Project Title: Clinical Research Centre for Neuromodulation in Psychiatry

HEALTHY VOLUNTEERS: INFORMATION BOOKLET

Introduction

This research study is being carried out at the Departments of Psychiatry at (1) NIMHANS, Bengaluru; (2) Central Institute of Psychiatry (CIP), Ranchi and (3) Kasturba Medical College, Manipal with due approval by the respective Institute Ethics Committees. This multi-center research project is funded by the Wellcome Trust – Department of Biotechnology India Alliance.

What is the purpose of this study and why am I being approached for participation?

We are conducting research studies in a group of individuals who have been diagnosed with severe mental illnesses like schizophrenia and depression. These studies come under the broader ambit of the Clinical Research Center for Neuromodulation therapies in Psychiatry at NIMHANS, which is funded by the Department of Biotechnology – Wellcome Trust India Alliance. There are two important aspects of these clinical research studies – (a) to identify biological markers of disease states by comparing results of certain investigations/assessments between persons with mental illness and healthy comparison subjects and (b) to examine patients with severe mental illnesses for understanding the effects of neuromodulatory treatments (details described below) on the brain and related such effects with clinical symptom improvement; this in turn, may help us to predict which patients might benefit with such treatments. Both these aspects require that we examine and evaluate individuals who do not suffer from these mental illnesses (i.e. healthy subjects). Comparing the research data from healthy subjects will help us to identify the abnormalities in patients. From our preliminary screening, we understand that you do not suffer from a mental illness and hence we are requesting you to participate in this study as a healthy volunteer.

What tests will be performed in this research?

In the following sections, we provide information regarding the various research investigations/tests/assessments that are employed in this research which we hope would address most of the questions that you may want clarity on before deciding to participate in this study. In addition to the information provided in these sections, you will be shown a video of all these procedures (MRI brain scans, neuromodulation tests, EEG & ECG) so that you can understand them better.

Research Investigations

The research investigations that will be done in this study include: Magnetic Resonance Imaging (MRI), electroencephalography (EEG), electrocardiography (ECG), neuromodulation tests,

detailed clinical assessments and blood sample collection. These investigations will take about 5 hours altogether. They will be done with adequate breaks & refreshments to ensure your comfort.

Magnetic Resonance Imaging (MRI)

MRI scan tests will help us to understand the structure (structural MRI), activation (functional MRI), connections (diffusion tensor imaging), and chemical nature (magnetic resonance spectroscopy) of the brain. We will be doing some related scanning procedures to make sure that you do not have any neurological disease as well as to meet the needs of specialized research studies. The duration of the MRI scan will be for about 1 hour.

The MRI scan uses a large magnet to obtain the scans and does not use radiation like X-rays. During the recording, you will be asked to lie on your back on a table with your head positioned in a padded headrest. The study coordinators and the MRI technicians will provide you with the necessary instructions and help during the recording.

If we notice any obvious brain structural abnormalities in your scan, we will inform you regarding the same and counsel you about the options for further treatment. If you so wish, we would refer you for consultation with the appropriate specialist for obtaining the necessary guidance regarding treatment. You will be provided with a printed report on structural MRI scan findings.

Though the MRI scan procedure is considered very safe, in extremely rare situations, there may be certain risks and discomforts associated with the same. Some people may get muscle aches and pains from lying on their back. This will be minimized by providing cushions at pressure points and beneath the knees as required. Earplugs or headphones will be used to dampen the sound inside the MRI room. You may feel nervous about being in a small space when you are in the MRI scanner; however, you will be able to communicate with us throughout the scan and can tell us whenever you want the scan to be stopped or interrupted.

The following items may interfere with MRI scans and some can be potentially hazardous: E.g., Cardiac pacemaker, aneurysm clips, implanted insulin/drug pump, neurostimulator (TENS unit), biostimulator/bone growth stimulator, hearing aid/cochlear implant, Gianturco coil (embolus coil), vascular clips, surgical clip or staples, heart valve prosthesis, Greenfield vena cava filter, middle ear implant, penile prosthesis, shrapnel or bullet, wire sutures, tattooed eyeliner, any type of dental item held in place by a magnet, any other implanted item not mentioned, diaphragm/Intra-Uterine Device, intraventricular shunt, wire mesh, artificial limb or joint, any orthopedic item (e.g., pins, rods, screws, nails, clips, plates, wire, etc.), dentures, dental braces or any type of removable dental items. If you have any of these items in your body, participation in the study could cause serious harm. Therefore, it is very important for you to notify the researcher if you have any of these items in your body and to avoid participating in this study. Please be reassured that we will also be examining you thoroughly to make sure that you do not have these items in your body.

