Citalopram as a Posterior Cortical Protective Therapy in Parkinson Disease

NCT04497168

Date of IRB Approval: April 12, 2022

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   - **Consent - Tracked**
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Study ID: HUM00146905 / Amendment ID: Ame00121031

Approval Date: 11/18/2021

Document Finalized: 4/12/2022 4:51 PM

UNIVERSITY OF MICHIGAN
CONSENT TO BE PART OF A RESEARCH STUDY

1. KEY INFORMATION ABOUT THE RESEARCHERS AND THIS STUDY

Study title:
Citalopram as a posterior cortical protective therapy in Parkinson disease

Company or agency sponsoring the study:
The National Institute on Aging

Names, degrees, and affiliations of the principal investigator:
Vikas Kotagal, MD, Department of Neurology, University of Michigan

1.1 Key Study Information

You may be eligible to take part in a research study. This form contains important information that will help you decide whether to join the study. Take the time to carefully review this information. You should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others such as your family, friends, or other doctors about joining this study. If you decide to join the study, you will be asked to sign this form before you can start study-related activities. Before you do, be sure you understand what the research study is about.

A research study is different from the regular medical care you receive from your doctor. Research studies hope to make discoveries and learn new information about diseases and how to treat them. You should consider the reasons why you might want to join a research study or why it is not the best decision for you at this time.

Research studies do not always offer the possibility of treating your disease or condition. Research studies also have different kinds of risks and risk levels, depending on the type of the study. You may also need to think about other requirements for being in the study. For example, some studies require you to travel to scheduled visits at the study site in Ann Arbor or elsewhere. This may require you to arrange travel, change work schedules, find child care, or make other plans. In your decision to participate in this study, consider all of these matters carefully.

This research is studying a drug called citalopram in people with Parkinson disease to learn about its effect on your body and brain. This study will involve you taking either citalopram (a common anti-depressant medication) or a placebo (sugar pill) once per day for two years. There will be study visits approximately every three months, with three longer in-person visits (approximately once per year). See section 4 for more information about what will be involved in each of the study visits. Your health-related information and DNA will be collected for this research study.

This study involves a process called randomization. This means that whether you receive citalopram or placebo is not chosen by you or the researcher. Participants will be assigned to separate groups, based on a 50/50 chance (like the flip of a coin), to compare different treatments. If you decide to be in the study, you need to be comfortable not knowing which study group you will be in.
There can be risks associated with joining any research study. The type of risk may impact whether you decide to join the study. For this study, some of these risks may include side effects from the study drug or placebo,

such as: sleepiness/drowsiness, nausea, and dry mouth. More detailed information will be provided later in this document.

This study may offer some benefit to you now if you are randomized to the study medicine by helping to prevent cognitive impairment in Parkinson's Disease, however, if you are randomized to placebo, this study may not offer any benefit to you now. If this study is successful, others may benefit in the future by reducing their risk of developing cognitive impairment in Parkinson disease. More information will be provided later in this document.

We expect the amount of time you will participate in the study will be approximately 28 months.

You can decide not to be in this study. Alternatives to joining this study include continuing with your usual Neurological care through your regular doctors.

Even if you decide to join the study now, you are free to leave at any time if you change your mind.

More information about this study continues in Section 2 of this document.

2. PURPOSE OF THIS STUDY

2.1 Study purpose:

Parkinson disease (PD) is a condition that affects about 1 million Americans. Between 50 and 80% of people with PD will go on to develop dementia in the years after their initial diagnosis. Currently, there are no known treatments for PD that reduce the risk of developing dementia.

Dementia in PD has some key differences from dementia in other common conditions like Alzheimer's disease. Unlike Alzheimer's, in PD, dementia can often manifest with visuospatial dysfunction such as difficulty navigating in space—for example bumping into doorways or getting lost in different places, visual hallucinations, and difficulties with problems solving in multi-dimensional spaces such as difficulty with Sudoku or cross-word puzzles.

Based on preliminary data, we are trying to find out whether citalopram, a well-known antidepressant drug, may reduce the risk for this type of dementia in PD.

3. WHO MAY PARTICIPATE IN THE STUDY

Taking part in this study is completely **voluntary**. You do not have to participate if you don't want to. You may also leave the study at any time. If you leave the study before it is finished, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled.

3.1 Who can take part in this study?

People with PD who are at least 65 years old, and have both sides of their body affected by PD, but are not fully-dependent on a cane or a walker to get around may be eligible for the study. People who take part in this study must not be taking a medication for depression or be claustrophobic. A full list of the inclusion and exclusion criteria is available from the study team if you are not sure whether you can participate or not.

