# Contact: Developing New Clinical Management Strategies

Protocol ID 7738

NCT03812588

Protocol Summary Form and Consent Form

Document Version Date:
December 17th, 2021

NEW YORK STATE PSYCHIATRIC INSTITUTE

# INSTITUTIONAL REVIEW BOARD

## MEMORANDUM

December 13, 2021

TO: Dr. Bret Rutherford

FROM: Dr. Edward Nunes, Co-Chair, IRB
Dr. Agnes Whitaker, Co-Chair, IRB

**SUBJECT**: **APPROVAL NOTICE: CONTINUATION**
**Expedited per 45CFR46.110(b)(1)(f)(8)(c)**

Your protocol **#7738** entitled **Developing New Clinical Management Strategies for Antidepressant Treatments** (version date 12-13-2021) and Consent Forms have been approved by the New York State Psychiatric Institute - Columbia University Department of Psychiatry Institutional Review Board from **December 17, 2021 to December 16, 2022.**

**Consent requirements:**

**X** Not applicable: (DATA BEING ANALYZED)

☐ Signature by the person(s) obtaining consent is required to document the consent process.

☐ Documentation of an independent assessment of the participant's capacity to consent is also required.

**Approved for recruitment of subjects who lack capacity to consent**: ☐ No ☐ Yes

**Field Monitoring Requirements:** ☐ Routine ☐ Special:

√ **Only copies of consent documents that are currently approved and stamped by the IRB may be used to obtain consent for participation in this study.**

√ **A progress report and application for continuing review is required 2 months prior to the expiration date of IRB approval.**

√ **Changes to this research may be not be initiated without the review and approval of the IRB except when necessary to eliminate immediate hazards to participants.**

√ **All serious and/or unanticipated problems involving risks to subjects or others must be reported immediately to the IRB. Please refer to the PI-IRB website at http://irb.nyspi.org for Adverse Event Reporting Procedures and additional reporting requirements.**

**CC: RFMH Business Office (Binational Science Fund)**

EN/AHW/Scr

Signed copy on file at IRB

Protocol Title:
**Developing New Clinical Management Strategies for Antidepressant Treatments**

Version Date:
**12/13/2021**

Protocol Number:
**7738**

First Approval:
**01/09/2019**

Expiration Date:
**12/16/2022**

Contact Principal Investigator:
**Bret Rutherford, MD**
**Email: brr8@columbia.edu**
**Telephone: 646 774 8660**

Co-Investigator(s):
**Sigal Mano**

Research Chief:
**Bret Rutherford, MD**

## Cover Sheet

Choose ONE option from the following that is applicable to your study
If you are creating a new protocol, select "I am submitting a new protocol." As 5 Year Renewals are no longer required, this option remains for historical purposes.
I am submitting an annual continuation without modifications

## Department & Unaffiliated Personnel

### Department

What Department does the PI belong to?
Neurobiology and Therapeutics of Aging
Within the department, what Center or group are you affiliated with, if any?
Clinic for Aging, Anxiety, and Mood Disorders (CAAM)

### Unaffiliated Personnel

List investigators, if any, who will be participating in this protocol but are not affiliated with New York State Psychiatric Institute or Columbia University. Provide: Full Name, Degrees and Affiliation.
Sigal Zilcha-Mano, PhD

Associate Professor and Licensed Clinical Psychology, University of Haifa

## Application for Continuation of Research

### Status

Current Status of Study:
All research interventions were completed. Only data analysis is ongoing.

### Summary of Experiences to Date

Please provide a summary of scientific progress of the study and the experience of research participants, to date. This requirement is designed to allow for the investigator and the IRB to reassess the study's risks and benefits in terms of developments in the field, changing practice patterns, and new IRB policies and procedures.
Subject enrollment for the Binational Science Foundation grant began on 01/22/2019. All eligible subjects offered participation at CAAM evaluations have agreed to participate in the study. Additionally, all subjects have agreed to the video consent form for taping of study visits. Overall, subjects have been complying well with the procedures of the clinical trial and study medication has been well tolerated. Many patients have expressed appreciation for the quality care that we provide and for their improvements in depressive symptoms.

Study recruitment was temporarily paused at the start of COVID-19 and restarted on 10/27/2020. Procedures were modified so study visits can be completed via telehealth video calls. To mitigate the added risks of contracting COVID-19, institute wide regulations and recommendations have been applied to the protocol for any visits that require in-person contact. Recruitment ended on 08/01/2021.

Data has been well maintained and internally monitored as we continue with analysis only.

### Funding

Have there been any changes in funding status since the prior approval?
No
Have the principal investigator and other investigators made all required disclosures of financial interest in the study sponsor/product?
Yes

### Summary

Have there been any study findings, recent literature, or untoward events occuring here or at other sites in the past year which might affect the analysis of the safety, risks or benefits of study participation?
No
Have there been any serious adverse events (serious and/or unanticipated problems involving risks to subjects or others at this site which occured in the past year)?

No
Have all study staff with a significant role in the design or implementation of the human subject components of this study received required training in human research subject protections?
Yes
Is the study covered by a certificate of confidentiality?
No

## Overall Progress

Approved sample size
104
Total number of participants enrolled to date
29
Number of participants who have completed the study to date
19
Have there been any significant deviations from the anticipated study recruitment, retention or completion estimates?
Yes
Describe actions taken or planned to address these problems.
Due to COVID-19 and the challenges associated with recruitment during this time, we were not able to enroll any patients since the last ACAR. Study recruitment has been discontinued, and we are focusing on data analysis only.
Comments / additional information

## Sample Demographics

Specify population
Adults 18-75 with diagnosis of Major Depressive Disorder
Total number of participants enrolled from this population to date
29
Gender, Racial and Ethnic Breakdown
Gender:
- Male: 38%
- Female: 62%

Race:
- Black/African-American: 41%
- White: 45%
- More than one: 7%
- Don't know/Other: 7%

Ethnicity:
- Hispanic or Latino: 14%
- Not Hispanic/Latino: 79%
- Unknown: 7%

**Summary of Current Year's Enrollment and Drop-out**

Number of participants who signed consent in the past year
0
Did the investigator withdraw participants from the study?
No
Did participants decide to discontinue study involvement?
No

## Procedures

**To create the protocol summary form, first indicate if this research will include any of the following procedures**

✓ Psychiatric Assessment
✓ Neuropsychological Evaluation
✓ Collection of Biological Specimens
✓ Medication Trial
✓ Use of Placebo or Sham Treatment
✓ Medication-Free Period or Treatment Washout
✓ Audio or Videotaping
✓ Internet-based Data Collection or Transmission

## Population

**Indicate which of the following populations will be included in this research**

✓ Adults
✓ Adults over 50
✓ Employees or Students

## Research Support/Funding

Will an existing internal account be used to support the project?
No
Is the project externally funded or is external funding planned?
Yes
Select the number of external sources of funding that will be applicable to this study

**Funding Source #1**

Is the PI of the grant/contract the same as the PI of the IRB protocol?
Yes
Select one of the following
The grant/contract is currently funded
Source of Funding
Foundation
Sponsor
Binational Science Fund
Select one of the following
Multicenter(NYSPI is the lead site)
Business Office
RFMH
Does the grant/contract involve a subcontract?
No

## Study Location

Indicate if the research is/will be conducted at any of the following
✓ NYSPI
This protocol describes research conducted by the PI at other facilities/locations
Yes
✓ International Sites

### International Sites

Type in location(s)
Department of Psychology, University of Haifa, Israel

## Uploaded Protocol Summary Form

### Upload Document

Select file to upload.
PSF_Version 3.29.21.pdf

## Lay Summary of Proposed Research

Lay Summary of Proposed Research

The goal of this study is to develop new methods of administering antidepressant medications that will result in improved drug/placebo separation in randomized controlled trials (RCTs) for Major Depressive Disorder (MDD) and enhanced medication response in open clinical treatment. The highly intensive, weekly visit schedule followed in most antidepressant RCTs radically differs from how antidepressant medications are prescribed in standard clinical practice and is believed to be a major reason why the majority of studies submitted to the Food and Drug Administration (FDA) fail to show a significant difference between medication and placebo. Moreover, a "one size fits all" approach to psychopharmacologic management (i.e., weekly visits for all patients) does not take into account differences between patients that may predispose some individuals to respond positively to frequent follow-up visits, while others may respond negatively or not at all. Clinic visits comprise multiple components that may be therapeutic for depression, including activating patients' behavior, exposing them to medical procedures, permitting social interactions with research staff, and providing supportive meetings with clinicians. Two independent meta-analyses have associated more frequent study visits with increased antidepressant and placebo response as well as decreased separation between medication and placebo. Despite the high costs and potential disadvantages of weekly follow-up visits for patients receiving antidepressant medication, this clinical management strategy has not been studied prospectively to date. It is unknown whether weekly follow-up visits are needed to ensure treatment compliance and patient safety in clinical trials and to what degree contacts with clinicians influence medication and placebo response.

This study utilizes a 2 x 2, double-blind, acute, prospective design randomizing adult outpatients with MDD to "Research Frequency Management" (RFM, weekly study visits) vs. "Community Frequency Management" (CFM, every 4 weeks study visits) and antidepressant medication vs. placebo. Specifying visit frequency as the independent variable in this study has the distinct advantages of being easily operationalized for research purposes avoiding a priori assumptions about which components of study visits influence antidepressant and placebo response (i.e., behavioral activation vs. doctor-patient relationship vs. medical procedures). Close monitoring of all subjects will be assured by telephone evaluations of individuals randomized to CFM at intervals between monthly visits, and additional study contacts will be scheduled as necessary to maintain patient safety (all extra-protocol contacts will be recorded and included as a variable in outcome analyses). Additionally, subjects will be characterized extensively on clinical, demographic, and psychological measures to pilot the study assessment battery and search for predictor variables influencing the effects of contact frequency on medication and placebo response.

## Description of Subject Population

### Sample #1

Specify subject population
104
Number of completers required to accomplish study aims
70
Projected number of subjects who will be enrolled to obtain required number of completers
104

Age range of subject population
18-75

Gender, Racial and Ethnic Breakdown
We anticipate the sample will be composed of approximately 60% women and 40% men. On the basis of previous depression studies conducted in the Clinic for Aging, Anxiety and Mood Disorders, it is anticipated that the sample will be composed of approximately 75% Caucasian, 15% African American, and 10% Hispanic subjects.
Description of subject population
104 subjects will be entered in the proposed study. Inclusion criteria are (1) men and women aged 18-75 years, (2) diagnosis with Diagnostic and Statistical Manual (DSM) V MDD, (3) 24-item Hamilton Rating Scale for Depression (HRSD) score ≥ 16 and ≤ 28 and 17-item Hamilton Rating Scale for Depression (HRSD) score < 25, (4) capable of providing informed consent and complying with study procedures, and (5) using appropriate contraceptive method if woman of child-bearing age. Exclusion criteria are (1) current comorbid Axis I DSM V disorder other than Mild Substance Use Disorder, Adjustment Disorder, Anxiety Disorder or Personality Disorder, (2) diagnosis of Moderate to Severe Substance Use Disorder within the past 12 months, (3) present or past history of psychosis, psychotic disorder, mania, or bipolar disorder, (4) baseline HRSD score > 28 or HRSD suicide item > 2, (5) history of allergic or adverse reaction to escitalopram and duloxetine, or non-response to adequate trial of escitalopram (at least 4 weeks at dose of 20mg) and duloxetine (at least 4 weeks at dose of 60mg) during the current episode (6) current treatment with psychotherapy, antidepressants, antipsychotics, or mood stabilizers, (7) Clinical Global Impressions (CGI)-Severity score of 6 or greater at baseline, and (8) acute, severe, or unstable medical illness.

