**MEDIA RELEASE**
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# SINGAPORE PILOTS PERSONALISED TRANSCRANIAL MAGNETIC STIMULATION FOR TREATMENT-RESISTANT DEPRESSION

1. The Institute of Mental Health (IMH), in collaboration with the Yong Loo Lin School of Medicine at the National University of Singapore (NUS Medicine), has embarked on two clinical pilots to study the efficacy of personalised Transcranial Magnetic Stimulation (TMS) in treating persons with treatment-resistant depression (TRD).

2. The trials, named APIC-TMS (Asia Pacific Individual Connectomics – Transcranial Magnetic Stimulation) and SPARK-D (Singapore's Precision Approach for Relief from Depression), are catalysed by Temasek Foundation (TF) and the National Medical Research Council (NMRC) respectively, with a grant of S$1 million each.

3. Both clinical trials will run concurrently from March 2024 to 2026. Both trials will only recruit individuals who have undergone conventional psychiatric treatment for Major Depressive Disorder and failed to achieve remission, and they will be screened for suitability.

4. Singapore is the first country in Southeast Asia to conduct such clinical trials of personalised TMS, modelled after the Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT) protocol[1]. In pilots done with American subjects who had treatment-resistant depression, approximately 80% of patients achieved remission[2] with SAINT. The Singapore pilots will pair IMH's clinical expertise in standard TMS with NUS Medicine's expertise in brain MRI to personalise a treatment plan for each participant, study its efficacy and make recommendations on implementing this as a mainstream treatment.

## Major Depressive Disorder and Treatment-Resistant Depression

5. Major Depressive Disorder, commonly known as "depression", is the most common psychiatric disorder among adults in Singapore. The 2016 Singapore Mental Health Study showed that 6.3% of the Singapore adult population – or one in 16 adults (aged 18 and above) – has experienced the disorder at some point in their lifetime.

[1] SAINT received FDA approval in September 2022 for use in the US for treatment-resistant depression: CTMSS Press Release: Regarding FDA Clearance of SAINT Neuromodulation System | Clinical TMS Society

[2] Remission: patient's symptoms as measured on a validated mood scale have reduced to a level where it no longer qualifies for a diagnosis of depression. It is not a complete absence of symptoms.

6. Persons diagnosed with depression may present with symptoms such as persistent sadness, insomnia (or sleeping more than normal), loss of interest, lethargy, irritability, poor concentration, and in severe cases, suicidal thoughts.

7. Depression is a treatable condition. Mild cases may be managed with psychotherapy, while moderate to severe cases are typically managed with antidepressant medication to alleviate the symptoms. However, some patients do not respond well to medication, failing two courses of different drug treatments – where a course would consist of adequate doses taken over a four to eight-week duration, and with adequate adherence during a major depressive episode. Such patients may see an alleviation but not a remission in their symptoms despite having been compliant with taking their antidepressants. Clinically, this is known as treatment-resistant depression (TRD).

8. There are no local studies on the prevalence of TRD. Figures from overseas literature vary with ranges between 12% – 55%[3] and 40% – 70%[4], depending on how the studies define TRD and the study methodologies.

**Clinical Management of Treatment-Resistant Depression (TRD)**

9. TRD is usually managed through a stepwise treatment approach that includes optimising medication dosage, switching to a different class of medications, and augmenting or combining treatments. Non-pharmacological treatments such as electroconvulsive therapy (ECT) and standard TMS are also recommended as appropriate options for persons with TRD.

10. IMH has been offering standard TMS treatment since 2015 for patients with TRD, under its Neurostimulation Service. TMS is a non-invasive medical procedure where an insulated coil is placed on a spot on the patient's scalp where the prefrontal cortex resides. The coil generates brief magnetic pulses that directly stimulate specific areas of the brain involved in depression. For more details on the mechanism of action involved in TMS, please refer to Annex A.