3.2 How many people are expected to take part in this study?

We are hoping to enroll 58 participants into this study

4. INFORMATION ABOUT STUDY PARTICIPATION

4.1 What will happen to me in this study?

After you go through the initial screening process (this typically happens by phone), we will have you come for a full-day visit to determine whether or not you are eligible (called the Baseline Visit). Either at this visit or in the days leading up to it, you will be asked to sign this informed consent form before any study procedures take place. If you don't qualify for the study but wish to be re-screened at a later time, we may be able to use some of your already collected information for repeat screening purposes. Full-day visits can be divided over multiple days if needed or if this option would be more convenient.

If you are eligible after the baseline visit, you will be randomized, like the flip of a coin, to receive either citalopram or placebo (sugar pill). You will have a 50-50 chance of receiving either one. This study is double-blinded, which means that neither you nor the study team members you interact with will know which drug you are taking. Once you have been randomized, we will mail you a supply of the study drug (Please note: In this consent form, the term "study drug" will refer to the blinded pills which could either be citalopram or placebo). You will begin by taking 10mg of study drug (one 10mg pill) once per day, and then after two weeks, the study team will call to check and see how you are doing, and if all is well, you will start taking 20mg of study drug once per day (one 20mg pill). You will continue to take the study drug every day for 24 months. After 24 months the study team will give you instructions on how to safely stop taking the study medication. Throughout the study, there will be study visits approximately every 3 months. Many of these "visits" can be

done by phone/video. Approximately once per year there will be a longer full-day study visit that will take place over two days. These longer visits can be divided up over 2 or more days as well if needed.

Following is a list of the tests and procedures that will be done as part of this study. Please note, that not all of these tests and procedures will be done at every study visit. In some cases, we may be able to send some questionnaires home with you to be filled out on your own and mailed back to the study team. Please take a look at the schedule of events (last page of this consent) to see what tests or procedures will be done at which visit.

Clinical Items: You will receive a physical and neurological examination including the measurements of weight, height, pulse and blood pressure. We will also ask you questions about your health and medications that you are taking. We will ask you about your PD diagnosis and your history of PD symptoms.

Motor tests: We will test your neurological function and balance on a physical examination. In order to obtain an accurate assessment that is not affected by dopaminergic medications, some of the motor testing and the neurologic examination rating will be performed in a dopaminergic "off" state which means you will be asked to not take some of your regular PD medications, such as Sinemet (levodopa) or dopamine agonists including Mirapex (pramipexole), Requip (ropinorole), or Neuropro (rotigotine patch) on the morning of your testing. After motor testing has completed (this typically takes about an hour) you can take your parkinsonian's medications. We will also ask you to fill out questionnaires about your balance, falling, and gait (walking).

Neuropsychological and neurobehavioral tests: The neuropsychological tests are designed to get an overall estimate of your ability to plan and make decisions ('executive functioning'), memory, concentration, and ability to react fast. These functions will be measured with a series of standard pencil and paper questionnaires. We will also ask you questions about your mood. Other questions are about sleep and fatigue.

EKG**:** 12-lead EKG will be performed at baseline (month 0), month 2, 14, 26, and 28 to make sure you aren't having any problems with your heart related to the study medication. It may be possible to substitute an outside EKG for s study-team-performed EKG if performed in the appropriate time interval. Please check with the study team for more details

Adverse Event Monitoring: At each study visit, you will be asked about any illnesses, injuries, medication side effects, or anything out of the ordinary that you may have noticed since your last study visit. Before starting any new medication, check with the study doctor. We will also ask you questions to monitor for depression and suicidal thoughts.

Study drug: You will be dispensed a new supply of study drug around the time of your in-person/remote visits starting at month 2, and we ask that you return all unused study drug and packaging at the time of your in-person visits.

Vision testing: We will do tests to see how sharp your vision is and how well you can see contrast (i.e. black and white versus various shades of gray and white).

Citalopram level: We will draw a small amount of blood to check for the amount of citalopram in your blood at months 14 and 26.

Optional MRI scan: Optional MRI scans will occur at months 0, 14, and 26. MRI scans allow the study team to visualize the brain in great detail by using a large magnet. An MRI scan of the brain involves lying on a table which slides into a scanner. You will be instructed to remove all jewelry and other metal-containing objects for the MRI scan and may be asked to change into an MRI-safe gown or outfit. During the MRI scan loud noises

may be heard. During the scan we will ask you to do different visuospatial cognitive tasks, similar to creating a "map" of a house in your mind, or remembering a series of turns using pictures inside a grocery store. Immediately after the MRI is completed, you answer some follow up questionnaires with the research team about what you saw or did during the visuospatial cognitive task part of the MRI.