Electroencephalography (EEG)

An electroencephalography (EEG) (or brain wave test) measures the electrical activity in the brain (brain waves) using electrodes (small metal discs or sensors) placed on the head with gel. The test does not hurt and usually takes about an hour. During EEG recording, you would be made to lie down comfortably. We would fix a net outside your head comprising of EEG recording electrodes which would be connected to the EEG amplifier. You will remain awake throughout the duration of the EEG recording. We will be doing some related EEG procedures to make sure that you do not have any neurological disease.

Electrocardiography (ECG)

An electrocardiography (ECG) is a test that gives us a measure of the heart's electrical activity. You will be asked to lie flat on a table and several small electrode pads (like stickers) will be placed on the body. This test takes about 10 minutes. At the same time of EEG recording, your ECG will also be recorded. Like MRI, EEG as well as ECG also are absolutely safe procedures and do not involve any radioactive or other significant risks.

Neuromodulation Tests

Neuromodulation tests are performed to understand the reactivity of brain cells (neurons). We will do the neuromodulation tests using non-invasive and safe brain stimulation techniques namely – Transcranial Magnetic Stimulation (TMS) and transcranial Direct Current Stimulation (tDCS).

Transcranial Magnetic Stimulation (TMS): In this method, the brain is stimulated using a magnetic field through a coil attached to a machine. The person sits comfortably on a chair. The magnetic coil will be placed on the head (scalp) to stimulate the brain region that represents your right thumb and the activity levels of right thumb muscle will be recorded using electromyography (EMG) leads placed on the right hand. The coil makes a ticking sound every time the brain is stimulated. The person remains awake and alert during the session

Transcranial Direct Current Stimulation (tDCS): tDCS procedure involves the application of weak, battery delivered direct current (2 mA) through electrodes on specific parts of the head (scalp). Please note that the batteries are part of the equipment and will not be placed on the subjects.

Details of Neuromodulation Tests Procedure:

The neuromodulation tests will take approximately 1 hour with adequate breaks in between to ensure your comfort. You will remain alert and awake during the whole session. The procedural details of these tests are as below:

- You will sit comfortably on a chair with hands rested on hand-rests. 3 electrodes will be attached to different areas of your right hand to record muscle activity. The TMS coil will be placed on the left side of your head and some brain reactivity recordings will be done. There will be twitches on your hand.
- After this, active or inactive tDCS will be used to stimulate your brain for 20 minutes. - After this, the same brain recordings which we have done using TMS coil earlier will be done again.

Please note that after the neuromodulation tests session, you will be able to leave immediately and do all the activities including driving.

Clinical Assessments
In addition to the above investigations, we shall carry out a detailed evaluation of your medical status by examining you as well as by interviewing you in detail. The study will involve you doing some computerised and paper-pencil tests for assessment of brain functions such as attention, concentration, memory, planning, and reasoning. All these assessments & tests will take about 2 hours.

Blood Sample Collection
A 15 ml sample of blood (about 3 teaspoons) will be collected for clinical blood investigations as well as research studies involving genetics and other assays. If any abnormality is found in clinical blood investigations, we will suggest the required treatment / refer you to another specialist doctor as appropriate. The blood sample (serum, plasma and DNA) will be stored and utilized for genetic tests of this project as well as for future research assays, that will be conducted after due approvals from the Institutional Ethics Committee.

What are the risks associated with these research investigations?

All the investigations/tests planned in this study are found to be mostly safe and are not commonly associated with any significant risks or adverse effects. This safety of these investigations is established through previous observations from numerous research studies conducted by us as well as other researchers internationally.

MRI: This does not involve any risk apart from tolerable discomfort during procedures.

EEG: The gel used to put the discs on your head is sometimes sticky and the discs may scratch a little bit.

ECG: The test may occasionally cause some redness or itching where the pads are placed. These effects (redness/itching), if it happens, will disappear after some time.