**Standard Transcranial Magnetic Stimulation (TMS) versus Personalised TMS**

11. Standard TMS delivers stimulation to the same spot of the brain for all participants. It is typically applied by using a manually manipulated holder. On the other hand, personalised TMS – which will be used in the SPARK-D and APIC-TMS clinical trials – is more targeted and precise. It uses individualised functional magnetic resonance imaging (fMRI) to find the ideal location in each patient's brain that should be stimulated to treat his/her depression, and a high precision robot arm to target the stimulation. This spot is unique for each individual and to identify it, an algorithm developed by Research Fellow Ruby Kong and Associate Professor Thomas Yeo from the Centre for Sleep and Cognition at NUS

[3] The Prevalence and National Burden of Treatment-Resistant Depression and Major Depressive Disorder in the United States | Psychiatrist.com

[4] Questions and Answers about the NIMH Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Study — Background - National Institute of Mental Health (NIMH) (nih.gov)

Medicine and NUS College of Design and Engineering, will be used to perform advanced analytics on the individual brain scans.

12. The data from the fMRI scans is then integrated with an advanced neuro-navigation robotic arm to mount the magnetic coil on the precise spot on the patient's head. Even if the patient moves during treatment, the robotic arm will keep the coil firmly trained on the spot so that stimulation can be precisely delivered without disruption for that patient.

13. ECT is the current gold standard treatment for TRD, with a remission rate of 50% – 60%[5]. That means, about half of patients who receive ECT will see a remission of symptoms, as fast as in 3 to 4 weeks while the other half may not. In comparison, other research has shown that TMS is able to achieve a lower remission rate of 33.6%[6] after 6 weeks. However, the SAINT pilot has shown that remission rates improve significantly to about 80% with personalised TMS after 1 week.

14. Dr Tor Phern Chern, Senior Consultant, Department of Mood & Anxiety and Head of Neurostimulation Service, IMH, and Principal Investigator for both clinical trials said, "The severity of depression lies on a spectrum – many people will see their symptoms improve or remit with initial treatments such as medication and psychotherapy. But there are some whose conditions are treatment-resistant, and who require a longer treatment period to achieve remission or sufficient alleviation to resume day-to-day functioning. Published evidence from SAINT has shown us that personalised TMS can potentially bring about a paradigm shift in the management of treatment-resistant depression, going from a months-to-years long treatment to a rapid procedural one that delivers significant outcomes in a much shorter period. The success with SAINT – which enabled patients to participate more fully in their lives and that of their loved ones after treatment, or return to work and find more fulfilment – gives us confidence that similar outcomes may be achieved in Singapore. With these clinical trials, we hope to validate the efficacy of this precision modality in helping persons with treatment-resistant depression achieve remission and improve their quality of life."

15. Assoc Prof Thomas Yeo, who is also Deputy Director of the Centre for Translational Magnetic Resonance Research at NUS Medicine and co-PI for the clinical trials, said, "Functional MRI is one of the few non-invasive approaches that can safely image the living human brain. By using this newly-developed machine-learning algorithm to clearly outline high-quality individualised brain networks from the limited quantity of functional MRI data, we are able to locate the exact spot unique to each patient, and stimulate it to treat their depression disorder as accurately as possible. These upcoming pilot trials provide a platform to demonstrate that the safety and efficacy from personalised transcranial magnetic stimulation can be assured for patients with treatment-resistant depression who are undergoing this procedure."

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[5] Randall T. Espinoza, & Charles H. Kellner (2022). Electroconvulsive Therapy. *The New England Journal of Medicine*, 386:667-672.

[6] Berlim, M. T., Van den Eynde, F., & Daskalakis, Z. J. (2013). Efficacy and acceptability of high frequency repetitive transcranial magnetic stimulation (rTMS) versus electroconvulsive therapy (ECT) for major depression: A systematic review and meta-analysis of randomized trials. *Depression and anxiety, 30(7), 614-623.*

16. Heng Li Lang, Head of Climate & Liveability at Temasek Foundation, added, "Major depressive disorder is a serious public health challenge. According to the Singapore Mental Health Study conducted in 2016, it affects one in 16 adults in Singapore. Temasek Foundation is committed to catalyse our support for breakthrough efforts in healthcare innovations such as this. The milestone pilot trials by IMH and NUS will be a transformative step to open up opportunities for patients with treatment-resistant depression, and their families. Temasek Foundation is heartened to partner both IMH and NUS on this journey, creating impactful work together with NMRC."

17. "The National Medical Research Council recognises the importance of advancing clinical practices in mental health through innovative research. Our investment in this study underscores our commitment to supporting research that has the potential to impact clinical practice and improve the quality of care for patients battling treatment-resistant depression," said Professor Tan Say Beng, Executive Director, NMRC.

