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INFORMED CONSENT FORM

1. Study Information

Protocol Title:

An N-of-1 pilot study of CURATE.AI to optimise cognitive training in post-brain radiotherapy patients

Principal Investigator & Contact Details:

Dr. Bala Vellayappan
Consultant, Department of Radiation Oncology
National University Cancer Institute Singapore (NCIS)
Tel:+65 6779 5555

Study Sponsor:

Singapore Cancer Society.

2. Purpose of the Research Study

You are invited to participate in a research study. It is important to us that you first take time to read through and understand the information provided in this sheet. Nevertheless, before you take part the study will be explained to you and you will be given the chance to ask questions. After you are satisfied that you understand this study, and that you wish to take part in the study, you must sign this informed consent form. You will be given a copy of this consent form to take home with you.

You are invited because you have been diagnosed with a brain tumour and you are being planned to be treated with radiotherapy. Patients treated with radiotherapy directed to the brain may experience cognitive decline post-treatment. There are drug-based approaches to counteract the unwanted effects of radiotherapy, but these are usually limited in efficacy. Alternatively, patients can be treated with digital therapy, which seeks to improve patient's cognitive performance. Digital therapeutics are a new category of apps that help prevent or treat diseases by modifying patient behavior and/or providing remote monitoring to improve long-term health outcomes. However, most digital therapies are administered at fixed intensity, without accounting for differences between patients. This study is carried out to find out whether personalised (as opposed to fixed) intensity training in a digital therapeutic platform can improve cognitive performance. To that end, an artificial intelligence platform called CURATE.AI will be used to dynamically vary the intensity of a digital cognitive test battery.

This study aims to recruit 15 participants over a period of two years. The subjects would be recruited from National University Hospital.

3. What procedures will be followed in this study

If you take part in this study, you will be asked to complete cognitive evaluation and quality of life questionnaires. Among other things, you will have to recall words that were read to you, do mathematical calculations, connect numbers in a certain order, and self-assess your health. You will also perform some cognitive tasks on a tablet. The digital cognitive test battery will consist of three tasks: the number memory task, the Gabor Patch perceptual

learning task and the MATB (Multi-Attribute Task Battery) task. In the number memory task, you will be asked to recall the last presented items (e.g. the last 4 numbers) from a list of continuously updated items. In the Gabor patches task, you will be asked to discriminate between two briefly presented patches, indicating which direction the patches rotated (clockwise or counterclockwise). In the MATB task, you will be asked to virtually turn lights on and off, track elements on the screen, keep a cursor in a certain place or virtually control the flux of liquid between tanks. Depending on the case, you might do all or some of the tasks.

Your participation in the study will last one year, during which you will use the digital cognitive intervention 35 times and visit the doctor's office 5 times.

If you agree to take part in this study, the following will happen to you:

Visit 1 (pre-radiotherapy): During your first visit, before radiotherapy starts, your baseline data will be collected, and you will complete a cognitive evaluation and a 10-15 minute cognitive training session.

Visit 2 (pre-intervention): after radiotherapy completion, and right before cognitive training, you will complete a cognitive evaluation and a 10-15 minute cognitive training session.

Visit 3 (post-intervention): you will complete a cognitive evaluation and a 10-15 minute cognitive training session.

Interview visit (post-intervention): you will complete a 60 minute semi-structured interview about your experience with the intervention. Ideally, this will happen at visit 3, but may occur up to 5 days after depending on your schedule. The questions will cover your experience performing the tasks of the interface. If you do decide to participate and later wish to withdraw you may do so as well. You do not have to answer any question you do not wish to. The interview will be audio taped and transcribed for purposes of data analysis. Your data will be confidential and will be used solely for research to improve the interface/intervention. The interviews can happen via video chat or in any place convenient to you and any day around the date you are doing the cognitive evaluation, also at your convenience. Audio recordings and transcripts will not reveal identifiers and will be coded (stripped of identifying information) at the earliest opportunity.

Visit 4 (16 weeks post-intervention): you will complete a cognitive evaluation and a 10-15 minute cognitive training session.

Visit 5 (32 weeks post-intervention): you will complete a cognitive evaluation and a 10-15 minute cognitive training session.

When your participation in the study ends, you will no longer have access to the cognitive test battery/CURATE.AI, unless special arrangements are made by the Principal Investigator.

Any individually-identifiable data obtained during the course of this study will be stored for the purposes of this study only and will not be used for future biomedical research. De-identified data will be kept for future studies only with your consent and only for the purpose you consent (either general research or research related to brain cancer).

Your personal information (name, contact number, email) and the document linking your information to your identification code will be collected and stored separately from the research data to ensure that you cannot be individually matched to your data. Personal data will be discarded upon completion of the study. De-identified data will be stored for a period of ten years on a password-protected computer kept in a locked office room. Only the PI and collaborators will have access to the data.

