes a request to extend the initial HREC approval period.

- **Contingency plan**

Additional section titled '16. Contingency Plan' added to action changes to the current protocol in the event that the current study is unable to proceed due to uncontrollable restrictions or regulations, such as those imposed in the current COVID-19 pandemic lock down restrictions. These changes are referred to in 'Appendix 8' as an addendum in the protocol document.

- **Appendix 8**

1. Study design
   Treatment will consist of home-based (in the participant's own home) PBMt to the head and nose (either active or placebo treatment), 6 daily treatments per week for 12 weeks. Outcome measures to be supervised and data collected vis use of video link by Specialist Examiners and the Physiotherapists.

2. Study setting/location
   Study location for both treatment outcome measures assessments will be changed to the participant's own home. The therapist will video call or video conference with participants to ensure that treatments are used correctly and to answer any questions regarding the study.

3. Inclusion criteria
   In addition to the inclusion criteria already stimulated, eligible participants will require:
   a) Sufficient space (around 9 m^2) to be able to perform motor

assessments.

b) Stable and sufficiently fast home-based internet connection for uninterrupted video calls and video conferencing.
c) Knowledge of using a phone and/or tablet applications on either IOS or Android platforms.

4. Study procedure

In the absence of researcher/specialist-directed intervention, to ensure blinding of participants from group allocations and to reduce the chance of participants inadvertently realising that they are in the sham group, participants will be informed that there are 3 groups instead of 2 (Group 1: receiving red and infra-red light (to account for lack of visible light production); Group 2: receiving infra-red light only; Group 3: receiving sham).

5. Outcome measures

Outcome measures will be performed at the commencement of the trial before intervention (baseline, week-0), then after 2, 4, 6, 8, 10-weeks of treatment, and at the end of the trial (12-weeks of treatment), and at 6-months (3-months of zero intervention wash out). These will be shortened assessments to give the give the therapist an opportunity to monitor participants in case there are any compliance questions or concerns.

All outcome measures will be conducted and recorded using a combination of self-reported assessment, visual assessment via video link with a specialist examiner (during live video or pre-recording by the participant).

The Kinesia ONE© system (Great Lakes Neurotechnologies, https://www.glneurotech.com/products/kinesia-one/) or similarly equivalent will be used to conduct some of the outcome measures. The Kinesia ONE© system (or similarly equivalent) has been chosen for its ability to provide objective motor scores based on clinically validated algorithms for PD and has been integrated in clinical trials (Phase I – IV) to investigate outcome measures in treatments for PD (https://www.glneurotech.com/resources/publications/kinesia-publications/).

Collection of faecal and saliva samples will still be conducted, with collection equipment provided to each participant via post or non-contact drop off outside their place of residence, and samples collected via similar non-contact procedures.

6. Consent process

All previous in-person appointments during the consent process will be conducted via video-link. For example:

a) Should a patient indicate an interest in participating in the study, the Principal Coordinating Investigator will contact the patient by phone or video link to answer any questions or to further explain the project and determine eligibility to participate in the project.
b) Patients and nominated carers will then be asked to re-read the Information Sheet and deliver the consent form electronically for live countersigning during their first video-link appointment.

- **PICF**

Additional section titled ’15. What happens if we are unable to participate in the trial due to uncontrollable restrictions or regulations that would prevent me from receiving the study treatment or conducting tests in person?’ to the PICF to inform patients of the contingency plan and subsequent changes in their involvement.

Reason for Requesting Amendment:

The requested amendments were made to comply with the conduct of an RCT during the current restrictions and regulations of the COVID-19 pandemic lockdown, or any other current or future restrictions to:
- The study site.
- The participant’s ability to participate in the currently proposed study protocol.
- The researcher’s ability to conduct the currently proposed study protocol.

What are the ethical implications of the Amendment?

These changes will ensure that minimum to no contact will be required during the conduct of this study, with the least amount or risk for both participants and researchers to the during the duration of this study.

Are changes to the Patient Information Sheet and/or Consent Form and/or Clinical Protocol necessary as a result of the Amendment request?
Please list and attach the revised documents which include a revised version number and date.

Yes, changes to the following have been made and attached to this application form:

- Patient Information Sheet and Consent Form
- Clinical Protocol

Additional documentation
Please list any additional documentation that you may have attached.

Is an extension to the period of HREC approval being sought?
Please be advised that requests for extensions to the period of approval can only be considered for projects where the period of approval is due to expire within 6 months.

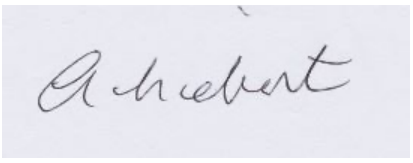
Please explain why an extension of the period of approval is required.

Please detail what study activities will be conducted during this extension period.

Please detail what period of extension is being requested. The maximum period granted will be1 year.

DECLARATION

I agree that the above information is accurate and that the project will continue in accordance with the original HREC conditions of approval.



_____ _____11/08/2021_____

Signature of Principal Investigator *Date*

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Previous amendment to this ethics application was approved on 25 August 2021 by The Sydney Adventist Hospital HREC. This is an additional application for amendments.

