SUBJECT INFORMATION AND CONSENT FORM TO PARTICIPATE IN A RESEARCH STUDY

Study Title:	An Open-Label Clinical Trial Evaluating Sensitivity to Change in Cognition using the THINC-it Following Treatment with Vortioxetine in Major Depressive Disorder
Study Sponsor:	Brain and Cognition Discovery Foundation (BCDF)

Investigator:	Roger McIntyre, MD, FRCPC
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Introduction

You are being asked to take part in a research study. Before agreeing to participate in this study, it is important that you read and understand the following explanation of the proposed study procedures. The following information describes the purpose and procedures of this study. It also describes your right to refuse to participate or withdraw from the study at any time. In order to decide whether you wish to participate in this research study, you should understand enough about its risks and benefits to be able to make an informed decision. This is known as the informed consent process.

Please ask the study doctor or study team to explain any words you do not understand before signing this consent form. Make sure all your questions have been answered to your satisfaction before signing this document.

Background

You have been asked to take part in this research study because you are currently suffering from depression and have been diagnosed with Major Depressive Disorder by a health care professional.

Major depressive disorder (MDD) is a common and often severe illness identified as the leading cause of disability in both developed and developing nations. The largest contributor to the overall burden of illness associated with MDD is having difficulties handling daily activities. Problems with concentration, making decisions, solving problems, or remembering things are all cognitive symptoms of MDD. These symptoms can cause problems at work, home and with activities such as planning and organization of everyday life.

Purpose

The purpose of this study is to evaluate the sensitivity of the THINC-it tool, in measuring change in cognitive deficits in individuals with MDD after receiving vortioxetine.

Vortioxetine is used in this study as an antidepressant to improve mood, cognition and quality of life. "Cognition" refers to intellectual functions such as thinking, understanding, learning and remembering. Vortioxetine is approved by Health Canada for the treatment of MDD. In addition, vortioxetine has been reported to have a beneficial effect on cognitive areas such as executive function, attention/speed of processing, and memory, that are commonly affected negatively by MDD. Vortioxetine is recognized by Health Authorities in the EU and many other countries as having a benefit on cognitive dysfunction (loss of intellectual functions) in patients with MDD.

All participants receiving vortioxetine will receive10 mg/day on days 1–14 of the study treatment period, with the option to increase to vortioxetine 20 mg/day at the end of Week 2 based on physician's judgment. For the remaining 6 weeks, the dose of vortioxetine will be flexible at 10 or 20 mg/day as decided by a research doctor.

You **should not be enrolled in this study** if you have/are:

1. A current alcohol and/or substance use disorder.
2. A comorbid psychiatric disorder other than MDD that is a focus of clinical concern.
3. Taking other medications for cognitive dysfunction (e.g., psychostimulants).
4. Taking any medication for a general medical disorder that in the opinion of the investigator may affect cognitive function.
5. Used benzodiazepines within 12 hours of cognitive assessments.
6. Drank alcohol within 8 hours of cognitive assessments.
7. Inconsistent/Recent use or abuse of marijuana
8. A physical, cognitive, or language impairment that might affect the cognitive assessments.
9. A reading disability or dyslexia and clinically significant learning disorder.
10. Electroconvulsive therapy (ECT) in the last 6 months.

11. A history of moderate or severe head trauma, other neurological disorders, or medical conditions that in the opinion of the investigator are likely to affect the central nervous system.
12. Pregnant and/or breastfeeding.
13. Received investigational agents as part of a separate study within 30 days of the screening visit.
14. Currently receiving treatment with Monoamine Oxidase Inhibitors (MAOIs) anti-depressants, antibiotics such as linezolid, or intravenous methylene blue.
15. Moderate hepatic impairment
16. History of seizures or epilepsy
17. Previous hypersensitivity reaction to vortioxetine or any components of the formulation. Angioedema (swelling of the deeper layers of the skin) has been reported in patients treated with vortioxetine.
18. Clinical worsening symptoms of depression and suicide risk – in both adult and pediatric age groups.
19. Serotonin syndrome (symptoms can range from mild to severe, and include high body temperature, agitation, increased reflexes, tremor, sweating, dilated pupils, and diarrhea. Severe serotonin syndrome can be fatal if not treated.)
20. Abnormal bleeding
21. Previous history of mania/hypomania
22. Angle closure glaucoma (increase in fluid in the eye. The high pressure can damage the optic nerve (the nerve to the eye) and lead to blindness)
23. Hyponatremia (the level of sodium in your blood is abnormally low)

This study will be performed by the Brain and Cognition Discovery Foundation (BCDF). The BCDF is an organization based in Toronto, Ontario, Canada led by Dr. Roger S. McIntyre.

- **You are advised to NOT use the THINC-it tool outside of the study, as to not affect study results during your participation.**

This consent form is for individuals with a diagnosis of MDD.