The selection criteria for this study were designed to obtain a sample having similar characteristics to the patient population studied in our meta-analyses and ongoing prospective studies of patient expectancy. In order to ensure patient safety given the potential to be randomized to CFM, we chose to exclude subjects having active suicidal ideation and who are severely ill . Subjects with current substance use disorder or dependence are excluded, but subjects with past substance use disorder or dependence who meet DSM V criteria for full sustained remission (12 months without meeting abuse or dependence criteria) will be allowed to participate. This approach will minimize persistent neuropsychiatric sequelae of past episodes of abuse or dependence and decrease the risk that subjects will relapse during the study period. Participants will be questioned at weekly visits regarding substance use, and urine toxicology will be obtained if there is concern of relapse. Any use of drugs or alcohol will be recorded, but subjects will not be dropped from the study unless substance use rises to a level meeting DSM V abuse or dependence criteria.

## Recruitment Procedures

Describe settings where recruitment will occur
Subjects will be recruited through radio, newspaper, Facebook, Craigslist, and ResearchMatch.com advertisements and referrals from other physicians.
How and by whom will subjects be approached and/or recruited?
Individuals presenting to the Clinic for Aging, Anxiety and Mood Disorders are evaluated under IRB #7284R, “Evaluation at the Adult and Late Life Depression Center.” Following this evaluation, one of the study psychiatrists authorized to obtain informed consent will discuss study participation with

subjects.
How will the study be advertised/publicized?

Newspaper and radio advertisements, flyers posted around CUMC and CU Morningside, physician referrals, the Columbia RecruitMe Website**,** the National Alliance on Mental Illness NYC Research Studies website, Facebook advertisements, Craigslist.com, and ResearchMatch.com advertisements.

Digital advertisement on Facebook under the "Columbia Psychiatry" page will include a link to a contact information form for users to complete if they wish to be contacted by our study team. Facebook users who see the ad will either 1) click the Facebook ad and it will direct them to a secure and encrypted survey website using Qualtrics to collect name, phone number, and email address or 2) not click the ad or provide any contact information.

Do you have ads/recruitment material requiring review at this time?
Yes
Does this study involve a clinical trial?
Yes
Please provide the NCT Registration Number
NCT03812588

## Concurrent Research Studies

Will subjects in this study participate in or be recruited from other studies?
Yes
Describe concurrent research involvement

- Antidepressant Response in the Treatment of Depressive Symptoms and Frailty Characteristics in Older Adults - IRB #7289R
- Optimizing Outcomes of Treatment-Resistant Depression in Older Adults (OPTIMUM) (PI Roose) - IRB #7409
- Mechanisms of Antidepressant Non-Response in Late-Life Depression (PI Rutherford) - IRB #6836
-Treating Hearing Loss to Improve Mood and Cognition in Older Adults (PI Rutherford) - IRB #7540
-A Study of L-DOPA for Depression and Slowing in Older Adults (PI Rutherford) - IRB #7270
- Cognitive and Neural Mechanisms of the Accelerated Aging Phenotype in PTSD - IRB #7489
- Tianeptine for Treatment-Resistant Depression - IRB# 7944

## Waiver of Consent/Authorization

Indicate if you are requesting any of the following consent waivers
Waiver of consent for use of records that include protected health information (a HIPAA waiver of

Authorization)
No
Waiver or alteration of consent
No
Waiver of documentation of consent
No
Waiver of parental consent
No

## Consent Procedures

Is eligibility screening for this study conducted under a different IRB protocol?
Yes
Indicate NYSPI IRB #
7284R
Describe Study Consent Procedures

Prior to undergoing evaluation, participants will be consented for remote clinical or research procedures. The consent discussion process will include discussion and explanation of WebEx, a HIPAA-compliant video communication platform. The study team will address any concerns the patient may have, such as access to a private space in which to take calls, or accessibility—access at home to adequate devices, cell signal, or wifi. Participants must first sign the CAAM evaluation consent form (IRB #7284R) and HIPAA consent form. A consent procedure note will include all information discussed with the participants regarding the remote consent process, procedures and also the risk involved in traveling for in-person visits during covid-19. The clinic coordinator or an CAAM research assistant will then do the 30-item Mini-Mental State Exam to get a general idea of the patient's global cognitive performance (this is especially important in older patients who may be experiencing cognitive/memory difficulties in addition to depression). The patient is then seen by one of the CAAM psychiatrists or a nurse practitioner (Galit Marcus, NP, MPH). Alternatively, the patient may be seen by medical PGY-1 psychiatry interns who come to our clinic for 4-week rotations and psychiatry fellows who come to our clinic for 6-month rotations during the Spring semester. Fellows rotate through the Statewide Geriatric Psychiatry Fellowship. All medical interns and fellows will have completed NYSPI-specific CITI training for human subjects research (specifically the Social & Behavioral Researchers & Key Personnel course or the Biomedical Researchers & Key Personnel course). Interns and fellows will be supervised by Steven Roose, MD, Bret Rutherford, MD, and Allegra Broft, MD. Following the MD/NP evaluation, the doctor may ask for a SCID (Structured Clinical Interview for the DSM), a structured diagnostic interview, and HAM-D (Hamilton Rating Scale for Depression) to be performed by a qualified rater (Nancy Turret or trained research assistant). Based on the information from the MD/NP evaluation, HAM-D score, and SCID diagnosis(es), the MD/NP will decide if the patient is eligible for any of the CAAM research protocols.

The NP is licensed and board certified as a Psychiatric and Mental Health NP. She has considerable experience in working with a late-life population but no prior research experience in this population. That is why she will have an extended period of time where all her work is directly in-person supervised. The NP will have a lengthy orientation where she will be observing evaluations done by Drs. Roose, Rutherford,

Brown and Broft. She will then do evaluations under the observation of the same MDs. Even when she is doing evaluations and follow-ups by herself, all cases are reviewed weekly at a clinic meeting. Even after orientation is over, it is the practice of the clinic that the doctors consult with and present cases to each other so all patients are essentially treated by the entire clinic team.

Due to the COVID-19 pandemic, beginning in October 2020, CAAM will be implementing a number of changes to this study's operating procedures in order to ensure a safe environment while continuing to provide patients depression treatment through research participation. These changes include implementing Telehealth resources to complete visits virtually and only evaluating/enrolling 50% of our normal participant capacity in order to minimize the risk of contracting the virus due to physical contact. All measures that do not require an in-person component will be completed virtually. The evaluation procedure will be altered to include virtual components. Detailed descriptions of these changes are provided below.

Evaluation: A two-visit evaluation procedure, one virtual and one in-person, will be implemented in order to reduce the risk of transmitting the virus by minimizing person-to-person contact. After an individual expresses interest in research participation and completes the initial phone screen process, the individual will be scheduled for a virtual evaluation with a research coordinator (trained study raters; BA, RN, SW) and a clinician. All assessments that are generally conducted during the evaluation process (Protocol #7284R) that can be conducted over the phone will be administered during the virtual portion. The individuals who may be eligible for study participation after completing the virtual evaluation will then be scheduled for an in-person evaluation at the clinic, in order to complete the remaining assessments that are necessary to determine eligibility. The virtual evaluation will be completed via WebEx or a secure FaceTime platform. After consenting the individual virtually and sending them a copy of the consent form (if they have Internet/email access; if the individual does not have these resources, a hard copy of the consent form will be mailed to them), the research coordinator will complete the following measures: the MMSE, HRSD, Logical Memory Test I and II, and the SCID. They will also gather the individual's pharmacy information, as well as their current physical location and emergency contact (in case of a mobile crisis). The research coordinator will subsequently explain how the individual can complete the self-report forms included in the evaluation protocol online, and will send them a link for completion (if the individual does not have Internet/email access, self-report forms are to be completed over the phone with the research coordinator). The evaluating clinician will then be notified that the individual is ready for the clinical interview, and send them the assessment scores collected during the first portion of the virtual evaluation. The evaluating clinician will then join the call, and complete the clinical interview with the research coordinator on mute during the duration of the interview. If the individual may still be eligible for study participation after the clinical interview, they will be scheduled for the in-person component of the evaluation. The evaluating clinician will discuss any COVID-19 risks related to travel for research purposes.

On the day of the in-person evaluation, the individual will be transported to the clinic via a car service. Social distancing procedures will be followed in order to ensure safety, including limiting the number of individuals in a clinic room, implementing the use of masks, and thoroughly cleaning clinic rooms and other assessment instruments (ex: blood pressure cuff, grip-strength machine, etc.) after each use. The rest of the evaluation procedures will be completed during the in-person visit.

If an individual is eligible after completing the in-person evaluation and consents to study participation, they will be scheduled for their next visit.

Indicate which of the following are employed as a part of screening or main study consent procedures
✓ Consent Form

## Persons designated to discuss and document consent

Select the names of persons designated to obtain consent/assent
Brewster, Katharine
Broft, Allegra, MD
Marcus, Galit
Roose, Steven, MD
Rutherford, Bret, MD
Type in the name(s) not found in the above list

## Off label and investigational use of drugs/devices

Choose from the following that will be applicable to your study

## Methods to Protect Confidentiality

*Will the study be conducted under a certificate of confidentiality?*
No

## Compensation and/or Reimbursement

Will compensation or reimbursement for expenses be offered to subjects?
Yes
Please describe and indicate total amount and schedule of payment(s).
Include justification for compensation amounts and indicate if there are bonus payments.

Compensation Plan:

In order to compensate for time, participant payment in the study is approved for all in-person visits to the clinic. Participants will be paid for the visits completed as follows:

- Screening: $50
- Baseline/Week 0 Visit: $20

- Acute Phase in-person Visits: $20
- Continuation Phase in-person Visits: $20

For the RFM track, compensation is up to $180 for the Acute Phase and up to $60 for the Continuation Phase for a total of $240. For the CFM track, compensation is up to $60 for the Acute Phase and up to $60 for the Continuation Phase for a total of $120.

Due to COVID-19, the methods for providing compensation to patients will be adjusted. Patients can choose to receive payments (either by an e-gift card, a physical gift card, or a check), or to receive one payment for all visits at the completion of the study. If the patient chooses to receive payments after each specified time point where compensation is provided, they will be mailed to the individual after the completion of each weekly visit.

## Uploads

Upload copy(ies) of unbolded Consent Form(s)
Upload copy(ies) of bolded Consent Form(s)
Upload copy(ies) of recruitment materials/ads to be reviewed
Upload copy(ies) of the HIPAA form
Upload any additional documents that may be related to this study

## Cover Page

Protocol Number: 7738 Version Date:3/29/2021

Protocol Title: Developing New Clinical Management Strategies for Antidepressant Treatments

Principal Investigator: Bret Rutherford, MD

Email:bret.rutherfors@nyspi.columbia.edu; Brr8@cumc.columbia.edu

Telephone:

Office: 646-774-8660 Cell Phone:917-716-7484

## Lay Summary

*This section is intended to provide a basic overview of the study including a description of its purpose, methods, and subject population. The summary should provide a concise overview of the study for non-scientific and scientific members of the IRB. Please avoid medical or technical terminology. In general, the abstract of a grant does not provide a suitable lay summary.*

*Please also paste of a copy of the Lay Summary into the PRISM PSF Form.*

The goal of this study is to develop new methods of administering antidepressant medications that will result in improved drug/placebo separation in randomized controlled trials (RCTs) for Major Depressive Disorder (MDD) and enhanced medication response in open clinical treatment. The highly intensive, weekly visit schedule followed in most antidepressant RCTs radically differs from how antidepressant medications are prescribed in standard clinical practice and is believed to be a major reason why the majority of studies submitted to the Food and Drug Administration (FDA) fail to show a significant difference between medication and placebo. Moreover, a "one size fits all" approach to psychopharmacologic management (i.e., weekly visits for all patients) does not take into account differences between patients that may predispose some individuals to respond positively to frequent follow-up visits, while others may respond negatively or not at all. Clinic visits comprise multiple components that may be therapeutic for depression, including activating patients' behavior, exposing them to medical procedures, permitting social interactions with research staff, and providing supportive meetings with clinicians. Two independent meta-analyses have associated more frequent study visits with increased antidepressant and placebo response as well as decreased separation between medication and placebo. Despite the high costs and potential disadvantages of weekly follow-up visits for patients receiving antidepressant medication, this clinical management strategy has not been studied prospectively to date. It is unknown whether weekly follow-up visits are needed to ensure treatment compliance and patient safety in clinical trials and to what degree contacts with clinician's influence medication and placebo response.