_____ Yes, I am interested in participating in the optional MRI scans (month 0, 14, and 26)

_____ No, I am not interested in participating in the optional MRI scans (month 0, 14, and 26)

PET scans (DTBZ and PiB): The PET scans will allow the investigators to "see" the specific markers of Parkinson Disease associated with thinking and memory problems. To do this, a radiotracer will be injected into your vein through an IV (intravenous catheter or plastic "tube" inserted in an arm vein). A tracer refers to a small amount of a radioactive substance that does not alter body function, but that can be detected (imaged) in the PET scanner. The tracer will be injected as you lie on a table, which will move into a hollow machine resembling an X-ray CT (or CAT) scanner. Images of your brain will be obtained over a period of time. At the baseline visit, there will be up to two PET scans done, an optional dopamine PET scan (DTBZ) and a required amyloid PET scan (PiB) to look for the presence of amyloid plaques in certain parts of the brain. At month 14 and 26 you will have a repeat (required) amyloid PET scan.

_____ Yes, I am interested in participating in the optional baseline DTBZ PET scan

_____ No, I am not interested in participating in the optional baseline DTBZ PET scan

Genetic testing: We are interested in investigating whether some genes may affect cognitive impairment in Parkinson's Disease. In order to do that, we will collect a saliva sample and a blood sample to analyze some of your DNA at the time of your baseline visit. After we collect these samples, we will submit them to the National Institute of Aging National Centralized Repository for Alzheimer's Disease and Related Dementias (NIA NCRAD) biorepository. A separate genetic sample will be collected, stored, and analyzed here at the University of Michigan (UM) and may also be stored in the UM Biorepository pending approval from this UM biorepository facility.

A biorepository contains biological information from many people. Researchers all over the world can take information from the repository and use it in their studies. Their studies may be similar to this one or may be completely different. We will label your genetic information with a code, instead of your name or other information so that people cannot directly identify you. Even so, there is a possibility that when your genetic information is combined with other information available to researchers, either now or in the future, they may be able to identify a group you belong to (like an ethnic group or a disease population) or, less likely, you personally.

If you decide in the future that you do not want your genetic data in the biorepository, you can ask us to remove it. Keep in mind, however, that we cannot take back information that other researchers have already obtained from the repository. With appropriate permissions, your biospecimens and collected information may also be shared with other researchers, here and around the world. Your identifiable private information or

identifiable biospecimens may be stripped of identifiers and used for future research studies or distributed to another researcher for future research studies without additional informed consent. Information used in scientific publications will not contain any identifying information. The University of Michigan collaborates with other organizations, and data and samples are generally shared. However, no data shared with other research institutions will include your name or other identifying information.

Besides the information about the main study, the following information is specific to unspecified future use of identifiable data and/or biospecimens. We would also like your permission to keep some of your blood/saliva and medical information collected in the main study, so that we may study it in future research. The future research may be similar to this study or may be completely different.

You can take part in the main study even if you decide not to let us keep your blood/saliva and medical information for future research.

If you give us your permission, we will use your blood/saliva and medical information for future research. Even if you give us permission now to keep some of your blood/saliva and medical information, you can change your mind later and ask us to destroy it. Keep in mind, however, that once we have analyzed your blood/saliva, we may not be able to take the information out of our research.

We may share your blood/saliva and medical information with other researchers, so that they can use it in their research. Their research may be similar to this study or may be completely different. Once we have shared your blood/saliva and medical information with other researchers, we will not be able to get it back.

There is no particular risk for physical harm with this saliva collection method. Future use of your identifiable data and/or specimens will be conducted in compliance with applicable regulatory requirements.

You will not find out the results of future research on your blood/saliva. Allowing us to do future research on your blood/saliva and medical information will not benefit you directly.

With appropriate permissions, your samples and collected information may also be shared with other researchers here, around the world, and with companies.

Your identifiable private information or identifiable biospecimens may be stripped of identifiers and used for future research studies or distributed to another researcher for future research studies without additional informed consent.

Research can lead to new discoveries, such as new tests, drugs, or devices. Researchers, their organizations, and other entities, including companies, may potentially benefit from the use of the data or discoveries. You will not have rights to these discoveries or any proceeds from them.

For some research studies, such as the one you are being asked to join, it is important that you do not learn the results of certain tests. Whether you intend it or not, sometimes learning this information may make you change your actions and behaviors in ways that could impact the outcome of the study.

For this study, you will not be able to see your research test results and you agree to have temporary, limited access placed on your Patient Portal in MyUofMHealth.org. You may not be able to see radiology test results (for example, results of MRIs, or PET scans). While you are on this study, you will still be able to see and use other parts of the Patient Portal in MyUofMHealth.org to refill prescriptions, set up appointments with your

doctor, or pay your medical bills on-line. When this study is over with, full access to the Patient Portal in MyUofMHealth.org will be returned to you.