Study Design

This is an 8-week, open-label study. "Open-Label" means you and the study doctor will both know what medication you are receiving. You will be receiving vortioxetine daily for a period of 8 weeks. You will need to take the study medication daily in order to take part in the study.

You will be asked to attend 5 study visits. The visit will last up to 1 hour each. As part of this study, your mood, cognition, functioning, overall well-being as well as lifestyle factors will be assessed. There may be instances when additional visits are required to complete study procedures.

A total of approximately 150 participants will be enrolled in this study; 100 individuals with MDD and 50 healthy controls will be included.

Study Enrollment

Only current antidepressants will be discontinued. Medication dosage will be decreased gradually over a course of 10-14 days. At the same time, you will be prescribed Trintellix. You will have access to a 24-hour study number (see Page 1) that you can use anytime to contact research staff, should you experience any adverse events.

Risks of Antidepressant Removal:

- Anxiety
- Insomnia or vivid dreams
- Headaches
- Dizziness
- Tiredness
- Irritability
- Flu-like symptoms, including achy muscles and chills
- Nausea
- Electric shock sensations
- Return of depression symptoms

Transition to Standard Care Upon Completing the Study

Upon completing the 8 week course of vortioxetine, if you benefit from this drug, you are encouraged to continue the treatment with your most responsible physician (MRP). Please note that not all drug plans will cover the cost of vortioxetine Should you wish to continue to use this drug post-study where there is no coverage, you will be personally responsible for the costs. There will be a gradual discontinuation of the medication for two weeks after the end of the study. However, you will not have further access to this drug from the research team after this period.

If you experience side effects during the study, a physician will make a recommendation regarding the discontinuation or dose reduction of the medication for the remainder of the study. If you do not experience any improvement upon study completion in mood or cognition, the

medication will be gradually discontinued over a two-week period upon study completion (week 8).

Vortioxetine can be safely discontinued however, you may experience side effects such as:

- Muscle tension
- Rebound depression
- Brain zaps/sensation of an electrical shock
- Depersonalization
- Not feeling like yourself
- Dizziness
- Flu-like symptoms
- Nausea and vomiting
- Sweating
- Headaches
- Suicidal thoughts

Study Visits and Procedures

Visit 1 (Screening Visit)

The following will be completed during this visit:

- Informed consent process will be completed.
- The study team will carry out an interview to confirm your suitability for the study.
- Your demographics will be documented, including current physical activity levels.
- Medical/psychiatric and medication history will be recorded.
- Your mood, functioning, and overall well-being will be assessed.
- Adverse events to any medications

Reminders:

- Please do not consume alcohol within 8 hours of any study visit.
- Some medications may be restricted within 8-10 hours of study visits.
- You are advised to **NOT** use the THINC-it tool outside of the study, as to not affect study results during your participation.

Pre-study visit

You will be seen by a research physician to monitor your medication washout period. You will be seen on a biweekly basis based on physicians assessments. You will have an assessment on your mood and any adverse events you may have. A 24 hour 7 days a week study line will be provided in the event that you wish to schedule an appointment with the psychiatrist sooner.

Visit 2 (Baseline, Week 0)

The following will be completed during this visit:

- **Receive study treatment medication - vortioxetine 10mg.**

- Adverse events
- Anthropometrics (weight, hip/waist circumference, height)
- THINC-it tool administration
- Participant interview consisting of mood questionnaires
- Secondary paper/pen questionnaires
- Fasting bloodwork for exploratory and standard biomarker and testing. This testing is done for research and clinical purposes. You can get your clinical results from your doctor.

Visit 3 (Week 2)

The following will be completed during this visit:
- Participant interview consisting of mood questionnaires
- Anthropometrics (weight, hip/waist circumference, height)
- Adverse events
- THINC-it tool administration
- Secondary paper/pen questionnaires
- **Participant will receive increase dosage of vortioxetine 20mg from physician.**

Visit 4 (Week 4)

The following will be completed during this visit:
- Participant interview consisting of mood questionnaires
- Anthropometrics (weight, hip/waist circumference, height)
- Adverse events

Visit 5 (Week 8)

The following will be completed during this visit:
- Participant interview consisting of mood questionnaires.
- Anthropometrics (weight, hip/waist circumference, height)
- Adverse events
- Return unused medications
- THINC-it administration
- Secondary paper/pen questionnaires
- Participant will be reimbursed for completion of study.
- Fasting bloodwork for exploratory biomarker and genetic testing

- **Participant will receive decrease dosage of vortioxetine from physician for two weeks if chosen to be discontinued by patient or psychiatrist.**
- Seen by psychiatrist to determine future plan. If the medication is to be discontinued, the physician will ask patient to take half of current dosage of medication for 1 week, and no medication for second week. You will be seen after these two weeks by the psychiatrist to determine your overall wellbeing, and if needed to be seen at our clinic for future visits.