This study utilizes 2 x 2, double-blind, acute, prospective design randomizing adult outpatients with MDD to "Research Frequency Management" (RFM, weekly study visits) vs. "Community Frequency Management" (CFM, every 4 weeks study visits) and antidepressant medication vs. placebo. Specifying visit frequency as the independent variable in this study has the distinct advantages of being easily operationalized for research purposes avoiding prior assumptions about which components of study visits influence antidepressant and placebo response (i.e., behavioral activation vs. doctor- patient relationship vs. medical procedures). Close monitoring of all subjects will be assured by telephone evaluations of individuals randomized to CFM at intervals between monthly visits, and additional study contacts will be scheduled as necessary to maintain patient safety (all extra-protocol contacts will

be recorded and included as a variable in outcome analyses). Additionally, subjects will be characterized extensively on clinical, demographic, and psychological measures to pilot the study assessment battery and search for predictor variables influencing the effects of contact frequency on medication and placebo response.

## Background, Significance, and Rationale

*In this section, provide a brief summary of the status quo of the relevant work field, and how the proposed study will advance knowledge. Specifically, identify the gaps in knowledge that your project is intended to fill. If no gaps exist that are obviously and directly related to your project, explain how your proposed research will contribute to the overall understanding of your field. Describe potential impacts of your project within your field of study and in a broader context. Provide a critical evaluation of existing knowledge. The literature review does not have to be exhaustive.*

Background:

In randomized controlled trials (RCTs) of antidepressants for adults with Major Depressive Disorder (MDD), placebo response averages 31% compared to a mean medication response of 50%. Placebo response rates have risen at an average rate of 7% per decade over the past 30 years. High placebo response has contributed to the majority of clinical trials of antidepressants submitted to the Food and Drug Administration (FDA) not showing a significant difference between medication and placebo. Increasing numbers of failed trials have made developing psychiatric medications progressively more time- consuming (average of 13 years to develop a new medication) and expensive ($800 million to $3 billion per new agent). These considerations recently led several large pharmaceutical companies to reduce or discontinue research and development on medications for brain disorders. Moreover, media coverage of failed trials has been used as a platform for critiques of the pharmaceutical industry and questioning the efficacy of antidepressants, which may have the dangerous public health consequence of dissuading patients with depression from accessing treatment. To address what has been called "psychopharmacology in crisis," it is imperative to develop methods of minimizing placebo response in antidepressant RCTs.

Minimizing placebo response would facilitate the valid evaluation of new antidepressant medications, but there is also a pressing public health need to optimize currently available treatments. Depressive disorders are the most common mental health disorders, affecting 9.5% (over 18 million) of American adults in any given year. MDD is currently the leading cause of disability among adults aged 15-44 and is predicted by 2020 to become the second overall cause of disability worldwide after heart disease.

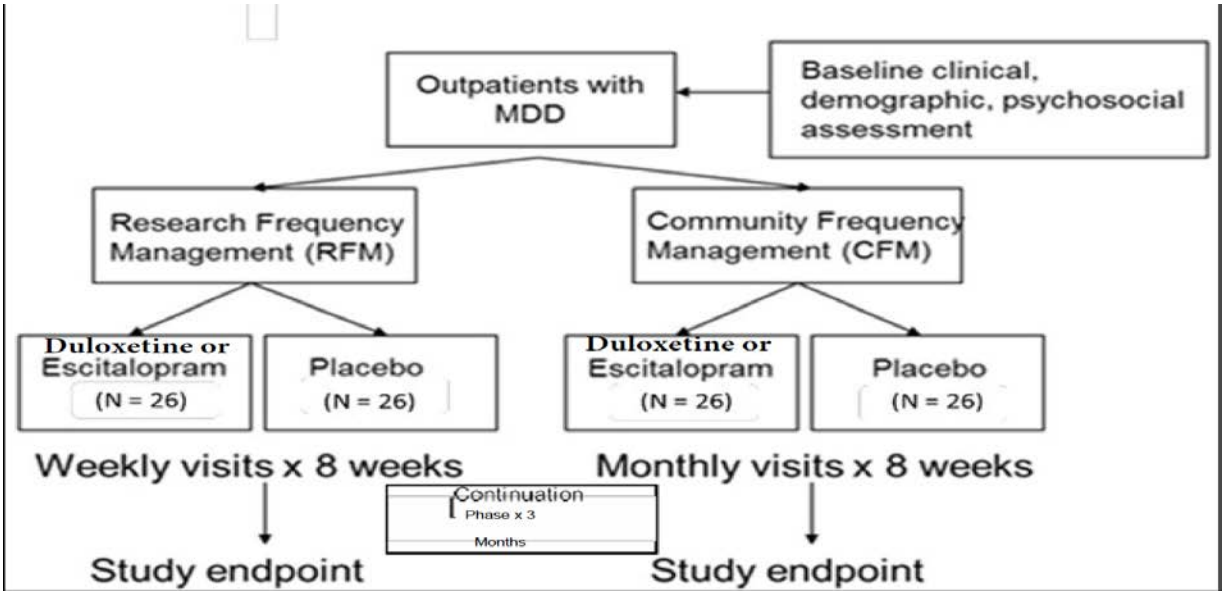
MDD is the psychiatric diagnosis most commonly associated with suicide, with the lifetime risk of suicide among patients with untreated depressive disorders being nearly 20%. Even with maximal treatment, many patients will not experience sustained remission of their depression. The cumulative percentage of patients achieving remission after 4 sequential antidepressant trials in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study was only 51%, and 28% of patients discontinued treatment during the study. Depression relapse rates after 1 year of follow up increased from 40.1% among Step 1 remitters to 71.1% among Step 4 remitters.

A feasible and effective way of addressing these public health needs may be to change the way clinicians manage the treatment of patients receiving antidepressant medications. Current clinical management entails weekly clinic visits for participants in most antidepressant RCTs, whereas depressed patients treated in standard clinical practice are seen at monthly intervals or less frequently. These practices are not based on experimental evidence, since it is unknown whether weekly follow-up visits are needed to ensure adherence and patient safety in clinical trials and what visit frequency is optimal in clinical treatment. In fact, recent data show that more frequent

study visits are associated with increased antidepressant and placebo response as well as decreased separation between medication and placebo, suggesting that current methods may be counterproductive in RCTs and insufficient in clinical practice. Additionally, more intensive follow- up may be beneficial for some patients while not for others, so determining the optimal visit frequency for different types of patients could increase antidepressant response, improve client satisfaction, and make RCTs more efficient.

To examine the influence of visit frequency on antidepressant and placebo response, this application proposes a double- blind, acute, prospective study randomizing subjects to "Research Frequency Management" (RFM, weekly study visits) vs. "Community Frequency Management" (CFM, every 4 weeks study visits) and escitalopram or duloxetine vs. placebo (see Figure 1). Close monitoring of all subjects will be assured by telephone contacts with individuals randomized to CFM between monthly visits, and additional study visits will be scheduled as necessary to maintain patient safety. The 104 subjects (26 per cell) participating in this study will be systematically characterized on measures of symptomatology, personality features, treatment history, therapeutic alliance, and treatment preferences to identify potential predictors of response to visit frequency. In this pilot study, we are particularly interested in examining the feasibility of our proposed experimental design and in detecting a signal of effect for visit frequency that will be followed up in a larger study. Pilot data from this study will allow us to determine whether patients can be recruited to participate in this novel study and be retained over the course of its up to 5-month duration. We will also obtain estimates of whether participants randomized to RFM vs. CFM have different rates of treatment adherence and adverse events, which could affect our interpretations regarding the effect of visit frequency on treatment response. In addition, piloting the assessment battery used in this study will allow us to assess the variability between subjects on the measures we plan to utilize, whether the recruited subjects are generalizable to the larger population of depressed patients enrolling in antidepressant RCTs, and whether there are initial indications that differences between clinical, demographic, and psychological characteristics of included subjects influence the effect of visit frequency on treatment response.

Figure 1



Significance:

Results from this study will have important significances for the pharmacologic treatment of MDD. First, the findings that participants in an antidepressant RCT can be safely followed and that separation between drug and placebo is increased using CFM (every 4 weeks with every two-week telephone check-ins) would have immediate implications for the design of Phase III clinical trials. Decreasing the number of follow-up visits to resemble community care could make RCTs cheaper, more efficient, and more generalizable to clinical practice. Second, if increased frequency of follow-up visits leads to increased medication response for some patients, then the management of these treatments could be intensified beyond the monthly or less follow-up currently practiced in order to enhance response to antidepressants. Third, differentiating patients likely to respond to more frequent therapeutic contact regimens from those who are not on the basis of clinical, demographic, or psychological data collected in this study would facilitate the development cost-effective, personalized treatment strategies tailored to the needs of individual patients. This information could be used to improve client satisfaction and advocate on behalf of patients with third party payers who currently influence treatment decisions by determining how many visits will be reimbursed.

Rationale:

Effective antidepressant medications cause salutary changes in the pathophysiology of MDD, which in turn lead to symptomatic improvements that are measured using rating scales for depression. These medications are provided within a therapeutic environment that possesses many elements of supportive psychotherapy. For example, patients experiencing social isolation and decreased activity levels due to their depressed state enter a behaviorally activating and interpersonally rich new environment. They are provided with diagnoses and psycho-education to explain their symptoms and regularly meet with research staff who listen to their experiences. Such interactions, combined with information provided during the informed consent process, instill and maintain faith in the potential effectiveness of the treatment.

Increasing or decreasing the visit frequency in an antidepressant RCT effectively varies the “dose” patients receive of these therapeutic factors. These aspects of clinical trials are often referred to as “non-specific factors,” but evidence suggests they have quite specific and quantifiable effects on treatment outcome.

The response observed in a clinical trial for a patient assigned to receive antidepressant medication thus reflects the specific effects of the medication combined with the therapeutic aspects of clinic visits. Expectancy of improvement, behavioral activation, and a therapeutic relationship with a clinician may modulate the effects of antidepressant medication or else directly ameliorate a patient’s depressive illness. In the case of patients assigned to placebo, we hypothesize that the expectancy of improvement, behavioral activation, and interpersonal experiences provided during clinic visits (in combination with natural history factors and measurement error) are the primary causes of placebo response. In the proposed study, we expect to find supporting evidence for this model by detecting a positive main effect of visit frequency on treatment response.

We will also attempt to identify an interaction between visit frequency and treatment assignment, since we anticipate that placebo response will be more affected by differences in visit frequency than medication response. Additionally, our model predicts that the effect of clinic visits on treatment outcome will be influenced by individual patient characteristics, and we expect to find indications in moderator analyses that this is the case.

Support for the therapeutic effects of meetings with clinicians comes from the report of Posternak and Zimmerman (2007), who investigated the influence of therapeutic contact frequency on antidepressant and placebo

response in 41 RCTs of antidepressants for MDD. These investigators calculated the change in HRSD scores observed over the first 6 weeks of treatment in patients assigned to antidepressant medication and placebo, comparing studies having 6 weekly assessments (weeks 1-6) to those having 5 (weeks 1-4 and 6) and 4 (weeks 1-2, 4, and 6) assessments. Participants treated with placebo who returned for a week 3 visit experienced 0.86 greater reduction in HRSD scores between weeks 2 and 4 compared to those who did not, while participants having a week 5 visit had 0.67 greater reduction in HRSD scores between weeks 4 and 6 compared to those who did not. A cumulative therapeutic effect of additional follow up visits on placebo response was found between weeks 2 and 6, patients with weekly visits improved 4.24 HRSD points, while those with 1 fewer visit improved 3.33 points and those with 2 fewer visits improved 2.49 points. Thus, the presence of additional follow up visits appeared to explain approximately 50% of the symptom change observed between weeks 2 and 6 among patients receiving placebo. Participants receiving active medication also experienced more symptomatic change with increased numbers of follow-up visits, but the relative effect of this increased therapeutic contact was approximately 50% less than that observed in the placebo group.