4.2 How much of my time will be needed to take part in this study?

You will be in the study for approximately 28 months (24 months on study medication). Most study visits will take about 45 minutes to an hour of your time. Three times during this study there will be "long" study visits which will take a full day each. These visits will include clinical testing and PET imaging. These visits can be divided over more than 1 day if needed.

4.3 When will my participation in the study be over?

Your participation in the study will take place over 28 months. The entire study is expected to last 5 years.

4.4 What will happen with my information and/or biospecimens used in this study?

Your biospecimens and collected information will be shared with the NIA NCRAD biorepository

With appropriate permissions, your biospecimens and collected information may also be shared with other researchers, here, around the world, and with companies.

Your identifiable private information or identifiable biospecimens may be stripped of identifiers and used for future research studies or distributed to another researcher for future research studies without additional informed consent.

5. INFORMATION ABOUT STUDY RISKS AND BENEFITS

5.1 What risks will I face by taking part in the study? What will the researchers do to protect me against these risks?

Citalopram: As with all medications, citalopram has the risk of side effects. Not all participants will have side effects with citalopram. If you do have side effects that you think are related to citalopram, please let the researchers know so they can be treated.

In a study where participants were randomized to either citalopram or placebo, the following side effects were observed:

Side Effect	Citalopram Arm	Placebo Arm
Nausea	21%	14%
Dry Mouth	20%	14%
Somnolence (Tiredness)	18%	10%
Insomnia	15%	14%
Increased Sweating	11%	9%
Tremor	8%	6%
Diarrhea	8%	5%
Ejaculation Disorder (men)	6%	1%
Indigestion	5%	4%
Upper Respiratory Tract Infection	5%	4%
Fatigue	5%	3%
Stuffy Nose	5%	3%
Vomiting	4%	3%
Anxiety	4%	3%
Lack of Appetite	4%	2%

Abdominal Pain	3%	2%
Painful Menstrual Cramps (women)	3%	2%
Agitation	3%	1%
Impotence (men)	3%	1%
Sinusitis	3%	1%
Agitation	3%	1%
Fever	2%	<1%
Decreased Libido	2%	1%
Yawning	2%	1%
Joint Pain	2%	1%
Muscle Pain	2%	1%

More serious, but rare, risks have been associated with citalopram and other medications in its class. These include an increased risk for suicidal thoughts and behaviors, heart function changes, serotonin syndrome, and eye pain or visual disturbances. Citalopram may also increase the risk for balance problems and falls.

i) Suicidal thoughts and behaviors: This risk is greater in younger adults under the age of 25, but is more rare in patients over 60. We will monitor you for suicidal thoughts and behaviors by having you fill out questionnaires that ask about these things.

ii) Citalopram can cause problems with your heart function, specifically a prolonged "QT interval" which may predispose you to an abnormal serious heart rhythm, which could be life threatening. While rare, symptoms may include dizziness, palpitations, or fainting which should be reported to your primary care doctor and the study team. To minimize this risk, the dose of citalopram used in this study (20mg maximum) is within FDA safety guidelines for patients of your age, and we are ensuring that you are not taking other medications which may increase this risk. Further, we will be monitoring your heart function with an EKG at some study visits. If changes in the EKG are found, the dose of study drug will be cut in half, or it will be discontinued. If there are other medications you take/will be taking that can affect the QT interval, you may still be able to be in the study with careful monitoring—our study team will investigate individual drug-specific issues on a case-by-case basis and will discuss any updating monitoring plans with you.

iii) Serotonin syndrome may include symptoms such as agitation, confusion, vomiting, and rigidity. Emergent medical care should be sought if these symptoms occur. We will be screening your medications to ensure that you are not taking other medications which may increase this risk.

iv) Eye pain or visual disturbances are rare; please contact your primary care doctor and your study coordinator if you experience any of these symptoms.

Confidentiality of Research Information: There is always a risk to confidentiality and privacy when more people have access to your medical records. In order to reduce the risk of inadvertent exposure, all your research records will be kept in a locked cabinet or locked office. Any information that is shared outside of the University of Michigan will only have a code on it; it will not contain your name or other identifying

information. See Section 9 of this document for more information on how the study team will protect your confidentiality and privacy.

Clinical, neuropsychological and behavioral testing: Risks in regard to the neuropsychological and behavioral assessment include fatigue, frustration and momentary embarrassment that may occur when one experiences difficulty performing a task or learning a new skill. Risk of motor examination in the (overnight) dopaminergic "off" state may result in some discomfort and may result in inconvenient reduction in functional abilities. Freezing is possible in this context, but is rare. Some patients will require additional assistance from their caretaker during this time. Parkinson's medications can be taken immediately at the end of the motor examination.