During the course of the study, there is a possibility that we might unintentionally come to know of new information about your health condition from the tests that are conducted as

part of the study. These are called “incidental findings”. You will be asked to indicate whether you wish to be re-identified and notified in the case of a clinically significant incidental finding that is related to you.

4. Your Responsibilities in This Study

If you agree to participate in this study, you should follow the advice given to you by the study team. You should be prepared to visit the hospital 5 times and undergo all the procedures that are outlined above.

5. What Is Not Standard Care or is Experimental in This Study

The study is being conducted because the CURATE.AI-modulated digital cognitive test battery is not yet proven to be a standard treatment in subjects with brain tumour undergoing radiotherapy. We aim to study CURATE.AI-modulated digital cognitive test battery as a potential treatment for your condition.

6. Possible Risks and Side Effects

No anticipated risks or side effects are expected from subjects' participation in the study.

7. Possible Benefits from Participating in the Study

There is no assurance you will benefit from participation in this study, but you may experience improved cognitive performance. Additionally, your participation in this study will add to the medical knowledge about the use of this intervention.

8. Alternatives to Participation

If you choose not to take part in this study, you will continue to receive the standard care for your condition. The benefits are, for primary brain tumour patients, improved tumour control; for brain metastasis patients, relief of symptoms.

Your decision not to participate in this study will in no way affect your continued care in this institution with your physician.

9. Costs & Payments if Participating in the Study

If you take part in this study, the following will be performed at no charge to you: digital cognitive training and cognitive evaluations. These costs will be borne by the Singapore Cancer Society.

If you take part in this study, you will have to pay for the following: standard care including diagnostic scans and radiotherapy treatment.

Only if you complete the study you will be compensated for the participation time with the computer tablet used for your digital therapy.

11. Voluntary Participation

Your participation in this study is voluntary. You may stop participating in this study at any time. Your decision not to take part in this study or to stop your participation will not affect

your medical care or any benefits to which you are entitled. If you decide to stop taking part in this study, you should tell the Principal Investigator.

However, the data that has been collected until the time of your withdrawal will be kept and analysed.

Your doctor, the Investigator and/or the Sponsor of this study may stop your participation in the study at any time if they decide that it is in your best interest. They may also do this if you do not follow instructions required to complete the study. If you have other medical problems or side effects, the doctor and/or nurse will decide if you can continue in the research study.

In the event of any new information becoming available that may be relevant to your willingness to continue in this study, you (*or your legally acceptable representative, if relevant*) will be informed in a timely manner by the Principal Investigator or his/her representative.

12. Compensation for Injury

If you follow the directions of the doctors in charge of this study and you are physically injured due to the trial substance or procedure given under the plan for this study, National University Hospital will pay the medical expenses for the treatment of that injury.

Payment for management of the normally expected consequences of your treatment will not be provided by National University Hospital.

National University Hospital without legal commitment will compensate you for the injuries arising from your participation in the study without you having to prove National University Hospital is at fault. There are however conditions and limitations to the extent of compensation provided. You may wish to discuss this with your Principal Investigator.

By signing this consent form, you will not waive any of your legal rights or release the parties involved in this study from liability for negligence.

13. Confidentiality of Study and Medical Records

Your participation in this study will involve the collection of "Personal Data". "Personal Data" means data about you which makes you identifiable (i) from such data or (ii) from that data and other information which an organisation has or likely to have access. This includes medical conditions, medications, investigations and treatment history.

Information and "Personal Data" collected for this study will be kept confidential. Your records, to the extent of the applicable laws and regulations, will not be made publicly available.

However, National University Health System, Regulatory Agencies, NHG Domain Specific Review Board and Ministry of Health will be granted direct access to your original medical records to check study procedures and data, without making any of your information public. By signing the Informed Consent Form attached, you (*or your legally acceptable representative, if relevant*) are authorising (i) the collection, access to, use and storage of your "Personal Data", and (ii) the disclosure to authorised service providers and relevant third parties.

Data collected and entered into the Case Report Forms are the property of NCIS. In the event of any publication regarding this study, your identity will remain confidential.

Research arising in the future, based on your "Personal Data", will be subject to review by the relevant institutional review board.

Any information containing your “Personal Data” that is collected for the purposes described in this Informed Consent Form will not be transferred out of Singapore.

By participating in this research study, you are confirming that you have read, understood and consent to the Personal Data Protection Notification available at <https://www.nuh.com.sg/Pages/Personal-Data-Protection-Act.aspx>.

14. Conflict of Interest Disclosure

1) Prof Ho is a co-inventor of *Phenotypic Personalised Medicine: Adaptive Optimization of Patient-Specific Combination Therapy*; The current study uses the same core technology but for a different functionality and it is unlikely to be affected by this conflict of interest.

2) Prof Ho is a co-inventor of *Nanomedicine Optimization with Feedback System Control and Cognitive Training Platform, which outlined the usage of CURATE.AI*. The current study relates to this inventions by using the same core technology and therefore it may be affected by this conflict of interest.