These results suggest that the way antidepressant medication is administered in a clinical trial has substantial effects on treatment outcome. Far from being “no treatment,” assignment to placebo in an antidepressant clinical trial represents an intensive form of clinical management that has therapeutic effects. This treatment may be contrasted with what patients being treated with antidepressants receive in the community. In community samples of patients receiving antidepressant medication, 73.6% are treated exclusively by their general medical provider as opposed to a psychiatrist. Less than 20% of patients have a mental health care visit in the first 4 weeks after starting an antidepressant, and fewer than 5% of adults beginning treatment with antidepressant medications have as many as 7 physician visits in their first 12 weeks on the medication. Thus, for patients who benefit from more intensive follow up, increasing visit frequency may be a safe and effective way of improving medication response in open clinical treatment.

## Specific Aims and Hypotheses

*Concisely state the objectives of the study and the hypothesis or primary research question(s) being examined. There should be one hypothesis for every major study procedure or intervention. For pilot studies, it is important not to overstate the study's objectives. If there are no study hypotheses, describe broad study goals/aims.*

Aim 1: The first aim of the proposed study is to examine the differential effect of visit frequency on placebo vs. medication response.
Hypothesis: Visit frequency contributes to treatment outcome for both medication and placebo responses, but especially for the placebo response.

Aim 2: Our second aim is to investigate the mechanisms underlying such an effect.
Hypothesis: Manipulation of visit frequency on outcome is mediated by the strength of the therapeutic alliance and the frequent use of supportive techniques

Aim 3: The third aim of the proposed study is to identify patient characteristics (clinical, demographic, and interpersonal) that moderate the effect of visit frequency on outcome.

## Inclusion/Exclusion Criteria

*This section details your study sample(s) and addresses the requirement for risk minimization.*
*You may choose to divide your sample by population (healthy controls vs. subjects) or by procedure (subjects who will have an MRI) and then define different sets of criteria for each.*

*For each sample, create or insert a table to describe detailed criteria for study inclusion and exclusion and the method you will use to ascertain each criterion. The method of ascertainment may describe tests, scales and instruments. When relevant, indicate the level of training of the person who will make the assessment (e.g. clinical interview by a psychiatrist).*

*Inclusion/Exclusion Criteria needs to be numbered and listed in outline form (see Table template below).*

| CRITERION | METHOD OF ASCERTAINMENT |
|---|---|
| **Inclusion:** | |
| 1. 1.Men and women aged 18-75 years | 1. Clinical interview |
| 2. Diagnosis with Diagnostic and Statistical Manual (DSM) 5 Major Depressive Disorder (MDD) | 2. Clinical interview, SCID |
| 3. 24-item Hamilton Rating Scale for Depression (HRSD) score ≥ 16 and ≤ 28; 17- item Hamilton Rating Scale for Depression (HRSD) score < 25 | 3. HRSD by trained rater |
| 4. Capable of providing informed consent and complying with study procedures | 4. Clinical interview |
| 5. Using appropriate contraceptive method if woman of child-bearing age and not currently pregnant | 5. Clinical interview |

| **Exclusion:** | |
|---|---|
| 1. Current comorbid Axis I DSM V disorder other than Mild Substance Use Disorder, Adjustment Disorder, Anxiety Disorder or Personality Disorder | 1. Clinical interview, SCID |
| 2. Diagnosis of Moderate to Severe Substance Use Disorder within the past 12 months | 2. Clinical interview, SCID, Urine tox |
| 3. Present or past history of psychosis, psychotic disorder, mania, or bipolar disorder | 3. Clinical interview, SCID |
| 4. baseline HRSD 24-item score > 28 or HRSD suicide item > 2 or baseline HRSD 17-item score ≥ 25 | 4. HRSD by trained rater |
| 5. History of allergic or adverse reaction to escitalopram and duloxetine, or non-response to adequate trial of escitalopram (at least 4 weeks at dose of 20mg) and duloxetine (at least 4 weeks at dose of 60mg) during the current episode | 5. Clinical interview |
| 6. Current treatment with psychotherapy, antidepressants, antipsychotics, or mood stabilizers | 6. Clinical interview |
| 7. CGI-Severity score of 6 or greater at baseline | 7. CGI based on Clinical interview |
| 8. Acute, severe, or unstable medical illness | 8. Clinical interview, Physical Exam, Screening Labs |

## Study Procedures

*Provide a clear, concise narrative of study procedures with special attention to the subjects' involvement. Detail the overall study timeline and location of study procedures, list all interventions, assessments and interviews, estimate the duration of each procedure, provide dosing schedules, identify study personnel involved in each procedure, and provide credentials for relevant personnel. For complicated study designs, we strongly encourage attaching tables, flow-charts, and study algorithms.*

COVID Restart:

I attest to follow the COVID-19 Safety Guidelines for Columbia Psychiatry and NYSPI Re-Entry outlined in the NYSPI Director's June 1st memo, which include but are not limited to:

- Infection Control/PPE – Guidelines
- Research participants will only come on-site if absolutely necessary for study procedures.
- No volunteers/externs on-site during Stage 1.
- Clinical research teams will screen their participants for COVID symptoms (night before and day of onsite visit, documenting this in the chart), and escort them in and out of the building.
- COVID/COVID-like symptoms in participants will be reported to the IRB via PRISM as an SAE.

Due to the COVID-19 pandemic, beginning in October 2020, CAAM will be implementing a number of changes to this study's operating procedures in order to ensure a safe environment while continuing to provide patients depression treatment through research participation. These changes include implementing Telehealth resources to complete visits virtually and only evaluating/enrolling 50% of our normal participant capacity in order to minimize the risk of contracting the virus due to physical contact. All measures that do not require an in-person component will be completed virtually. The evaluation procedure will be altered to include virtual components. Detailed descriptions of these changes are provided below.

<u>Evaluation:</u>

A two-visit evaluation procedure, one virtual and one in-person, will be implemented in order to reduce the risk of transmitting the virus by minimizing person-to-person contact. After an individual expresses interest in research participation and completes the initial phone screen process, the individual will be scheduled for a virtual evaluation with a research coordinator (trained study raters; BA, RN, SW) and a clinician. All assessments that are generally conducted during the evaluation process (Protocol #7284R) that can be conducted over the phone will be administered during the virtual portion. The individuals who may be eligible for study participation after completing the virtual evaluation will then be scheduled for an in-person evaluation at the clinic, in order to complete the remaining assessments that are necessary to determine eligibility.

The virtual evaluation will be completed via WebEx a HIPAA compliant video conferencing platform or a secure FaceTime platform. After consenting the individual virtually and sending them a copy of the consent form (if they have Internet/email access; if the individual does not have these resources, a hard copy of the consent form will be mailed to them), the research coordinator will complete the following measures: the MMSE, HRSD, Logical Memory Test I and II, and the SCID. They will also gather the individual's pharmacy information, as well as their current physical location and emergency contact (in case of a mobile crisis). The research coordinator will subsequently explain how the individual can complete the self-report forms included in the evaluation protocol online, and will send them a link for completion (if the individual does not have Internet/email access, self-report forms are to be completed over the phone with the research coordinator). The evaluating clinician will then be notified that the individual is ready for the clinical interview, and send them the assessment scores collected during the first portion of the virtual evaluation. The evaluating clinician will then join the call, and complete the clinical interview with the research coordinator on mute during the duration of the interview. If the individual may still be eligible for study participation after the clinical interview, they will be scheduled for the in-person component of the evaluation.

On the day of the in-person evaluation, the individual will be transported to the clinic via a car service. Social distancing procedures will be followed in order to ensure safety, including limiting the number of individuals in a clinic room, implementing the use of masks, and thoroughly cleaning clinic rooms and other assessment instruments (ex: blood pressure cuff, grip-strength machine, etc.) after each use. The rest of the evaluation procedures will be completed during the in-person visit. These assessments include:

Physical: vitals (height, weight, blood pressure, temperature), blood and urine collection, and EKG. RA-Administered Assessments: WAI-P Intake and the QIDS-SR Expectancy.

If an individual is eligible after completing the in-person evaluation and consents to study participation, they will be scheduled for their next visit.

Standard Evaluation :

At the evaluation visit, subjects will first undergo an initial evaluation comprising a psychiatric interview (MD/NP) as well as SCID-V-RV and HRSD by trained raters. A psychiatrist will review the consent form with eligible subjects and invite them to participate.

Subjects who sign the consent form will complete the remainder of the baseline evaluation, including further paper measures (see assessment instruments section), as well as urine tests, blood tests, and EKG (RN or qualified research assistant). These subjects will return the following week to review findings from these tests, confirm their continuing eligibility to participate (i.e., no acute or unstable medical conditions were found), and be randomized. This will be considered the Week 0 visit. The Week 0 visit will include the Columbia-Suicide Severity Rating Scale (C-SSRS), a questionnaire used for suicide assessment. Any score above 0 on the C-SSRS categories warrants physician notification and review. If at any point in time the patient presents with suicidal ideation, the C-SSRS Since Last Visit will be administered for determination of suicidal risk. Prior to randomization, patients of childbearing potential (female patients age 18-60) will be instructed regarding potential risks to the fetus of Escitalopram and/or duloxetine and the importance of using adequate birth control. Patients will be given instructions regarding use of effective methods of birth control, and asked to please let us know if they become pregnant in order to ensure safety of the mother and fetus. After receiving instruction, the study physician will evaluate the participant's willingness and reliability to practice effective birth control. Potential study participants who cannot agree to consistently practice effective birth control, or who the physician judges to be unreliable in practicing effective birth control, will not be included in the study. If a subject does become pregnant, she will be withdrawn from the study and evaluated on clinical grounds as to whether the medication should be continued or stopped.

As part of the evaluation, participants will be asked to be video recorded during study visits, and video recorded during the initial diagnostic interview. The purpose of these recordings is to check the quality of the evaluations and interviews being delivered, and to improve available treatments for depression. Video recordings are optional, and participants do not need to agree to the recordings in order to be evaluated. Participants will be provided with separate Video Recording Consent Forms to document whether they agree to be recorded.

Acute Phase Treatment Procedures:

At the Week 0 visit, subjects will be randomized to Research Frequency Management (RFM) or Community Frequency Management (CFM) (see Figure 1 above). They will be apprised of the results of this randomization and provided with a schedule of study visits. Within each track (RFM and CFM), subjects will be randomized to medication, escitalopram or duloxetine (if they cannot tolerate or have had an adverse reaction to escitalopram,) or to placebo. Assignment to medication or placebo will be blinded by over-encapsulating study pills such that they appear identical.

Each clinic visit will last approximately 45 minutes and follow a set structure, regardless of group assignment. Patients will arrive to the Clinic on Aging Anxiety, and Mood Disorders (CAAM) and be greeted by the clinic coordinator (1 min). Then, the clinical research assistant will meet with the patient to measure vital signs, collect used pill bottles, and distribute self-report measures (10 min). Next, the study clinician will meet with the patient to assess the status of their depressive symptoms, discuss side effects and other issues related to study medication, and fill out clinician-rated scales (15 min). Finally, a blinded rater will complete rater- administered measures (15 min), and the clinical research assistant will collect completed self-report measures and make a follow up appointment (4 min). Patient questionnaires and some assessments at Week 0 and for the duration of the study will be administered using Qualtrics, a HIPAA-compliant application accessible by smart phone or computer, by which raters and participants can access and complete online surveys.

All visits will be videotaped, and all videotaped sessions will be coded systematically under the supervision of the Israeli PI. Trained raters will code for aspects of the doctor-patient relationship (alliance development) and a variety of techniques (clinical management techniques as well as the facilitative conditions techniques, including warmth, empathy, involvement, rapport, conveyed expertise, communication style, supportive encouragement) using software for analyzing observational data (including Observer XT), which enable coders to code behavior on-the- go, accurately and quantitatively. The Week 0, 4, and 8 visits of each patient will be coded for both therapeutic alliance and use of therapeutic techniques, so that three scheduled sessions will be coded for each patient. The three time points were chosen because they overlap the two Acute Phase track assignments.