Blood testing and Genotyping: In order to extract DNA, a saliva sample will be collected using a saliva collection kit. There is no particular risk for physical harm with this collection method. Results of the genotype analysis will not be used for predictive, diagnostic, or prognostic testing of individuals. The risks of blood draw include dizziness or fainting, pain, bruising, and infection. The risks of genetic research include the inadvertent disclosure of genetic information for a given participant. We will take steps to protect against these risks by using only a code to label samples.

Optional MRI scan: The MRI can be loud and disturbing or uncomfortable to some individuals. Headphones, blankets, and pillows will be provided in order to achieve maximum comfort. Some people may experience claustrophobia, back or body discomfort, or anxiety while in the scanner. This fear dissipated for many within approximately 15 minutes of being in the scanner, or if needed, after exiting the scanner. If you feel claustrophobic or afraid at any point during the MRI, please let the staff know. If at any point you wish to not undergo further MRI testing, we can always end your MRI session early and/or alter plans for future scheduled MRIs without jeopardizing your ability to remain in the overall study.

There is a substantial risk to persons who have metallic objects inside their bodies, as the magnet in the MR scanner can cause these to move. People with pacemakers or metallic objects located in the eye, ear, brain or blood vessel walls are not allowed to take part in this study. There is a potential risk of heart rhythm disturbances in patients who have previous heart rhythm abnormalities or in patients who have certain types of heart pacemakers. If you aren't sure if you have metal in your body, an X-ray may need to be done. If this is required, the maximum radiation dose to the involved body area will be 0.3 rems, with minimum exposure of the other areas of the body.

There also is the potential that imaging could reveal a previously unrecognized but pre-existing abnormality. Many such abnormalities are not clinically significant, but they may cause anxiety or require further investigation by a personal physician. If one of the investigators identifies such an abnormality, they will contact the personal physician, who will arrange for appropriate care. Necessary additional imaging studies and treatment would not be paid for by this study.

PET scans & Venipuncture:
Insertion of an IV for intravenous injection of the PET radiopharmaceutical may be commonly associated with slight pain or bruising at the puncture site and rare chance of infection.

Participation in this research study will involve exposure to radiation associated with the PET transmission scans and the administration of the radioactive drugs. You will be instructed to use the bathroom two hours post injection to minimize the exposure of your bladder to radiation. The entire amount of radiation exposure due to PET scans while in this study (4 PET scans over 28 months), will be 0.887 rem, which is approximately

8.8% of the radiation exposure (10 rem) permitted to radiation workers by federal regulations over two years (24 months). This radiation dose is not expected to produce any harmful effects, although there is no known minimum level of radiation exposure for non-radiation workers considered to be totally free of the risk of causing genetic defects or cancer. The risk associated with the amount of radiation exposure participants receive in this study is considered low and comparable to every day risks. If needed due to technical issues affecting image interpretation, scheduled PiB PET scanning sessions may be repeated x1 for each subject. This would increase the entire amount of radiation exposure for a given subject to 1.094 rem over 28 months, which is approximately 10.9% of the radiation exposure (10 rem) permitted to radiation workers by federal regulations over two years (24 months).

No PET studies will be performed on pregnant or potentially pregnant women, and will be confirmed by pregnancy testing if necessary. The use of these PET tracers is considered to be generally safe and effective as approved by the University of Michigan Radioactive Drug Research Committee in accordance with Food and Drug Administration regulations.

Adverse reactions to the radioactive tracers used in this study have not been reported. However, the possibility exists for a rare reaction to any of the drugs or procedures to which you will be exposed. ACLS-certified staff will be in attendance at all times during the study and an emergency cart will be in close proximity.

Other physical risks involve possible body or muscle aches from lying still.

As with any research study, there may be additional risks that are unknown or unexpected.

There also is the potential that PET scans could reveal a previously unrecognized but pre-existing abnormality. Many such abnormalities are not clinically significant, but they may cause anxiety or require further investigation by a personal physician. If one of the investigators identifies such an abnormality, they will contact the personal physician, who will arrange for appropriate care.

5.2 What happens if I get hurt, become sick, or have other problems as a result of this research?

The researchers have taken steps to minimize the risks of this study. Even so, you may still have problems or side effects, even when the researchers are careful to avoid them. We will monitor for side effects through regular study visits and using questionnaires to ask about suicidal thoughts or feelings and EKGs to monitor cardiac QT interval. Please tell the researchers listed in Section 10 about any injuries, side effects, or other problems that you have during this study. You should also tell your regular doctors**.**

5.3 If I take part in this study, can I also participate in other studies?
Being in more than one research study at the same time, or even at different times, may increase the risks to you. It may also affect the results of the studies. You should not take part in more than one study without approval from the researchers involved in each study.