You will be seen by physician 2 weeks post week 8, to monitor your well being. Should you need to see physician sooner, you are encouraged to contact the 24/7 study line to schedule an appointment.

Optional: During your last study visit, you will be asked if you are interested in participating in a 20-minute computer based behavioral task to explore effort-based decision-making. You will be awarded the monetary value of the amount you win from doing this task.

Post-Study Visits

You will be seen by the research team psychiatrist to monitor safe medication discontinuation. This visit will consist of research psychiatrist, assessment of your overall well being. After one post study clinical visit two weeks after end of the study, you will be asked to continue your care with your main responsible physician. The visit will consist of your overall well-being and management plan with your main responsible physician.

Calendar of Visits

Visit	Interview	Physician Assessment	Cognitive Test	Bloodwork	Self-Report Questionnaires	Study Treatment	**Time (hours)**
Screening (Visit 1)	X						**2**
(Baseline, Visit 2 Week 0)	X		X	X	X	X	**3.5** *(including blood work and 1 hour break)*
Visit 3 (Week 2)	X	X	X		X	X	**1.5**
Visit 4 (Week 4)	X					X	**1**
Visit 5 (Week 8)	X	X	X	X	X	X	**3.5** *(including blood work and 1 hour break)*
Post-study visit after 2 weeks or as needed		X					**0.5**

Risks Related to Being in the Study

Taking part in this study has risks. Some of these risks we know about. There is also a possibility of risks we do not know about and have not been seen in humans to date. Please call the study doctor if you have any side effects even if you do not think it has anything to do with this study.

The known risks associated with vortioxetine are:

Most Common:

- Gastrointestinal adverse events; including nausea, vomiting, constipation/diarrhea, dry mouth, flatulence. These occur most commonly during the first week of study treatment. (21-32%)
- Sexual dysfunction (14-34%)

Less Common: (1-10%)
- Dizziness
- Dyspepsia (discomfort of the abdomen)
- Dizziness
- Somnolence (sleepiness)/sedation
- Fatigue
- Insomnia
- Abnormal dreams
- Hyperhidrosis (increase sweating)
- Arthralgia (joint pain)
- Decreased appetite
- Itchy skin

Rare: (less than 1%)
- Nervous system disorders
- Skin and subcutaneous tissue disorders
- Psychiatric disorders
- Abnormal bleeding
- Clinical worsening or suicide risk

- Serotonin Syndrome has been reported with serotonergic anti-depressants (SSRIs, SNRIs, and others), including with Vortioxetine both when taken alone, but especially when coadministered with other serotonergic agents (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort).

- Treatment with serotonergic antidepressants (SSRIs, SNRIs, and others) may increase the risk of abnormal bleeding. Patients should be cautioned about the increased risk of bleeding when Vortioxetine is coadministered with nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, or other drugs that affect coagulation.

- Activation of Mania/Hypomania can occur with antidepressant treatment.

- Angle Closure Glaucoma: Angle closure glaucoma has occurred in patients with untreated anatomically narrow angles treated with antidepressants.

- Hyponatremia can occur in association with the syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Risk of Blood Sampling:
Blood samples will be drawn from a vein with a sterile needle, usually in the arm. The risks with drawing blood are pain, swelling, bruising, feeling faint, and rarely, infection at the site of the needle stick.

The main risk associated with genetic analysis is misuse of personal genetic information. It is possible that genetic information about a person could be used to deny access to employment or insurance or otherwise lead to discrimination. The sponsor has taken special precautions to keep your genetic information confidential. However, absolute confidentiality cannot be guaranteed.

Voluntary Participation

Your participation in this study is voluntary. You may decide not to be in this study, or to be in the study now and then change your mind later.

You will be provided in a timely manner with new information that is learned during the study that might affect your decision to stay in the study.

If you decide not to participate, or to withdraw from the study, your medical care or legal rights will not be affected.

The study doctor may also withdraw you from the study if your condition worsens, if you do not follow the doctor's instructions, if the study doctor feels it is in your best interests to be withdrawn, if the study sponsor discontinues the study, or for administrative reasons. You can be withdrawn without your consent, but the study doctor will tell you why.

You may also withdraw from the study should you become pregnant, have an increase in risk of suicide ideation and any adverse events that, in the opinion of the investigator, puts the subject at risk at any point during the study,

Alternatives to Being in the Study

You may opt not to participate in this study. You do not have to take part in this study to receive treatment for your condition. A number of other medications are available. Possible treatments may include alternative anti-depressants. Your study doctor will discuss with you these alternative treatments, including their important potential risks and benefits.

Confidentiality

Personal Health Information

If you agree to join this study, the study doctor and his study team will collect your personal health information that they need for the study. Personal health information is any information that could be used to identify you and includes your:

- Name
- Address

- Date of Birth
- New or existing medical records, which includes types, dates and results of medical tests or procedures.