In the CFM arm of the study, telephone assessments will occur between monthly clinic visits at weeks 2 and 6, so subjects will be evaluated with standardized measures every 2 weeks during the study. During these telephone assessments, the research assistant will greet the subject and assess medication adherence, a trained rater will administer the HRSD, and the study clinician will briefly interview the subject to discuss interval events and fill out clinician-rated scales. An additional in-person clinic visit will be scheduled as soon as possible for patients (1) requesting to meet with the study clinician before the next scheduled visit, (2) who have begun experiencing a significant new side effect, (3) who have CGI Improvement score of 6 or 7, (4) who are showing a 24-item HRSD score increase >30%, or (5) who have HRSD suicide item score >2.

## Medication Treatment

Subjects assigned to receive treatment with escitalopram will begin at a daily dose of 10mg or duloxetine 30mg. The default medication will be escitalopram. After 4 weeks, if subjects do not meet remission criteria (HRSD ≤ 7), escitalopram dose will be increased to 20mg for the remaining 4 weeks of the study. Participants who have not responded to or tolerated escitalopram in the current depressive episode will be started on duloxetine. They will take 30mg for the first 4 weeks, then be increased to 60mg for the remaining 4 weeks of the study.

Subjects unable to tolerate the increased dose of medication will have their dosage reduced to the maximum previously tolerated dose. Absence of remission was selected to trigger dosage increases, because it is a clinically meaningful outcome denoting the absence of significant depressive symptoms and reduction in the risk of depression recurrence and adverse medical outcomes. We judged 4 weeks at a stable dose of the medications mentioned above to be a reasonable interval in which to observe the effects of that dosage. Patients who are assigned to placebo will receive placebo for the duration of the study.

If a patient discontinues study medication due to tolerability problems, ineffectiveness, patient preference, or other reasons, the patient will be dropped out of the study and enter the 3-month open treatment phase. Appropriate medication options will be discussed with the patient based on their symptoms and history. If the patient wishes, they will be provided referrals for psychotherapy or treatment options outside of our research clinic. No further research measures will be conducted once a patient enters the open treatment phase.

Criteria for early discontinuation are either (1) significant clinical worsening in the judgment of the study clinician, (2) a CGI-Improvement rating of 6 (worse) or 7 (much worse) for 2 consecutive visits, or 3a) C-SSRS category score >3 and 3b) significant suicide risk in the judgment of the study clinician. Any subjects meeting one or both of these criteria will be dropped from the study and treated openly. Subjects in the CFM group who meet one or both of these criteria will be scheduled for an in-person clinic visit the following week to permit serial assessment. Furthermore, subjects may be dropped form the trial if they repeatedly miss scheduled appointments or clinical worsening necessitates more intensive treatment.

<u>Continuation Phase Procedures:</u>

The blind will be broken at the end of the 8-week study period for subjects who are non-classified responders and appropriate clinical options will be discussed with patients. Patients taking escitalopram or duloxetine, who are classified responders (HRSD decrease by at least 50% and HRSD ≤ 12) or remitters (HRSD ≤ 8) will likely be continued on the same medication. Placebo non-responders will be treated openly with escitalopram or duloxetine, while escitalopram or duloxetine non-responders will be treated as clinically indicated with augmentation or switch in class of antidepressants.

In the Continuation Phase, classified responders will continue double-blind study medication and come to clinic for monthly study visits for three months. All responders, regardless of Acute Phase track assignment, will continue double-blind study medication and come to the clinic for monthly study visits. There will be Q2 week phone calls in between. Study assessments and early discontinuation criteria will be kept the same as in the Acute Phase procedure.

## Study Assessment Timepoints:

| | Study Assessment – RFM Track | SCREENING | WEEK 0 | WEEK 1 | WEEK 2 | WEEK 3 | WEEK 4 | WEEK 5 | WEEK6 | WEEK 7 | WEEK 8 | Cont. Call 1 | Cont. Month 1 | Cont. Call 2 | Cont. Month 2 | Cont. Call 3 | Cont. Month 3 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Phy | Electrocardiogram | X | | | | | | | | | | | | | | | |
| | Vital signs | X | X | X | X | X | X | X | X | X | X | | X | | X | | X |
| | Medical history and physical examination | X | | | | | | | | | | | | | | | |

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Demographic information | X | | | | | | | | | | | | | | | |
| | Serumlaboratoryexamination | X | | | | | | | | | | | | | | | |
| | Urinalysis | X | | | | | | | | | | | | | | | |
| | Urinetoxicology | X | | | | | | | | | | | | | | | |
| **Rater-administered measures** | SCID | X | | | | | | | | | | | | | | | |
| | HRSD | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | HARS | | X | X | X | X | X | X | X | X | X | | X | | X | | X |
| | CGI | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | Structured Pill Count Interview | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | TESS | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | Blind assessment—Clinician & Patient Version | | X | X | X | X | X | X | X | X | X | | X | | X | | X |
| | WAI – T | | X | X | X | X | X | X | X | X | X | | X | | X | | X |
| | C-SSRS | | X | | | | | | | | | | | | | | |
| **Self-report measures** | ECR | | X | | | | | | | | | | | | | | |
| | WAI – P | | X | X | X | X | X | X | X | X | X | | X | | X | | X |
| | WAI – P (intake) | X | | | | | | | | | | | | | | | |
| | QIDS-SR | X | X | X | X | X | X | X | X | X | X | | X | | X | | X |
| | QUIDS-SR (intake) | X | X | X | X | X | X | X | X | X | X | | X | | X | | X |
| | CES | | X | | | | | | | | | | | | | | |
| | IIP-C | | X | | | | | | | | | | | | | | |
| | CSQ – 8 | | X | | | | | | | | | | | | | | |
| | LOT-R | | X | | | | | | | | | | | | | | |
| | Big Five | | X | | | | | | | | | | | | | | |
| | Cornell Treatment Preference Index | | X | | | | | | | | | | | | | | |

| | Study Assessment – CFM Track | SCREENING | WEEK 0 | Acute Call 1 | WEEK 4 | Acute Call 2 | WEEK 8 | Conti. Call 1 | Cont. Month 1 | Cont. Call 2 | Cont. Month 2 | Cont. Call 3 | Cont. Month 3 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Electrocardiogram | X | | | | | | | | | | | |
| | Vital signs | X | X | | X | | X | | X | | X | | X |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Medical history and physical examination | X | | | | | | | | | | | |
| | Demographic information | X | | | | | | | | | | | |
| | Serumlaboratoryexamination | X | | | | | | | | | | | |
| | Urinalysis | X | | | | | | | | | | | |
| | Urine toxicology | X | | | | | | | | | | | |
| Rater-administered measures | SCID | X | | | | | | | | | | | |
| | HRSD | X | X | X | X | X | X | X | X | X | X | X | X |
| | HARS | | X | | X | | X | | X | | X | | X |
| | CGI | X | X | X | X | X | X | X | X | X | X | X | X |
| | Structured Pill Count Interview | | | X | X | X | X | X | X | X | X | X | X |
| | TESS | X | X | X | X | X | X | X | X | X | X | X | X |
| | Blind assessment—Clinician & Patient Version | | X | | X | | X | | X | | X | | X |
| | WAI – T | | X | | X | | X | | X | | X | | X |
| | C-SSRS | | X | | | | | | | | | | |
| Self-report measures | ECR | | X | | | | | | | | | | |
| | WAI – P | | X | | X | | X | | X | | X | | X |
| | WAI – P (intake) | X | | | | | | | | | | | |
| | QIDS-SR | X | X | | X | | X | | X | | X | | X |
| | QUIDS-SR (intake) | X | X | | X | | X | | X | | X | | X |
| | CES | | X | | | | | | | | | | |
| | IIP-C | | X | | | | | | | | | | |
| | CSQ – 8 | | X | | | | | | | | | | |
| | LOT-R | | X | | | | | | | | | | |
| | Big Five | | X | | | | | | | | | | |
| | Cornell Treatment Preference Index | | X | | | | | | | | | | |

## Criteria for Early Discontinuation

*Define criteria that will be used to exit or drop subjects from the study. Indicate the time points when such criteria will be applied, and describe the rating instruments, parameters, and thresholds that will lead to a decision to terminate a subject's participation. In addition, explain procedures for managing subjects who are dropped from the protocol.*

*For treatment studies: To minimize risks to subjects, operationalized drop-out criteria should be defined so that subjects who worsen, or in some cases, fail to improve, are removed from the study and offered standard care. The threshold for drop-out should consider the level of risk associated with non-improvement for the specific disorder, the availability of alternatives, and the typical required duration of treatment. For example, emergence of suicidal intent, or psychosis, should prompt immediate clinical evaluation and withdrawal from the study.*

Criteria for early discontinuation are either (1) significant clinical worsening in the judgment of the study clinician, (2) a CGI- Improvement rating of 6 (worse) or 7 (much worse) for 2 consecutive visits, or 3a) C-SSRS category score >3 and 3b) significant suicide risk in the judgment of the study clinician. Any subjects meeting one or more of these criteria will be dropped from the study and treated openly. Subjects in the CFM group who meet one or more of these criteria (at an in person visit or phone call) will be scheduled for an in-person clinic visit the following week to permit serial assessment. If such a subject continues to have a CGI-I of 6 or 7, he or she will be dropped from the study and treated openly. Any score above 0 on the C-SSRS categories warrants physician notification and review. An overall score of 0-3 on the C-SSRS categories indicates low-risk suicidal ideation. If at any point in time the patient presents with suicidal ideation, the C- SSRS Since Last Visit will be administered for determination of suicidal risk. Furthermore, subjects may be dropped form the trial if they repeatedly miss scheduled appointments or clinical worsening necessitates more intensive treatment. The same discontinuation criteria apply regardless of Acute Phase track assignment.

## Blood and other Biological Samples

*Describe how the sample will be used and indicate, when relevant, the amount of the sample. The IRB wants to know that the sample is sufficient for the purposes of the study, but that sampling is limited to what is minimally necessary.*

*If you've indicated that you intend to store a sample for future use, indicate where the sample will be stored, how long the sample will be stored, and to what purposes the sample will eventually be put. Check the IRB website at [http://irb.nyspi.org/irbdnn/Policies/GeneticResearch/tabid/96/Default.aspx](http://irb.nyspi.org/irbdnn/Policies/GeneticResearch/tabid/96/Default.aspx) for specific guidance and additional information about future use of DNA samples.*

2 tubes of blood will be drawn and sent for CBC, Chem 7, LFTs, TSH, B12, folate, total cholesterol. Urine will be sent for urinalysis and toxicology.

## Assessment Instruments

*List all assessment instruments, indicate who will administer them, and provide an estimate the duration of each. The IRB wants to know that assessments instruments are appropriate measures for the purposes of the study and are no more burdensome than is necessary. The IRB will consider the burden of assessment instruments (in terms of time, sensitivity of material, etc.) in the risk/benefit analysis. Please attach copies or otherwise provide all non-standard instruments.*

Overview:

The assessment schedule was designed to replicate standard practice in RCTs for RFM and open clinical treatment for CFM. All participating subjects will be characterized on the below measures at baseline screening, then return the following week (Week 0) to review test results and be randomized (see Table 1). Subjects in the

RFM arm will be evaluated on follow-up measures weekly (Weeks 1-8), while participants in the CFM arm will be evaluated in person monthly (Weeks 4, 8) and via telephone

check-ins between visits (Weeks 2, 6). The function of telephone ratings is to ensure close monitoring of patients for safety purposes rather than assessment of outcome, so ratings at Weeks 2 and 6 will be limited to CGI, HRSD, and measures of adherence and side effects.

Clinical and demographic information: we will collect information about the number of prior depressive episodes, age, age of first depressive episode onset, gender, marital status, ethnicity, employment status and income, years of education, and family history. Physiologic measures: Baseline assessment will include 12-lead electrocardiogram, vital signs, medical history and physical examination, complete blood count (CBC), basic metabolic panel (BMP, including electrolytes and liver function tests), thyroid profile, urinalysis, and toxicology.