5.4 How could I benefit if I take part in this study? How could others benefit?
You may not receive any personal benefits from being in this study. If you receive citalopram it is possible you may experience a slight elevation in your mood. If you receive placebo, you may not receive any personal benefits from being in this study. If our study meets its goals, we hope your efforts will allow us to find a way to reduce the risk of cognitive impairment in PD for many others.

5.5 Will the researchers tell me if they learn of new information that could change my willingness to stay in this study?

Yes, the researchers will tell you if they learn of important new information that may change your willingness to stay in this study. If new information is provided to you after you have joined the study, it is possible that you may be asked to sign a new consent form that includes the new information. Please note that evaluations conducted as part of this research study including brain MRIs and EKGs are being obtained for research purposes only and may not be useful for a clinical or medical evaluation.

6. ALTERNATIVES TO PARTICIPATING IN THE STUDY

6.1 If I decide not to take part in this study, what other options do I have?

You may continue to take your regular PD medications throughout this study. Your decision to participate in this study is completely voluntary. We also want to note that citalopram is actually a clinically available drug that has been approved by the FDA for the treatment of depression. We are not advocating that people take the drug on their own ("off-label") for a cognitive impairment-prevention purpose because these studies have not yet been completed in humans with Parkinson's disease. We are hoping this study will help determine if this medication will be effective. Additionally, the reason to participate in this trial isn't necessarily to get a drug. It is to be part of something bigger than that. If this study is successful, we hope your involvement may actually lead to larger studies that could help tens of thousands of people with Parkinson disease in future.

7. ENDING THE STUDY

7.1 If I want to stop participating in the study, what should I do?

You are free to leave the study at any time. Your standard medical treatment does not depend on your participation in this study. If you leave the study before it is finished, there will be no penalty to you. You will not lose any benefits to which you may otherwise be entitled.

If you wish to stop participating in the study, please let the research team know so that your study medication can be stopped in a safe manner. You will be asked to come in for a final visit to return any unused study medication and to have a physical and neurological exam for your safety.

If you choose to tell the researchers why you are leaving the study, your reasons for leaving may be kept as part of the study record. If you decide to leave the study before it is finished, please tell one of the persons listed in Section 10 "Contact Information".

7.2 Could there be any harm to me if I decide to leave the study before it is finished?

Yes, it is important that the study medication be discontinued in a safe manner and not stopped abruptly. If you stop taking the study medication abruptly, you may experience withdrawal side effects. Please contact the research team if you decide you do not want to participate so they can give you instructions on how to stop the study medication safely.

7.3 Could the researchers take me out of the study even if I want to continue to participate?

Yes. There are many reasons why the researchers may need to end your participation in the study. Some examples are:

- The researcher believes that it is not in your best interest to stay in the study.
- You become ineligible to participate.
- Your condition changes and you need treatment that is not allowed while you are taking part in the study.
- The study Physician may contact your personal physician if any significant findings occur, appropriate care may be necessary, which may take precedence over your study participation.

- You do not follow instructions from the researchers.
- The study is suspended or canceled.

8. FINANCIAL INFORMATION

8.1 Who will pay for the costs of the study? Will I or my health plan be billed for any costs of the study?

The study will pay for research-related items or services that are provided only because you are in the study. If you are not sure what these are, see Section 4.1 above or ask the researchers for a list. If you get a bill you think is wrong, call the researcher's telephone number listed in Section 10.1.

If you are injured or in the event of a medical emergency, dial 911 or visit your nearest Emergency Room. If you believe the study has made you sick or caused you injury, contact one of the people listed in section 10 of this document (Contact Information). If taking part in the study makes you sick or causes you injury, you or your insurance provider will be billed for all costs of treatment as the study does not provide compensation for sickness or injury caused by the study. It is possible that your insurance will not cover these costs.
You or your health plan will pay for all the things you would have paid for even if you were not in the study, like:

- Health care given during the study as part of your regular care

By signing this form, you do not give up your right to seek payment if you are harmed as a result of being in this study.

8.2 Will I be paid or given anything for taking part in this study?

You will receive $25 for each short study visit (months 2, 5, 8, 11, 17, 20, 23, and 28) and an additional $400 for longer visit that includes imaging and in-person clinical testing (months 0, 14, and 26). We will also provide subjects with a voucher for lunch (estimated to be approximately $10 per lunch or $20 if subject is accompanied by a care-partner) at month 0, month 14, and month 26. For the purposes of these payments, a single "visit" includes both required clinical and imaging testing days combined. Payments will be made on a prorated, per-visit basis. Subjects will receive $250 for each of the 4 optional imaging tests (3 MRIs and 1 DTBZ PET) scan. Each subject could receive as much as $2460 over the 28 months of their individual study participation. If needed, participants will also be offered a hotel room or study-funded taxi/car-service in order to accommodate multi-day testing and/or early morning or late in-the-day appointments.