18. A cohort of 20 participants with treatment-resistant depression will be recruited for the APIC-TMS trial, and 70 for the SPARK-D trial. Participants will have to undergo fMRI scans as well as TMS. APIC-TMS will offer participants the personalised target, and SPARK-D will randomly assign patients to either the personalised target or the current standard one-size-fits all target. IMH is committed to patient safety and welfare by ensuring appropriate consent from the prospective participants in accordance with the Human Biomedical Research Act (HBRA).

19. For more information on the clinical trials, please refer to Annexes B and C.

20. Persons who wish to enquire about the pilot may email the IMH Neurostimulation Service at swc_clinic@imh.com.sg.

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**About the Institute of Mental Health (IMH)**

The Institute of Mental Health (IMH), a member of the National Healthcare Group, is the only tertiary psychiatric care institution in Singapore. Located on the sprawling 23-hectare campus of Buangkok Green Medical Park in the north-eastern part of Singapore, IMH offers a multidisciplinary and comprehensive range of psychiatric, rehabilitative and therapy services in hospital-based and community-based settings. The 2,000-bedded hospital aims to meet the needs of three groups of patients – children and adolescents (aged below 19 years), adults and the elderly. Besides providing clinical services, IMH dedicates resources to carry out mental health promotion and raise mental health literacy. IMH also leads in mental health research and training the next generation of mental health professionals in Singapore. For more information, please visit https://www.imh.com.sg.

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**About National University of Singapore (NUS)**

The National University of Singapore (NUS) is Singapore's flagship university, which offers a global approach to education, research and entrepreneurship, with a focus on Asian perspectives and expertise. We have 16 colleges, faculties and schools across three campuses in Singapore, with more than 40,000 students from 100 countries enriching our vibrant and diverse campus community. We have also established more than 20 NUS Overseas Colleges entrepreneurial hubs around the world.

Our multidisciplinary and real-world approach to education, research and entrepreneurship enables us to work closely with industry, governments and academia to address crucial and complex issues relevant to Asia and the world. Researchers in our faculties, research centres of excellence, corporate labs and more than 30 university-level research institutes focus on themes that include energy; environmental and urban sustainability; treatment and prevention of diseases; active ageing; advanced materials; risk management and resilience of financial systems; Asian studies; and Smart Nation capabilities such as artificial intelligence, data science, operations research and cybersecurity.

For more information on NUS, please visit nus.edu.sg.

**About the NUS Yong Loo Lin School of Medicine (NUS Medicine)**

The NUS Yong Loo Lin School of Medicine is Singapore's first and largest medical school. Our enduring mission centres on nurturing highly competent, values-driven and inspired healthcare professionals to transform the practice of medicine and improve health around the world.

Through a dynamic and future-oriented five-year curriculum that is inter-disciplinary and inter-professional in nature, our students undergo a holistic learning experience that exposes them to multiple facets of healthcare and prepares them to become visionary leaders and compassionate doctors and nurses of tomorrow. Since the School's founding in 1905, more than 12,000 graduates have passed through our doors.

In our pursuit of health for all, our strategic research programmes focus on innovative, cutting-edge biomedical research with collaborators around the world to deliver high impact solutions to benefit human lives. The School is the oldest institution of higher learning in the National University of Singapore and a founding institutional member of the National University Health System. It is one of the leading medical schools in Asia and ranks among the best in the world (Times Higher Education World University Rankings 2024 by subject and the Quacquarelli Symonds (QS) World University Rankings by subject 2023).

For more information about NUS Medicine, please visit https://medicine.nus.edu.sg/.

**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**<br>**(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**<br><br>**(Each session includes 10 minutes stimulation treatment and 50 minutes recovery in recovery room, for a total of 10 sessions).**<br><br>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<br>Senior Consultant, Department of Mood & Anxiety<br>Head, Neurostimulation Service<br>Institute of Mental Health | 戴鹏程医生<br>情绪管理及焦虑障碍部门高级专科顾问<br>神经刺激服务主任<br>心理卫生学院 |
| Associate Professor Thomas Yeo<br>Centre for Sleep and Cognition<br>NUS Yong Loo Lin School of Medicine | 杨文泰副教授<br>睡眠认知中心<br>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 |