Annex A

Mechanism of Action for Transcranial Magnetic Stimulation

Transcranial Magnetic Stimulation (TMS) is a non-invasive therapeutic modality that utilises magnetic fields to modulate neural activity in specific brain regions. The procedure involves placing an insulated coil on the scalp, through which a rapidly changing magnetic field generates small electrical currents. These magnetic pulses are the same type and strength as those used in magnetic resonance imaging (MRI) machines. These currents stimulate neurons in the targeted brain area, influencing the activity of neural circuits.

The mechanism of action is believed to involve the depolarisation of neurons, leading to changes in neurotransmitter release and neuroplasticity. Depending on the frequency of the magnetic pulses, TMS can either enhance (high frequency) or inhibit (low frequency) the activity in the targeted brain region, making it a versatile tool for treating various neurological and psychiatric disorders.

There are 3 basic types of TMS: single-pulse, paired pulse, or repetitive TMS (rTMS). Within these types of TMS, there are also newer protocols that allow different frequencies of magnetic stimulation, which in turn require a shorter treatment time and potentially better treatment results for a range of different illnesses.

TMS is safe, tolerable and an effective treatment modality for persons with treatment-resistant depression, and typically has little or no side-effects. It is known that TMS can lead to long-term changes in brain function, suggesting its potential in rewiring neural connections and altering pathological patterns of brain activity.

Annex B

About APIC-TMS and SPARK-D

APIC-TMS (Asia Pacific Individual Connectomics – Transcranial Magnetic Stimulation) is a feasibility trial/pilot where an advanced targeting algorithm will be implemented in a clinical environment to ensure that the novel treatment can be conducted in real-world settings. The data will be reflective of real-world outcomes we can expect from individually neuro-navigated treatment for treatment-resistant depression.

The APIC-TMS clinical trial is funded by Temasek Foundation (TF) at a cost of S$1 million.

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SPARK-D (Singapore's Precision Approach for Relief from Depression) is a randomised controlled trial where we compare the difference between a group-level treatment target (one-size-fits-all) versus the individually-derived treatment target provided by the advanced targeting algorithm in the treatment of treatment resistant depression. This is important because getting individually-derived targets requires advanced neuroimaging and analysis only available at specialised centres, and so we need to know how much better the results are with individual targeting in order to assess the extra value it brings to patients and society.

The SPARK-D clinical trial is funded by the National Medical Research Council (NMRC) at a cost of S$1 million.

Key researchers in the APIC-TMS and SPARK-D trials:

Principal Investigator (PI)

1. Dr Tor Phern Chern, Senior Consultant, Department of Mood & Anxiety and Head, Neurostimulation Service, Institute of Mental Health (IMH)

Dr Tor Phern Chern is a psychiatrist and gained proficiency in advanced invasive and non-invasive neurostimulation technology in Black Dog Institute (Sydney, Australia) and Toronto Western Hospital (Toronto, Canada). He is currently Head, Neurostimulation Service in the Institute of Mental Health, chairman of the Singapore ECT and Neurostimulation Society, and serves as treasurer for the International Society of Neurostimulation. Dr Tor is a certified clinical TMS practitioner and a teaching faculty for the College of Psychiatry TMS course in Singapore. He is the PI of several local studies on the efficacy of accelerated TMS in the treatment of drug-resistant depression. For the APIC-TMS and SPARK-D studies, the Dr Tor will be actively involved in study design, project management, TMS intervention, data interpretation and report, etc.

Co-PI

2. Associate Professor Thomas Yeo, NUS Yong Loo Lin School of Medicine (NUS Medicine) and NUS College of Design & Engineering (CDE)

Thomas Yeo is an Associate Professor at the Centre for Sleep & Cognition at NUS Medicine and the Department of Electrical & Computer Engineering (CDE) at NUS. A/Prof Yeo is also the deputy director of the Centre for Translational MR Research (TMR) at NUS Medicine, and is internationally renowned for the development of machine learning algorithms for MRI analysis. He is a Top 1% "highly cited researcher" (Clarivate Analytics) since 2019. His 2011 study on estimating large-scale brain networks has been referenced more than 7,000 times. As Co-PI, A/Prof Yeo's team will analyse the MRI data to estimate individualised stimulation locations for TMS. His team will work closely with Dr Tor's team to integrate the MRI data with the robotic arm for the clinical trials.