8.3 Who could profit or financially benefit from the study results?
This study is funded by the National Institutes of Health. No specific individual, company, or party is expected to potentially profit or financially benefit from these study results. However, research can lead to new discoveries, such as new tests, drugs, or devices. Researchers, their organizations, and other entities, including companies, may potentially benefit from the use of the data or discoveries. You will not have rights to these discoveries or any proceeds from them.

9. CONFIDENTIALITY OF SUBJECT RECORDS AND AUTHORIZATION TO RELEASE YOUR PROTECTED HEALTH INFORMATION

The information below describes how the confidentiality of your research records will be protected in this study, and any sub-studies described in this document.

9.1 How will the researchers protect my information?

A copy of your informed consent document will be uploaded into your medical record. Your research information will be stored in a secure data file, locked cabinet, or locked office and will not be made a part of your regular medical record. However, some research test orders and test results may become part of your regular medical record at UM. Any information that is shared outside of the University of Michigan will only have a code on it; it will not contain your name or other identifying information.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

The Certificate of Confidentiality will not be used to prevent disclosure as required by federal, state, or local law of such as harm to self or others.

The Certificate of Confidentiality will not be used to prevent disclosure for any purpose you have consented to in this informed consent document.

The federal Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. Under this law:

- Health insurance companies and group health plans may not request your genetic information that we obtain from this research
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums
- Employers with 15 or more employees may not use your genetic information that we obtain from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment

GINA does not apply to the following groups; however, these groups have policies in place that provide similar protections against discrimination:

- Members of the US Military receiving care through Tricare
- Veterans receiving care through the Veteran's Administration (VA)

- The Indian Health Service
- Federal employees receiving care through the Federal Employees Health Benefits Plans

A description of this clinical trial will be available on http://www.clinicaltrials.gov/, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

9.2 What protected health information (PHI) about me could be seen by the researchers or by other people? Why? Who might see it?

Signing this form gives the researchers your permission to obtain, use, and share information about you for this study, and is required in order for you to take part in the study.

Medical information and billing records are protected by the privacy regulations of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA). This type of information is called protected health information (PHI). PHI about you may be obtained from any hospital, doctor, and other health care provider involved in your care, including:

- Hospital/doctor's office records, including test results (X-rays, blood tests, urine tests, etc.)
- Mental health care records (except psychotherapy notes not kept with your medical records)
- All records relating to your condition, the treatment you have received, and your response to the treatment
- Demographic information
- Personal identifiers

There are many reasons why information about you may be used or seen by the researchers or others during or after this study. Examples include:

- The researchers may need the information to make sure you can take part in the study.
- The researchers may need the information to check your test results or look for side effects.
- University, Food and Drug Administration (FDA) and/or other government officials, auditors, and/or the IRB may need the information to make sure that the study is done in a safe and proper manner.
- Study sponsors or funders, or safety monitors or committees, may need the information to:
    - Make sure the study is done safely and properly
    - Learn more about side effects
    - Analyze the results of the study
- The researchers may need to use the information to create a databank of information about your condition or its treatment.
- Information about your study participation may be included in your regular UMHS medical record.
- If you receive any payments for taking part in this study, the University of Michigan accounting department may need your name, address, Social Security number, payment amount, and related information for tax reporting purposes.
- Federal or State law may require the study team to give information to government agencies. For example, to prevent harm to you or others, or for public health reasons.

The results of this study could be published in an article, but would not include any information that would let others know who you are.

9.3 What happens to information about me after the study is over or if I cancel my permission to use my PHI?

As a rule, the researchers will not continue to use or disclose information about you, but will keep it secure until it is destroyed. Sometimes, it may be necessary for information about you to continue to be used or disclosed, even after you have canceled your permission or the study is over.

Examples of reasons for this include:

- To avoid losing study results that have already included your information
- To provide limited information for research, education, or other activities. (This information would not include your name, social security number, or anything else that could let others know who you are.)
- To help University and government officials make sure that the study was conducted properly

As long as your information is kept within the University of Michigan Health System, it is protected by the Health System's privacy policies. For more information about these policies, ask for a copy of the University of Michigan "Notice of Privacy Practices". This information is also available on the web at http://www.uofmhealth.org/patient+and+visitor+guide/hipaa. Note that once your information has been shared with others as described under Question 9.2, it may no longer be protected by the privacy regulations of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA).