Description of Amendment:

Include whether the amendment includes a request to extend the initial HREC approval period.

- **Study Investigators**

Addition of nominated PhD student: Ms Claire McGee (Torrens University Australia, Sydney) supervised by Prof Hosen Kiat (CI).

- **Sites**

Clarity of study sites to include either two of the currently approved sites constituting the Northshore Musculoskeletal and Laser Physiotherapy Clinic (6/110 – 114 Hampden Rd, Hampden ln, Artarmon, and the Specialist GP Centre, 187 Fox Valley Rd, Wahroonga), or Suite 211, the Tulloch building, Sydney Adventist Hospital, Wahroonga.

- **Sponsor**

Nominated sponsor for the study has been added as SYMBYX Biome Pty Ltd, 2/50 Yeo Street, Neutral Bay, NSW 2089. They will also be the supplier of devices for this study.

- **Recruitment Strategy**

Added recruitment strategy involving paper advertisements and specialist clinicians and neurologists from Sydney Adventist Hospital and others within the Sydney local health districts.

- **Section 16 'Contingency plan'.**

Additional information regarding the use of public media platforms for participant recruitment purposes has been added.

- **Appendix 8**

Addition of Section 7 'Additional screening, selection, and other considerations' confirming that assessments related to inclusion criteria and screening protocols for participant selection will be conducted via video telehealth communication, with potential risk factors such as falls, and cardiac comorbidities assessed live by qualified medical geriatrician and cardiologist.

Additional exclusion criteria has been added to include any evidence of severe and unstable dysautonomia, recent cardiac surgeries, unstable arrhythmias, and evidence of cardiac dysautonomia.

Included additional instructions for added duty of care to ensure that extra time be allowed, and considerations on the overall speed and pace of any interactions bet taken between the research team and participants during inclusion and outcome measure assessments.

Included additional recruitment strategy employing public media platforms supplementing original recruitment strategy.

Removed 'Outcome measures' section point c) and d). The Kinesia ONE© system will no longer be used for this study. Collection of faecal and saliva samples will no longer be collected.

- **PICF**

Addition of SYMBYX Biome as the main trial sponsor and supplier of devices and information regarding the three study sites where the trial will take place in the 'Invitation' section.

In section 4 'What does this study involve?', information on the self-collection of faecal and saliva samples have been removed.

In section 11 'What happens with the results?', the additional statement informing the participant that all information including personal recordings will be stored for analysis for this study only, before being destroyed at the end of the trial. De-identified data from this study may be shared with the sponsor SYMBYX Biome.

In section 14 'What happens if we are unable to participate in the trial due to uncontrolled restrictions or regulations that would prevent me from receiving the study treatment or conducting tests in person?', information regarding collection of faecal and saliva samples have been removed.

Reason for Requesting Amendment:

The requested amendments were made to:

1. Add the addition of a nominated PhD student and supervisor.
2. Addition of SYMBYX Biome as trial sponsor.
3. Addition of information relating to the advertising of the study on public medial platforms in section 16 'Contingency Plan' to broaden recruitment to potential participants who were not within a reasonable distance to the study site, to reflect the switch to a completely home-based clinical study that does not require participant travel to a designated study site.

4. Addition of screening protocol items to attempt to mitigate potential risk factors related to falls and cardiac comorbidities that are common amongst the age group recruited from.
5. Removal of Kinesia ONE© system based on the decision of the trial PIs.
6. Removal of instructions regarding collection of biological samples based on the decision of the trial PIs. Removal of biological sample collection procedures will ensure zero-contact between the participants the study researchers during the trial.
7. Changes in PICF made to reflect new trial sponsor and omission of the collection of biological samples
8. Declaration of potential sharing of de-identified data with the sponsor SYMBYX Biome as is ethically appropriate to ensure that the participant is aware before agreeing to participate in the trial.

What are the ethical implications of the Amendment?

These are minor updates to the currently approved ethics application to ensure clarity of study sites, information regarding the sponsor and provider of devices, and additional measures to facilitate running of a home-based trial, and not thought to have any additional ethical implications for the study. Removal of any biological sampling will ensure that there is no need for participants to come into any physical contact with the trial researchers for the duration of the study.

Are changes to the Patient Information Sheet and/or Consent Form and/or Clinical Protocol necessary as a result of the Amendment request?
Please list and attach the revised documents which include a revised version number and date.

Yes, changes to the following have been made and attached to this application form:

- Patient Information Sheet and Consent Form
- Clinical Protocol

Additional documentation
Please list any additional documentation that you may have attached.

Is an extension to the period of HREC approval being sought?
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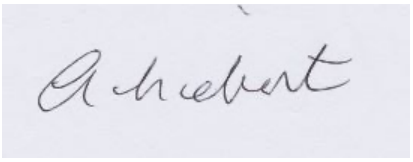
Please explain why an extension of the period of approval is required.

Please detail what study activities will be conducted during this extension period.

Please detail what period of extension is being requested. The maximum period granted will be1 year.

DECLARATION

I agree that the above information is accurate and that the project will continue in accordance with the original HREC conditions of approval.



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Signature of Principal Investigator *Date*