Collaborators[7]

3. Associate Professor Juan Helen Zhou, Director, Centre for Translational MR Research, NUS Yong Loo Lin School of Medicine

Juan Helen Zhou is an Associate Professor at the Centre for Sleep & Cognition at NUS Medicine and the Department of Electrical & Computer Engineering (CDE) at NUS. A/P Zhou is also the director of the Centre for Translational MR Research (TMR) in NUS Medicine. She is internationally well-known for the use of neuroimaging to study neuropsychiatric disorders. Brain scans of patients will be collected at TMR.

4. Associate Professor Luca Cocchi, Team Head, Clinical Brain Networks Group, QIMR Berghofer Medical Research Institute

A/P Luca Cocchi is an Associate Professor at QIMR Berghofer Medical Research Institute. He was a member of the Australian study team who developed a state-of-the-art individualised connectome-guided localisation approach. He is the co-founder of the first Australian clinic to provide individualised connectome-guided TMS for treatment-resistant depression.

5. Dr Michael D. Fox, Director, Center for Brain Circuit Therapeutics, Harvard Medical School

Dr Michael Fox is the director of the Center for Brain Circuit Therapeutics (CBCT) in the Harvard Medical School. Michael was among the first to propose using resting-state fMRI to guide brain stimulation. He holds one of the main patents for connectome-guided brain stimulation in the United States. He has received multiple awards, including the inaugural "Trailblazer Prize" from the Foundation for the U.S. National Institutes of Health Collaborator.

6. Dr Shan Siddiqi, Assistant Professor of Psychiatry, Harvard Medical School & Director, Psychiatric Neuromodulation Research, Center for Brain Circuit Therapeutics, Brigham & Women's Hospital

[7] A/P Luca Cocchi and Dr Bjorn Burgher trained the Singapore team and advised on the practical setup of the equipment, based on their experience setting up the first-in-Australia personalised TMS service in Brisbane. Dr Michael Fox and Dr Shan Siddiqi are advisers on the targeting algorithm to individualise treatment location.

Dr Shan Siddiqi is the director of Psychiatric Neuromodulation Research in CBCT. He is the first author of several recent high-profile studies that developed novel brain stimulation targets for different brain disorders.

Annex C

Participation Details for the APIC-TMS and SPARK-D Clinical Trials

The APIC-TMS and SPARK-D clinical trials are designed for patients (aged 21 years and older) who have depression, and who are not responding to standard treatment by their doctors.

Patients in both trials will get real antidepressant treatment through neurostimulation that targets spots at the left frontal part of the brain.

APIC-TMS offers participants their personalised target, and SPARK-D will randomly assign patients to either their personalised target or the current standard one-size-fits all target.

Participation in the APIC-TMS and SPARK-D clinical trials is not guaranteed. All referrals have to undergo an assessment by IMH clinicians, and participation in the trials will depend on the pre-treatment assessment outcome.

If they are assessed to be suitable for the trial, they will be offered both trial options and they can choose which one they want to participate in. Participants will be required to visit the IMH TMS clinic for treatment/follow-up assessment for a total of 8 times, and the NUS Centre for Translational Magnetic Resonance Research (NUS-TMR) for MRI braining scanning 2 times:

Visit	**Time** **(not including travelling time)**	**Venue**	**To-do**
Visit 1	About 2 hours	IMH TMS Clinic	TMS assessment and MRI pre-screening.
Visit 2	30 – 50 minutes	NUS-TMR	MRI scanning
Visit 3-7	**10 hours each day for continuous 5 working days** **(Each session includes 10 minutes stimulation treatment and 50 minutes recovery in recovery room, for a total of 10 sessions).** On the last day of treatment, the research team will conduct post-treatment assessment (30 minutes to 1 hour)	IMH TMS Clinic	TMS treatment and post-treatment assessment
Visit 8	30 – 50 minutes	NUS-TMR	MRI scanning
Visit 9	30 minutes to 1 hour	IMH TMS Clinic	1-month post-treatment Follow-up assessment
Visit 10	30 minutes to 1 hour	IMH TMS Clinic	3-month post-treatment Follow-up assessment

Patients will be given an inconvenience fee.

Annex D

English-Mandarin Glossary

English Translation	**Mandarin Translation**
Dr Tor Phern Chern Senior Consultant, Department of Mood & Anxiety Head, Neurostimulation Service Institute of Mental Health	戴鹏程医生 情绪管理及焦虑障碍部门高级专科顾问 神经刺激服务主任 心理卫生学院
Associate Professor Thomas Yeo Centre for Sleep and Cognition NUS Yong Loo Lin School of Medicine	杨文泰副教授 睡眠认知中心 新加坡国立大学杨潞龄医学院
Transcranial Magnetic Stimulation (TMS)	经颅磁刺激
Personalised Transcranial Magnetic Stimulation (TMS)	个性化经颅磁刺激