Rater-administered measures:

Structured Clinical Interview Diagnostic for DSM-IV TR (SCID), First, Spitzer, Gibbon, & Williams, 1996; alternatively, SCID-5- RV may be used): semi-structured diagnostic interview designed to assist researchers in making reliable and valid DSM-IV TR psychiatric diagnoses. SCID diagnoses will allow us to determine whether patients meet selection criteria and document the presence of covariates such as past substance abuse and dependence, and past or present anxiety disorders.

Hamilton Rating Scale for Depression (HRSD) scale for depressive symptoms administered by trained raters. The HRSD is the standard measure of depression severity for clinical trials of antidepressants, and was chosen as the primary outcome measure.

Hamilton Anxiety Rating Scale (HARS) 14-item scale: scale for anxiety symptoms administered by trained rater. The HARS is a standard measure of anxiety severity in pharmacotherapy studies that has been shown to have acceptable reliability and validity in studies of depressed patients.

CGI Severity and Improvement (Spielmans & McFall, 2006): scales developed to measure the clinician's view of patients' global functioning before and after initiating study medication. The CGI correlates well with other standard outcome measures for depression (e.g., HRSD), is sensitive to change in antidepressant trials, and offers clinically understandable anchor points (Bandelow, Baldwin, Dolberg, Andersen, & Stein, 2006).

CGI ratings will provide clinical assessment of patients at each visit, and help us maintain the safety of study participants by identifying significant clinical worsening that requires patients to be dropped from the study.

Structured Pill Count Interview assessment of medication compliance, to account for each dose of prescribed study medication, during the study period. This standard means of determining medication compliance in a pharmacotherapy study will allow us to assess whether contact frequency is associated with differences in behavior among study patients.

Treatment Emergent Symptom Scale (TESS): rating scale for physical symptoms reported during the study. This standard means of recording drug-related adverse effects will allow us to assess whether contact frequency is associated with differences in side effects among study patients.

Columbia–Suicide Severity Rating Scale (C-SSRS): an assessment tool that evaluates suicidal ideation and behavior. This is the institutional standard used to assess suicidal risk.

Self-report questionnaires:

Quick Inventory of Depressive Symptoms— Self Report (QIDS-SR) 16 item scale: rating scale for depressive symptoms based on DSM criteria. A self-report measure for depressive symptoms is valuable in this study, because it is less susceptible to clinician and rater bias. The QIDS-SR has been increasingly used in antidepressant studies (e.g., STAR*D) due to its equivalent weightings for each symptom item, clearly understandable anchor points, and inclusion of all DSM criteria for depression.

Working Alliance Inventory-Short Revised (WAI; Tracey & Kokotovic, 1989), using the patient (WAI-P) and therapist (WAI-T) versions: rating scale for the working relationship between physician and patient. The WAI, the most widely used measure of the therapeutic alliance, has excellent psychometric properties (Elvins & Green, 2008) and has been consistently correlated with psychotherapeutic outcome (Horvath et al., 2011). Similarly, to previous ADM studies, we have slightly modified the scale to substitute "pharmacotherapy" for "counseling" on relevant questions (e.g., Zilcha-Mano et al., 2015). The WAI total score will be used for analyses.

Treatment Credibility and Expectancy Scale (CES; Borkovec & Nau, 1972): patients rate their impression of the credibility of the treatment and their estimated expectation of improvement on an 8-item scale. Given previous studies on the effect of patients' pre- treatment expectancy on placebo response, all analyses in the proposed study will be repeated controlling for the potential effect of expectancy (Rutherford et al., 2016).

Experiences in Close Relationships Scale-Short Form (ECR; Wei et al., 2007): scale assessing patients' attachment orientation. Both ECR dimensions will be used and assessed at baseline: 6 items assess the attachment anxiety dimension and 6 the avoidance dimension. A self-report questionnaire will be used for assessing attachment orientation because it will be easy and inexpensive to implement, enabling translation of the findings into personalized medicine in clinical practice.

Inventory of Interpersonal Problems– Circumplex (IIP-C; Alden, Wiggins, & Pincus, 1990): a 64-item self-report questionnaire assessing interpersonal difficulties and distress.

Patients rate two types of items: interpersonal behaviors that are "hard for you to do" (e.g., "it is hard for me to let other people know when I am angry") and interpersonal behaviors that "you do too much" (e.g., "I am too afraid of other people"). Ratings of the degree to which each problem is distressing are made on a 5-point scale, ranging from 0 (not at all) to 4 (extremely).

Client Satisfaction Questionnaire 8 (CSQ 8): self-administered scale with items rating respondents' satisfaction with mental health services they are receiving on a 4 point Likert scale. Use of the CSQ 8 will allow us to determine whether CFM and RFM are associated with differences in participant satisfaction.

Cornell Treatment Preference Index: scale used in mental health studies to document the type and strength of patients' treatment preferences. We will use a modified version in this study asking subjects "Based on your experience and how you feel right now, which of the visit frequencies in this study would be your first choice?" The strength of this preference will be measured on a 5-point Likert scale.

Revised Life Orientation Test (LOT-R): scale developed to assess individual differences in generalized optimism versus pessimism. Degree of optimism on this scale has been correlated with the magnitude of placebo response observed in studies of placebo analgesia, and we will determine whether LOT-R scores moderate effects of therapeutic contact.

Big Five Personality Traits (BFI): this questionnaire is a widely used assessment tool for personality traits that we will also use to identify predictors of response to varying visit frequency.

Blind assessment— Clinician and Patient Version: rates clinician's and patient's guess as to the identity of study condition (ADM vs placebo) and the confidence in that guess.

This assessment is necessary to document the effectiveness of the methods of treatment allocation concealment for ADM and placebo.

Coding systems: Working Alliance Inventory— Observer Form (WAI-O; Berk, 2013): Alliance will be coded using the 12-item version of the Working Alliance Inventory- Observer form (WAI-O) (Darchuk et al., 2000). The items and anchors for the WAI-O were sampled directly from Darchuk's measures. The WAI-O validity and reliability have been documented (Berk, 2013), as was the utility of coding distinct types of treatments (Zilcha- Mano, Adler, & Shahar, 2017).

Collaborative Study Psychotherapy Rating Scale (Hollon et al., 1988): techniques will be coded using two of the CSPRS observer-rated measures of adherence: the clinical management (CM) techniques and the facilitative conditions (FC) techniques. The CSPRS was developed for the Treatments of the Depression Collaborative Research Project (TDCRP; Elkin et al., 1989). Each item on the CSPRS describes a specific intervention and is rated on a 7-point Likert scale as to how extensively the intervention was used during a given session. The CM subscale, based largely on the Fawcett et al. (1987) manual, consists of 20 items that cover medication management and generally supportive interventions. It includes items such as symptom inquiry, biochemical rationale, pharmacological rationale, medication effects expected, concerns about medication, occurrence of side effects, medication dosage, and adherence to regimen. The FC subscale consists of 8 items that represent relationship-building practices assumed to exist across all treatments for psychiatric disorders, including supportive encouragement, warmth, empathy, rapport, involvement, and conveying expertise.

## Research Related Delay to Treatment

*Research involving participants who are in need of treatment invariably involves delay to care, and this delay is associated with risk. Scheduling of procedures must be carefully organized to minimize delay. Other delay must involve only that minimally necessary to accomplish the aims of the research while respecting subject well- being and safety. Describe the delay, by virtue of research participation in this study, before a participant can receive treatment of known efficacy or standard care routinely offered in the community.*

Research may possibly result in a delay in treatment. Patients who present to CAAM who are not taking antidepressant medication will not have a delay in treatment caused by research. We recognize that some subjects may present for a screening visit while taking an antidepressant or having had recent treatment with an antidepressant medication. Subjects demonstrating a partial response on their medication regimen or who have not been on an adequate dose of medication for an adequate duration will not be tapered off medication. They will be referred back to their treating clinician with a recommendation to complete an adequate trial of medication. Subjects taking an antidepressant who have not responded to an adequate trial of the medication at the time of their screening assessment and who are interested in participating in the study will undergo a medication washout. Patients eligible for medication washout include patients eligible for study enrollment. Please see Inclusion/Exclusion Criteria for further information. Supervised by the study clinicians, these subjects will be tapered off of their current antidepressant medication for 1-2 weeks and remain off medication for 2 weeks. Subjects undergoing a medication taper will be seen weekly for clinic visits. If subjects are unable to tolerate this taper or washout period as evidenced by meeting one of the criteria for early discontinuation, they will be treated openly with the goal of achieving remission of their depression for three months. Subjects will receive 3 months of free doctor/np visits in the clinic and at least 1 month of free medication. Every effort will be made to provide free medication for 3 months total, but we cannot guarantee the availability of free medication beyond 1 month. At the end of the three-month period, patients will be referred out for further psychiatric follow up.

Maximum duration of delay to standard care or treatment of known efficacy Patients assigned to placebo (50% of sample) will have a treatment delay of up to 5 months (Acute + Continuation Phase).

<u>Treatment to be provided at the end of the study</u>

At the end of the acute treatment protocol, appropriate treatment (medication continuation, change in medication, and/or follow-up) will be provided free for 3 months. Subjects will receive 3 months of free doctor/np visits in the clinic and at least 1 month of free medication. Every effort will be made to provide free medication for 3 months total, but we cannot guarantee the availability of free medication beyond 1 month. At the end of the three-month period, patients will be referred out for further psychiatric follow up.

## Clinical Treatment Alternatives

*Describe what other treatment or assessment options are available to subjects who do not participate in research.*

Patients with Major Depressive Disorder do not have to participate in this study in order to receive treatment. They may be evaluated by a clinician in a private office, on their insurance plan, or in a low cost clinic and receive treatment with escitalopram and/or duloxetine for their depression. They also have the option of trying other antidepressant medications that a clinician recommends for their condition.

## Risks/Discomforts/Inconveniences

*"Risk" is a broad term used to convey the potential for harm, burden, and inconvenience related to research participation. Use this section to provide a comprehensive description of foreseeable physical, psychological, social, interpersonal, and economic risks introduced by the research. Include the source of the information. Consider both the probability and magnitude of harm and its impact. Describe the foreseeable harms associated with the research (untoward effects of a medication) and those related to delay to individualized treatment. Include data from the literature, and local data, if available, on risk rates and subject experiences with research procedures. Describe procedures in place to minimize risk. In general, please create a numbered list of risks/categories of risk, and in general put the list in the order of significance or level of risk, the most significant risks first followed by others.*

1. One risk to subjects in this study is the possibility of being randomized to monthly as opposed to weekly study visits. It is possible that a reduced visit schedule may adversely influence medication compliance, timely reporting of symptom changes and side effects, and motivation to continue participation in the study. Additionally, 52 subjects will be assigned to pill placebo for the 8-week Acute Phase of the study. Assignment to placebo places subjects at risk for continued or worsening depressive symptoms when there is treatment available of known efficacy for depression. Subjects completing the study will receive free open clinical treatment for 3 months following the study, and subjects whose depressions do not remit to placebo will have a treatment of known efficacy started immediately upon the study's conclusion.

2. Another significant risk to subjects is related to drug administration. Side effects of escitalopram include somnolence, diarrhea, nausea, impaired ejaculation, impotence, dry mouth, tremor, and sweating. The most common side effects reported for duloxetine are insomnia, constipation or diarrhea, dry mouth, sweating, nausea and small increase in blood pressure. The less common side effects of duloxetine are abnormal orgasm, fainting, and headache. Escitalopram and duloxetine have a black box warning regarding an increased risk for suicidal thinking and behavior in adolescents and young adults (less than 24 years old) given the drug. Since the proposed study will enroll subjects aged 18-75 years, participants will be apprised of this potential side effect and asked to tell their doctors immediately if they experience suicidal thoughts.