3) Prof Ho is a co-inventor of *Multi-Drug Therapies for Tuberculosis Treatment and Novel Optimised Drug Combinations for Drug-Resistant and Drug-Sensitive Multiple Myeloma Developed Using A Systematic Phenotypic Personalised Medicine*. These inventions do not relate to the same technology as the current study and hence this conflict of interest does not affect the current study.

4) Prof Dean Ho is a co-founder and shareholder in KYAN Therapeutics. KYAN Therapeutics is in the process of finalizing licensing agreement for some of the technology platforms listed above, that may be used for this study and therefore it may be affected by this conflict of interest.

1) Dr Blasiak is a co-inventor of *Cognitive Training Platform, which outlined the usage of CURATE.AI*. The current study relates to this inventions by using the same core technology and therefore it may be affected by this conflict of interest.

15. Who To Contact if You Have Questions

If you have questions about this research study, you may contact the Principal Investigator,

Dr. Bala Vellayappan
Consultant, Department of Radiation Oncology
National University Cancer Institute Singapore (NCIS)
Tel:+65 6779 5555

The study has been reviewed by the NHG Domain Specific Review Board (the central ethics committee) for ethics approval.

If you want an independent opinion to discuss problems and questions, obtain information and offer inputs on your rights as a research subject, you may contact the NHG Domain Specific Review Board Secretariat at 6471-3266. You can also find more information about participating in clinical research, the NHG Domain Specific Review Board and its review processes at www.research.nhg.com.sg.

If you have any complaints or feedback about this research study, you may contact the

Principal Investigator or the NHG Domain Specific Review Board Secretariat.

16. Consent to be Contacted for Future Research

You are being asked for permission to be contacted in the future for participation in research studies that you may be suitable for. If you agree to be contacted, your information and contact details will be entered and stored in a secured database in NCIS. Your information and contact details will not be released to any parties outside NCIS without your permission. When investigators from NCIS identify you to be suitable for a particular research study, the investigators or authorised personnel from NCIS will contact you to inform you about the research study. Your decision to be contacted for future research studies is completely voluntary and separate from your decision to participate in this study. Your decision will not affect your medical care or any benefits to which you are entitled. You may change your mind at any time by contacting the principal investigator.

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I voluntarily consent to take part in this research study. I have fully discussed and understood the purpose and procedures of this study. This study has been explained to me in a language that I understand. I have been given enough time to ask any questions that I have about the study, and all my questions have been answered to my satisfaction. I have also been informed and understood the alternative treatments or procedures available and their possible benefits and risks.

By participating in this research study, I confirm that I have read, understood and consent to the National University Hospital Personal Data Protection Notification

Consent for the Participation in Volunteer Interviews

- Yes, I agree to participate in the voluntary interviews.
- No, I do not agree to participate in the voluntary interviews

Consent for the Use of Data for Future Research

- Yes, I agree to donate my data for future research.

Please also check one of these boxes:

- There are no restrictions on the kind of research that may be done with my data.
- The Investigator may use my data for future research as long as the research is related to brain cancer.
- No, I do not agree to donate my data for future research.

Consent to be Re-Identified and Notified in the Case of an Incidental Finding

- Yes, I agree to be re-identified and notified in the case of an incidental finding from this research.

In the event that I cannot be reached, please contact my next of kin

Name of next of kin:

Contact:

No, I do not agree to be re-identified and notified in the case of an incidental finding from this research.

Consent to be Contacted for Future Research

Yes, I agree to be for contacted for future research that I may be eligible for.
I agree to be contacted via:

Phone _____

Mail _____

Email _____

Others _____

No, I do not agree to be contacted for future research.

Name of Participant

Signature

Date

Witness Statement

I, the undersigned, certify that:

- I am 21 years of age or older.
- To the best of my knowledge, the participant/ the participant's legally acceptable representative signing this informed consent form has the study fully explained in a language understood by him/ her and clearly understands the nature, risks and benefits of his/ her participation in the study.
- I have taken reasonable steps to ascertain the identity of the participant/ the participant's legally acceptable representative giving the consent.
- I have taken steps to ascertain that the consent has been given voluntarily without any coercion or intimidation.

Name of Witness

Signature

Date

1. In accordance with Section 6(d) of the Human Biomedical Research Act and Regulation 25 of the Human Biomedical Research Regulations 2017, appropriate consent must be obtained in the presence of a prescribed witness who is 21 years of age or older, and has mental capacity. The witness must be present during the entire informed consent discussion, and must not be the same person taking the appropriate consent. The witness may be a member of the team carrying out the research.
2. However, if the participant/ the participant's legally acceptable representative is unable to read, and/ or sign and date on the consent form, an impartial witness should be present instead. The impartial witness should not be a member of the study team.

Investigator Statement

I, the undersigned, certify that I explained the study to the participant and to the best of my knowledge the participant signing this informed consent form clearly understands the nature, risks and benefits of his / her participation in the study.

Name of Investigator /
Person administering consent

Signature

Date