TMS: During stimulation with TMS, you may experience mild pain over your scalp. Most people tolerate this well. However, if you find it intolerable, let us know. We will take appropriate measures. Extremely rarely, TMS has caused individuals to experience seizures. International professional bodies have provided guidelines to minimize the risk of seizure and we would strictly adhere to these. Moreover, we would have done other tests as part of this study and ruled out risk factors for seizures in your case. Please be reassured that our lab has required medicines and expertise to treat seizures immediately if it occurs in spite of these precautions.

tDCS: Sometimes, during the tDCS, you may experience mild and tolerable tingling/itching in the place where the tDCS electrodes are positioned near / on your scalp. However, these sensations are tolerable and most often transient – i.e. will disappear within 2 or 3 minutes. At the maximum, these tolerable sensations will be present usually only during the period of administration of tDCS. Very rarely, you may get mild headache or discomfort. In such situations, the required medical help will be provided.

Blood Sample Collection: The collection of the blood sample is expected to be minimally painful. All aseptic precautions will be taken during the procedure.

What will happen in this research study if I take part?

If you agree to participate in this study and provide your consent, you will be assessed with questionnaires and research investigations - cognitive function tests, MRI brain scan, electroencephalography (EEG) & electrocardiography (ECG), neuromodulation tests, as well as blood sample collection. As we have mentioned earlier, you will have the freedom to withdraw your consent at any time during the study. Adequate breaks and rest will be given in between tests. Also, refreshments will be provided at the end of the tests.

What are the potential benefits and risks of participating in the research?

If you do not take part in this study, we will not contact you again. If you take part in this study, we will provide you with reports of all the evaluations performed for your record. You will also be contributing to the enhancement of scientific knowledge which has potential direct impact on patient care in the near future. The risks of participating in the study are less than minimal as elaborated earlier with respect to the risks involved with the specific investigations.

What if I feel uncomfortable during the tests being performed?

In case you develop discomfort to the level that you wish to discontinue participating in this study, we would oblige and stop the assessments/tests.

How long will these procedures take?

MRI, EEG, ECG and TMS tests will altogether take about 3 hours. The other assessments (clinical interview and cognitive tests) and blood sample collection will take about 2 hours to complete.

How often will these tests be performed?

All these tests will be performed only once.

Is it compulsory for me to take part in this research?

Participation in this research is optional and it is voluntary, meaning that the decision to take part in this study will be as per your wish. You will be given a copy of this information sheet and have adequate time to read through, think and ask any questions before deciding. If you do decide to take part you will be asked to sign a consent form and given a signed copy of the consent form to keep. If you decide to take part you are still free to withdraw at any time during the study without giving a reason.

Do I have the choice to withdraw my choice of participation at any time of the study? If I withdraw, do I have to justify or give reasons for the same?

Yes, you can withdraw anytime you wish to. You can willingly share with us your concerns and reasons for backing out of the study. But you are not obligated to tell us your reasons. If you do not wish to confide in us, no questions will be asked.

Can I ask, enquire or question any doubts I have during the entire time of my participation in the study?

Yes. At any time during the study, you are free to clarify your doubts and questions with respect to the research procedure.

Do I have to pay anything from my side for the tests or procedures that are a part of the study?

As you are participating in the study, all your tests and procedures are carried out for the research purpose. You do not have to pay anything from your side.

Will there be any reimbursement for my travel expenses?

Yes, we will compensate for your time and incidental expenses including travel and refreshment costs.

How likely is that I might suffer from any injury attributable to my participation in the research procedures? If any such injury happens, will I be compensated?

We will implement all the research procedures taking utmost care to avoid any injury or adverse event. In the unlikely event that you suffer any injury attributable to your participation in the research procedures of this project, you will be compensated financially as per the National Ethical Guidelines for Biomedical and Health Research involving Human Participants by the Indian Council of Medical Research.

Will the test results obtained in the study be made available to others? Will my participation confidentiality be maintained?

Your identity will be completely protected. All information from the study will be stored under code to maintain strict confidentiality and will be reviewed only by the investigators, ethics committee or regulatory bodies. This coded and de-identified data (and its copies) will be stored in encrypted format with password protected and secured access control in database of computer servers at NIMHANS, collaborating institutes, cloud storage and any other storage media like CDs, DVDs, hard drives / similar others. This data will be used for further advanced analyses as well as future research studies. If you agree, as per the guidelines of scientific organizations and with the approval of relevant regulatory bodies, your data (in coded and de-identified format) will be shared with interested national and international researchers/collaborators, working on similar / related research ideas to foster greater understanding of the results; this, in turn may lead to the larger good of patients suffering from depression / other diseases or scientific advances worldwide.