3. Regarding pregnancy, escitalopram and duloxetine are Category C pregnancy risk drug, meaning there are no adequate studies in humans to determine the risk. Therefore, determination of the risk/benefit ratio will be left up to the clinician's judgment and is dependent on the risk of depression in the mother. Female participants will be required to use effective methods of birth control (e.g., condom with spermicide, diaphragm with spermicide, or oral contraceptive pills). Patients will also be advised to please let the study

physician know if they have become pregnant. If a subject does become pregnant, she will be withdrawn from the study and evaluated on clinical grounds as to whether the medication should be continued or stopped.

4. The clinical interviews, rating scales, and questionnaires should not pose significant risk to study subjects. All procedures are consistent with HIPAA requirements, including the completion of online assessments using Qualtrics. Their major disadvantage is the time required to complete them and that some questions might be embarrassing or distressing to subjects. Subjects are informed that they may refuse to answer any questions and may ask to stop at any time. If participants become upset during the interviews and/or assessments, assistance will be made available for them. Another risk of this process is that it may be upsetting for the patient to be videotaped during the study visit. Blood drawing may cause slight discomfort at the site of needle entry and result in a small bruise.

5. Due to the COVID-19 pandemic, the additional risk of contracting the virus with any human interaction is present, due to the method of how the virus is transmitted.

Procedures for Minimizing Risk

The proposed study's selection criteria are designed to minimize the medical and psychiatric risks to subjects as described above. Subjects undergo a comprehensive medical and psychiatric evaluation during the screening visit, including physical examination, complete blood count, chemistry profile, liver function tests, thyroid stimulating hormone, urinalysis, and electrocardiogram, which is designed to detect unstable medical illnesses. Vital signs will be obtained at each weekly clinic visit. Subjects will be monitored for adverse effects, and dose adjustments will be made if indicated.

The risk of being randomized to the CFM group is addressed in several ways. First, subjects with severe MDD (as indicated by a score of 6 or greater on the CGI—Severity scale) as well as subjects with significant suicidal ideation (as indicated by a HRSD item 2 score > 2) will be excluded from the study. Second, subjects in the CFM group will be evaluated by study personnel no less frequently than every 2 weeks. The visit schedule for patients randomized to the CFM group will be as follows: baseline evaluation in clinic, week 0 visit in clinic (1 week following evaluation visit to review evaluation data and begin study), week 2 telephone assessment, week 4 visit in clinic, week 6 telephone assessment, and week 8 visit in clinic.

Biweekly phone assessments and monthly clinic visits apply to those eligible for the Continuation Phase. This schedule will permit in-person evaluation of all patients at critical time points in the monitoring and management of patients receiving antidepressant medications (i.e., consideration of dosage increases at 4 weeks).

Telephone assessments will have 3 components: (1) research assistant will greet the subject and fill out Structured Pill Count Interview, (2) trained rater will administer the HRSD, and (3) study clinician will briefly interview the subject to discuss their subjective state and interval events, fill out Treatment Emergent Side

Effect Scale (TESS), and complete Clinical Global Impressions – Severity and Improvement. This will permit standardized assessment of interval change in the subject's adherence to study medication, experience of side effects related to escitalopram and duloxetine, symptom severity, and clinical deterioration such as evolution of suicidal ideation. An additional in-person visit will be scheduled for subjects (1) requesting to meet with the study clinician before the next scheduled visit, (2) who have begun experiencing a significant new side effect, (3) who have CGI Improvement score of 6 or 7, (4) who are showing a 24-item HRSD score increase >30%, or (5) who have HRSD suicide item score >2. Third, patients will be extensively educated in the availability of 24-hour coverage by a psychiatrist in addition to having an Emergency Department at CUIMC that is thoroughly familiar with our protocol. Participants will receive a printed card to keep on their person that details the procedures to reach the on-call psychiatrist and access the CUMC emergency room.

We have implemented a plan for monitoring and treating suicidal ideation developed for research studies by colleagues at NYSPI (Drs. Maria Oquendo and John Mann). If the patient expresses any recent suicidal behavior or suicidal ideation during an interview, this is indicated in the chart note and quantitatively measured with the suicide item of the HRSD. The HRSD score itself is not used as a clinic standard to determine emergency care procedures; rather, clinical interview and physician judgment use the HRSD score alongside other quantitative and qualitative factors in assessing patient risk.

Should a research subject manifest severe suicidal ideation, arrangements for emergency care, in consultation with the principal investigator, will be made. The Columbia University Medical Center Emergency Department is located near the Clinic for Aging, Anxiety, and Mood Disorders (CAAM), and security services are available to assist with patient transportation to the emergency room. For subjects who may experience suicidal ideation between assessments, our department provides 24-hour coverage by a psychiatrist in addition to having an Emergency Department that is thoroughly familiar with our protocol. As described above, all patients are given the pager number for the Doctor on Call, and this number is also recorded on all outgoing phone messages of the clinical staff. If the suicidal ideation can be managed as an outpatient, the subject will be given an appointment within the next two days and contact will be maintained with phone check ins. If the suicidal ideation is more severe, the patient will be given information to access emergency care and/or be escorted to the emergency room.

The risk of receiving placebo or non-response to escitalopram and/or duloxetine during the study period is addressed by having close clinical follow up of study subjects and stringent drop-out criteria. These criteria are (1) significant clinical worsening in the judgment of the study clinician or (2) a CGI-Improvement rating of 6 (worse) or 7 (much worse) for 2 consecutive visits. Any subjects meeting one or both of these criteria will be dropped from the study and treated openly. Subjects in the CFM group who meet one or both of these criteria will be scheduled for an in-person clinic visit the following week to permit serial assessment. Furthermore, subjects may be dropped form the trial if they repeatedly miss scheduled appointments or clinical worsening necessitates more intensive treatment. Pregnant or lactating women, or those not practicing reliable birth control, are excluded. Subjects are instructed to inform their study physician immediately if they suspect they may be pregnant.

History of adverse or allergic reaction to escitalopram and duloxetine is exclusionary. Because subjects might potentially attempt to overdose with escitalopram and/or duloxetine, they will be provided with at most a 30-day supply of medication at one time during the study. Subjects will be informed of the potential side effects and risks enumerated above through extensive discussions with the study physicians and research staff throughout the study. Subjects will be warned that risks, as yet unknown, may occur when combining study medication with alcohol, drugs, or other prescription medications. Subjects will give informed consent prior to participation in the study and are provided with the phone number of the on call doctor, who is available 24 hours per day.

Confidentiality will be protected by storing all patient records in locked cabinets. Computer records will be identifiable only by a subject's study code number. Information will be available to subjects' physicians or other health services only if directly requested in writing and the subject signs a release of medical information form. All procedures at NYSPI are in compliance with HIPAA requirements. Subjects will be asked to sign a notice of privacy protection.

Specifically, for in-person visits to NYSPI, individuals are at increased risk for exposure to COVID-19 both in transit to NYSPI as well as during their time at NYSPI. Procedures are in place to minimize this risk. We plan to offer car transportation subject to a maximum of $50 each way, which minimizes exposure to public transportation for those participants. At NYSPI, personal protective equipment such as masks will be utilized at all times both by staff and participants, and social distancing will be adhered to when possible (exceptions exist for procedures such as blood draws and EKGs). Screen shields between patient and staff will be used during neuropsychological testing to further minimize exposure risk.

## Methods to Protect Confidentiality

*Describe the data management plan and the methods you will employ to protect subject privacy and the confidentiality of research data. The section should detail how information will be collected, recorded, coded, stored, transmitted, and as applicable, shared with other investigators so as to minimize risks related to breach of confidentiality. Confirm that identifiers are removed, to the extent possible, from research data, and explain if there are links between subject identity and research data, or if the data is anonymous. Also, indicate where the data is stored, who is responsible for its safekeeping, and who has access to subject identity and codes, if any, which cross-link research data and subject identity. Confirm that identifiable data is not collected, stored, or transmitted by mail, fax, on removable drives, laptops, or via the internet without proper protections, e.g. encryption.*

All records of the participating subjects will be kept in a locked room with access provided only to staff members. Patients' names will be linked with code numbers in a password protected file to which only the research assistant has access. Only these code numbers will appear on all pill bottles and paper measures collected during study. All data collected will be kept confidential and used for professional purposes only.

Publications using these data will be done in a manner that protects the subjects' anonymity. All electronically stored data will be accessible by password known only to the principal investigator and research assistants for the study.

There may be future analyses of all the research data conducted by the study investigators, yet unplanned, dealing with other aspects of illnesses of late-life. Additionally, research data may also be shared and provided to other investigators for the purpose of secondary analyses or distributed to another investigator for future research studies. The results of this study may also be published or presented at professional meetings. In each of these instances, all personal identifiers (such as name, birth date) will have been removed (de-identified) and replaced with a specific code number. The information linking this code number to subject's identity will be kept in a separate, secure location.

Patient questionnaires and some assessments at Week 0 and for the duration of the study will be administered using Qualtrics, a HIPAA-compliant application accessible by smart phone or computer, by which raters and participants can access and complete online surveys.

All study visits will be videotaped and shared for analysis via the NYSPI Office 365 Sharepoint.com platform for secure collaboration with pre-approved collaborators. Via SharePoint, video data will be moving securely between NYSPI and Haifa University in Israel for coding analysis. This platform has been registered with NYSPI IT and is approved for confidential data exchange and collaboration, as advised by Chris Stanley. This is the same solution being used to support parts of the OPAL Center.

Due to the implementation of virtual visits, additional measures to protect patient confidentiality will be employed. These include using only secure platforms for virtual calls (CUIMC Zoom Pro etc.), the use of headphones during virtual calls, and not continuing to use Qualtrics forms for data collection during week 0 and follow up calls.

## Direct Benefits to Subjects

*Describe only benefits to individual subjects that are likely to accrue during the study itself. Do not include subject compensation or treatment to be provided at the end of the study, as these do not figure into the IRB's risk benefit considerations. Do not describe diagnostic and evaluation components unless subjects receive clinical feedback. Do not describe the anticipated scientific benefits of the research. Some studies offer no direct benefit to subjects.*

As this is protocol includes a treatment medication approved for depression, the patient's symptoms may or may not improve. There are no other direct benefits in this study.

## References

1. American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). Arlington, VA: American Psychiatric Publishing.

2. Attkisson, C. C., & Zwick, R. (1982). The Client Satisfaction Questionnaire: Psychometric properties and correlations with service utilization and psychotherapy outcome. Evaluation and program planning, 5, 233-237.

3. Bandelow, B., Baldwin, D. S., Dolberg, O. T., Andersen, H. F., & Stein, D. J. (2006). What is the threshold for symptomatic response and remission for major depressive disorder, panic disorder, social anxiety disorder, and generalized anxiety disorder?. Journal of Clinical Psychiatry, 67, 1428-1434.

4. Barber, J. P., Barret, M. S., Gallop, R., Rynn, M. A., & Rickels, K. (2012). Short-term dynamic psychotherapy versus pharmacotherapy for major depressive disorder: A randomized, placebo-controlled trial. Journal of Clinical Psychiatry, 73(1), 66–73. doi:10.4088/JCP.11m06831

5. Berk, E. (2013). Detecting alliance ruptures and rupture repair with the Segmented Working Alliance Inventory—Observer Form (S-WAI-O) (Unpublished Dissertation).The New School for Social Research, NY.

6. Bernecker, S. L., Levy, K. N.,& William, D. E. (2013). A meta-analysis of the relation between patient adult attachment style and the working alliance. Psychotherapy Research, 24, 12-24.

7. Borkovec, T. D., & Nau, S. D. (1972). Credibility of analogue therapy rationales. Journal of Behavior Therapy and Experimental Psychiatry, 3, 257-260.

8. Borkovec, T. D., & Costello, E. (1993). Efficacy of applied relaxation and cognitive- behavioral therapy in the treatment of generalized anxiety disorder. Journal of Consulting and Clinical Psychology, 61, 611-619.