The information that is collected for the study will be kept in a locked and secure area by the study doctor for 25 years. Only the study team or the people or groups listed below will be allowed to look at your records.

The blood collected for exploratory biomarker and genetic testing will be kept in a locked and secure facility, as would all data related to this information, and will not be shared with any outside sponsor or external vendor.

The study team can tell you what information about you will be stored electronically and may be shared outside of the study team.

The following people may look at the study records and at your personal health information to check that the information collected for the study is correct and to make sure the study followed proper laws and guidelines:

- The study sponsor or its representatives/partner companies.
- Representatives of the IRB Services - an independent ethics committee that reviewed the ethical aspects of this study to help protect the rights and welfare of study participants.
- Representatives of Health Canada, or other regulatory bodies (groups of people who oversee research studies), outside of Canada, such as the United States Food and Drug Administration

Lundbeck may transfer your information to organizations and countries outside of Canada for the purposes described in this document. All data that is transferred will be coded to prevent identification of individual participants. The Canadian Data Protection Law will be followed, as a minimum.

Study Information That Does Not Identify You

Some study information will be sent outside of the study team. Any information about you that is sent out will have a code and will not show your name or address, or any information that directly identifies you. The code, with which your data is identifiable, will be stored for a minimum of 15 years.

The information may be shared with the Sponsor's partner companies or with national and international regulatory agencies to help answer the study question, to develop future studies on this product or for research related to this study.

All information collected during this study, including your personal health information, will be kept confidential and will not be shared with anyone outside the study unless required by law. You will not be named in any reports, publications, or presentations that may come from this study.

If you decide to leave the study, the information about you that was collected before you left the study will still be used. No new information will be collected without your permission.

Rights as a Participant

If you are harmed as a direct result of taking part in this study, all necessary medical treatment will be made available to you at no cost.

By signing this form, you do not give up any of your legal rights nor does this form relieve the investigator or involved institution from their legal and professional responsibilities.

Benefits of Participation

No direct benefit is guaranteed to you from taking part in this study. Your condition may or may not improve, and could possibly even worsen. The results of this study may help the study team validate a digital tool for the assessment of cognitive function in individuals with MDD.

Costs and Compensation

There is no cost to you, your private medical insurance (if any), or the public health insurance plan, for study procedures. Study medication will be provided at no cost for the duration of the study.

You will receive a compensation of $150 CAD at the **end** of the study. You will also receive maximum of $30 per visit for your food and transportation costs during each visit. You will need to provide receipts/transfers/proof of payment to receive reimbursement for food and transportation costs. You must pick up your reimbursement/compensation **in person** – it cannot be mailed to you.

Questions about the Study

If you have any questions, concerns, complaints regarding this study or adverse effects of study medication, or would like to speak to the study team for any reason, please call: Dr. Roger McIntyre at 416-603-5279.

In case of emergency, please go to the nearest hospital emergency department.

Please contact IRB Services, which is not affiliated with the research or the research team, if you:

- have questions about your role and rights as a research participant
- wish to obtain more information about clinical research in general
- have concerns, complaints or general questions about the research, or
- wish to provide input about the research study

You can do so in the following ways:

In writing: 300-372 Hollandview Trail, Aurora, ON L4G 0A5
By phone: 1-866-449-8591
By email: subjectinquiries@irbservices.com

Please reference the following number when contacting IRB Services: Pro00020418.

You will be given a signed copy of this consent form.

Consent

1. I confirm that the information regarding the study has been explained to me, that I have read all pages of the subject information sheet, and that I have had the opportunity to ask questions regarding the study and these have been answered to my satisfaction.
2. I understand the risks and the benefits that may result from taking part in the study.
3. I understand that my participation is voluntary and that I am free to withdraw from the study at any time, without giving a reason, and without my medical care or legal rights being affected
4. I understand that I have the possibility to withdraw my consent without giving a reason. The consequences of my withdrawal will be that no new information will be collected, but that already collected data will be used.
5. I accept that data collected for the study may be disclosed by Brain and Cognition Discovery Foundation to its partners as well as the authorities in and outside of the Canadian territory, including the European Union with the purpose of evaluating safety, efficacy, and cost/effectiveness of the THINC-it Tool. I am aware that an identification number and my date of birth (month and year only) are linked to the data; however, other identifying information will not be transferred.
6. I agree to take part in the above study by signing below.
7. The study doctor has my permission to tell my regular doctor about my being in this study:
   ❒ YES ❒ NO

_____	_____	_____
Study Participant's Name	Study Participant's Signature	Date
_____	_____	_____
Name of Person Obtaining Consent	Signature	Date
_____	_____	_____
Name of Principal Investigator	Signature	Date