9.4 When does my permission to use my PHI expire?

Your permission expires at the end of the study, unless you cancel it sooner. You may cancel your permission at any time by writing to the researchers listed in Section 10 "Contact Information" (below). If you withdraw your permission, you may no longer be eligible to participate in this study.

10. CONTACT INFORMATION

10.1 Who can I contact about this study?

Please contact the researchers listed below to:

- Obtain more information about the study
- Ask a question about the study procedures or treatments
- Talk about study-related costs to you or your health plan
- Report an illness, injury, or other problem (you may also need to tell your regular doctors)
- Leave the study before it is finished
- Express a concern about the study

Principal Investigator: Vikas Kotagal
Mailing Address: Building 18 mailroom
UM North Campus Research Complex
2800 Plymouth Road, Ann Arbor, MI 48109
Telephone: 734-764-6831

Study Coordinators: Emily Herreshoff and Cate Lewis
Telephone: 734-647-9224 / 734-232-1199
Email: citalopram@umich.edu

You may also express a question or concern about a study by contacting the Institutional Review Board listed below:

University of Michigan Medical School Institutional Review Board (IRBMED)
2800 Plymouth Road
Building 520, Room 3214

Ann Arbor, MI 48109-2800
Telephone: 734-763-4768 (For International Studies, include the appropriate calling codes.)
Fax: 734-763-1234
e-mail: irbmed@umich.edu

If you are concerned about a possible violation of your privacy or concerned about a study you may contact the University of Michigan Health System Compliance Help Line at 1-866-990-0111.
When you call or write about a concern, please provide as much information as possible, including the name of the researcher, the IRBMED number (at the top of this form), and details about the problem. This will help University officials to look into your concern. When reporting a concern, you do not have to give your name unless you want to.

11. RECORD OF INFORMATION PROVIDED

11.1 What documents will be given to me?

Your signature in the next section means that you have received copies of all of the following documents:

- This "Consent to be Part of a Research Study" document. You will receive a signed and dated copy of this consent document. (*Note: In addition to the copy you receive, copies of this document will be stored in a separate confidential research file and may be entered into your regular University of Michigan medical record.)*

12. SIGNATURES

Sig-A

Consent/Assent to Participate in the Research Study

I understand the information printed on this form. I have discussed this study, its risks and potential benefits, and my other choices with _____. My questions so far have been answered. I understand that if I have more questions or concerns about the study or my participation as a research subject, I may contact one of the people listed in Section 10 (above). I understand that I will receive a copy of this form at the time I sign it and later upon request. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

Print Legal Name: _____

Signature: _____Date: _____

Sig-D

Consent/Assent to Collect for Unspecified Future Research

This project involves the option to allow the study team to keep your identifiable specimens/data for use in future research. I understand that it is my choice whether or not to allow future use of my specimens. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

_____ Yes, I agree to let the study team keep my specimens for future research.

_____ No, I do not agree to let the study team keep my specimens for future research.

Print Legal Name: _____

Signature: _____

Sig-G

Principal Investigator or Designee

I have provided this participant and/or his/her legally authorized representative(s) with information about this study that I believe to be accurate and complete. The participant and/or his/her legally authorized representative(s) indicated that he or she understands the nature of the study, including risks and benefits of participating.

Printed Legal Name: _____

Title: _____

Signature: _____Date: _____

Schedule of Events

Evaluation	Baseline Visit (Month 0)	Month 1[R]	Month 2	Month 5[R]	Month 8[R]	Month 11[R]	Month 14	Month 17[R]	Month 20[R]	Month 23[R]	Month 26	Month 28	Early Termination visit (if needed	Unscheduled visit
Informed Consent	X													
Randomization	X													
Demographic Information	X													
Medical History	X													
Medical Check-up	X						X				X	X	X	
Vital Signs (in person visits only)[1]	X		X	X	X	X	X	X	X	X	X	X	X	
Motor tests	X						X				X			
Titration/Taper Phone Call		X									X			
Blood Draw Citalopram Level							X				X			
EKG	X		X				X				X		X	X
Neuropsychological and Neurobehavioral Tests	X						X				X			
Adverse event monitoring		X	X	X	X	X	X	X	X	X	X	X	X	X
Vision Testing	X													
Genetic testing[2]	X													
Optional MRI	X						X				X			
PET Scan (PiB PET and optional DTBZ PET)	X						X				X			
Study Drug Collection			X				X				X	X	X	X
Study Drug Dispensing		X	X	X	X	X	X	X	X	X	X			
[1] Temperature, weight, height (baseline only), blood pressure, pulse [2] Saliva and blood sample [R] Remote visits (phone/video) can be conducted or in-person depending on subject preference														