9. Bowlby, J. (1980). Attachment and loss (Vol. 3). New York, NY: Basic books. Bowlby, J. (1982). Attachment and loss: retrospect and prospect. American journal of Orthopsychiatry, 52, 664-678.

10. Brennan, K. A., Clark, C. L., & Shaver, P. R. (1998). Self-report measurement of adult attachment: An integrative overview. In J.A Simpson W.S Rholes (eds.), .Attachment theory and close relationships (pp.46-76) New York, NY: Guilford Press.

11. Cressey, D. (2011). Psychopharmacology in crisis. Nature, 14.

12. Crits-Christoph, P., Gibbons, M. B. C., & Mukherjee, D. (2013). Psychotherapy process- outcome research. In M. J. Lambert (Ed.), Bergin and Garfield's handbook of psychotherapy and behavior change (pp. 298-340). (6th ed.). Hoboken, NY: John Wiley & Sons, Inc.

13. Darchuk, A., Wang, V., Weibel, D., Fende, J., Anderson, T., & Horvath, A. (2000). Form, W.A. I. O. Department of Psychology Ohio University December.

14. DeRubeis, R. J., Cohen, Z. D., Forand, N. R., Fournier, J. C., Gelfand, L. A., & Lorenzo- Luaces, L. (2014). The Personalized Advantage Index: translating research on prediction into individualized treatment recommendations. A demonstration. PloS one, 9, e83875.

15. Devilly, G. J., & Borkovec, T. D. (2000). Psychometric properties of the credibility/expectancy questionnaire. Journal of Behavior Therapy and Experimental Psychiatry, 31, 73-86.

16. Dolev, T., & Zilcha-Mano, S. (2016). The role of alliance in treatment: A mediation model. In preparation.

17. Elkin, I., Shea, M. T, Watkins, J. T, Imber, S. D., Sotsky, S. M., Collins, J. F., Glass, D. R., Pilkonis, P. A., Leber, W. R., Dockerty, J. P., Fiester, S. J., & Parloff, M. B. (1989). NIMH Treatment of Depression Collaborative Research Program: General effectiveness of treatments. Archives of General Psychiatry, 46, 971 -983.

18. Elvins, R., & Green, J. (2008). The conceptualization and measurement of therapeutic alliance: An empirical review. Clinical psychology Review, 28, 1167-1187.

19. Falkenström, F., Granström, F., & Holmqvist, R. (2013). Therapeutic alliance predicts symptomatic improvement session by session. Journal of Counseling Psychology, 60(3), 317-328. doi: 10.1037/a0032258

20. Faul, F., Erdfelder, E., Lang, A.-G., & Buchner, A. (2007). G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behavior Research Methods,39, 175-191.

21. Fawcett, J. P. S. I. J., Epstein, P., Fiester, S. J., Elkin, I., & Autry, J. H. (1987). Clinical management--imipramine/placebo administration manual. NIMH Treatment of Depression Collaborative Research Program. Psychopharmacology Bulletin, 23, 309- 324.

22. First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. (1996). Structured clinical Interview for DSM-IV Axis I Disorders SCID-I: Clinician Version. Washington, D.C.: American Psychiatric Press, Inc.

23. Furukawa, T. A., Cipriani, A., Atkinson, L. Z., Leucht, S., Ogawa, Y., Takeshima, N., ... & Salanti, G. (2016). Placebo response rates in antidepressant trials: a systematic review of published and unpublished double-blind randomised controlled studies. The Lancet Psychiatry, 3(11), 1059-1066. (ECDEU) Assessment Manual for Psychopharmacology. Rockville, MD: National Institute of Mental Health.

24. Hamilton, M. (1967). A rating scale for depression. Journal of Neurology, Neurosurgery, and Psychiatry, 23, 56-62.

25. Hollon, S. N, Evans, M. D., Auerbach, A., DeRubeis, R. J., Elkin, I, Lowery, A., Kriss, M., Grove, W, Tuason, V B., & Piasecki, J. (1988). Development of a system for rating therapies for depression: Differentiating cognitive therapy, interpersonal psychotherapy, and clinical management pharmacotherapy. Unpublished manuscript.

26. Hollon, S. D., Thase, M. E., & Markowitz, J. C. (2002). Treatment and prevention of depression. Psychological Science in the Public Interest, 3, 39-77.

27. Horvath, A. O., Del Re, A. C., Flückiger, C., & Symonds, D. (2011). Alliance in individual psychotherapy. Psychotherapy, 48, 9-16.

28. Hothorn, T., Hornik, K., & Zeileis, A. (2006). Unbiased Recursive Partitioning: A Conditional Inference Framework. Journal of Computational and Graphical Statistics, 15(3), 651--674.

29. Jensen, K., & Kelley, J. M. (2016). The therapeutic relationship in psychological and physical treatments, and their placebo controls. Psychology of Consciousness: Theory, Research, and Practice, 3(2), 132.

30. Kessler, R. C. (2012). The costs of depression. Psychiatric Clinics of North America, 35, 1- 14.

31. Khan, A., Bhat, A., Kolts, R., Thase, M. E., & Brown, W. (2010). Why has the antidepressant– placebo difference in antidepressant clinical trials diminished over the past three decades?. CNS Neuroscience & Therapeutics, 16, 217-226.

32. Khan, A., & Brown, W. A. (2015). Antidepressants versus placebo in major depression: an overview. World Psychiatry, 14(3), 294-300.

33. Lambert, M.J. (2013). The efficacy and effectiveness of psychotherapy. In Lambert, M.J. (Ed.), Bergin and Garfield's handbook of psychotherapy and behavior change. (pp 169-218). New-York: John Wiley & Sons.

34. Leibovich, L., & Zilcha-Mano, S. (2016). Can supportive treatment outperform a more "active" one? In preparation.

35. Levy, K. N., Ellison, W. D., Scott, L. N., & Bernecker, S. L. (2011). Attachment style. Journal of Clinical Psychology, 67, 193-201.

36. Lorenzo-Luaces, L., DeRubeis, R. J., & Webb, C. A. (2014). Client characteristics as moderators of the relation between the therapeutic alliance and outcome in cognitive therapy for depression. Journal of Consulting and Clinical Psychology, 82, 368-373. change. New York: Guilford Press.

37. Morrato, E. H., Libby, A. M., Orton, H. D., deGruy III, MD, F. V., Brent, D. A., Allen, R., & Valuck, R. J. (2008). Frequency of provider contact after FDA advisory on risk of pediatric suicidality with SSRIs. American Journal of Psychiatry, 165(1), 42-50.

38. Posternak, M. A., & Zimmerman, M. (2007). Therapeutic effect of follow-up assessments on antidepressant and placebo response rates in antidepressant efficacy trials Meta- analysis. The British Journal of Psychiatry, 190, 287-292.

39. Preacher, K. J., & Hayes, A. F. (2004). SPSS and SAS procedures for estimating indirect effects in simple mediation models. Behavior research methods, instruments, & computers, 36, 717-731.

40. Preacher, K. J., Zyphur, M. J., & Zhang, Z. (2010). A general multilevel SEM framework for assessing multilevel mediation. Psychological Methods, 15, 209-233.

41. Rush, A. J., Trivedi, M. H., Wisniewski, S. R., Nierenberg, A. A., Stewart, J. W., Warden, D.,. & Fava, M. (2006). Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR* D report. The American Journal of Psychiatry, 163, 1905-1917.

42. Rutherford, B. R., Cooper, T. M., Persaud, A., Brown, P. J., Sneed, J. R., & Roose, S. P. (2013). Less is more in antidepressant clinical trials: a meta-analysis of the effect of visit frequency on treatment response and drop-out. The Journal of Clinical Psychiatry, 74, 703-715.

43. Rutherford, B. R., & Roose, S. P. (2013). A Model of Placebo Effects in Antidepressant Clinical Trials. American Journal of Psychiatry, 170, 723-733.

44. Rutherford, B. R., Sneed, J. R., Roose, S. P. (2009). Does study design affect outcome? the effects of placebo control and treatment duration in antidepressant trials. Psychotherapy and Psychosomatics, 78, 172-181.

45. Rutherford, B. R., Tandler, J., Brown, P. J., Sneed, J. R., & Roose, S. P. (2014). Clinic visits in late- life depression trials: effects on signal detection and therapeutic outcome. The American Journal of Geriatric Psychiatry, 22, 1452-1461.

46. Rutherford, B. R., Wall, M. M., Brown, P. J., Choo, T. H., Wager, T. D., Peterson, B. S., ... & Roose, S. P. (2016). Patient expectancy as a mediator of placebo effects in antidepressant clinical trials. American Journal of Psychiatry.

47. Simpson, J. A., & Rholes, W. S. (Eds). (2015). Attachment theory and research: new directions and emerging themes. New York, NY: Guilford Press.

48. Spielmans, G. I., & McFall, J. P. (2006). A comparative meta-analysis of clinical global impressions change in antidepressant trials. The Journal of Nervous and Mental Disease, 194, 845-852. care for adult and pediatric patients during initiation of antidepressant therapy. The American Journal of Managed Care, 12, 453-461.

49. Stiles, W. B., & Goldsmith, J. Z. (2010). The alliance over time. In J. Muran & J. Barber (Eds.), The Therapeutic Alliance: An Evidence-Based Guide to Practice (pp. 44-62). New York: Guilford Press.

50. Strasser, H., & Weber, C. (1999). On the asymptotic theory of permutation statistics. Mathematical Methods of Statistics, 8, 220–250.

51. Strobl, C., Malley., J., & Tutz, J. (2009). An Introduction to Recursive Partitioning: Rationale, Application, and C haracteristics of Classification and Regression Trees, Bagging, and Random forests. Psychological Methods, 14(4), 323–348.

52. Tracey, T. J., & Kokotovic, A. M. (1989). Factor structure of the Working Alliance Inventory. Psychological Assessment: A Journal of Consulting and Clinical Psychology, 1, 207–210.

53. World Health Organization. (2004). The World Health Report 2004: Changing History, Annex Table 3: Burden of disease in DALYs by cause, sex, and mortality stratum in WHO regions, estimates for 2002. Geneva: WHO, 2004.

54. Zhang, Z. (2014). Monte Carlo based statistical power analysis for mediation models: methods and software. Behavior research methods, 46(4), 1184-1198.

55. Zilcha-Mano, S. (2016a). Is alliance really therapeutic? A systematic answer based on recent methodological developments. American Psychologist.

56. Zilcha-Mano, S. (2016b). New analytic strategies help answer the controversial question of whether alliance is therapeutic in itself. World Psychiatry, 15(1), 84-85.

57. Zilcha-Mano, S., Adler, G., & Shahar, B. (2016). Alliance development within- and between- sessions as predictors of treatment outcome. Under review.

58. Zilcha-Mano, S., & Errázuriz, P. (2015). One size does not fit all: examining heterogeneity and identifying moderators of the alliance–outcome association. Journal of Counseling Psychology, 62, 579-591. http://dx.doi.org/10.1037/cou0000103

59. Zilcha-Mano, S., & Errázuriz, P. (2016). Early development of mechanisms of change as a predictor of subsequent change and treatment outcome: The case of the working alliance. Accepted with minor changes, Journal of Consulting and Clinical Psychology.

60. Zilcha-Mano, S., Keefe, J., Rubin, A., & Barber J. P. (2016). Dropout in treatment for depression: Translating research on prediction into individualized treatment recommendations. Journal of Clinical Psychiatry

61. Zilcha-Mano, S., Muran, C. J., Hungr, C., Eubanks-Carter. C. F., Safran, J., & Winston. A. (2016). The relationship between alliance and outcome: Analysis of a two-person Psychology, 84(6), 484-496.

62. Zilcha-Mano, S., Roose, S. P., Barber, J. P., & Rutherford, B. R. (2015). Therapeutic alliance in antidepressant treatment: cause or effect of symptomatic levels?. Psychotherapy and Psychosomatics, 84, 177-182.

New York State Psychiatric Institute
Developing New Clinical Management Strategies for Antidepressant Treatments

## OVERVIEW

Below is a summary of the study that you are asked to participate in. This outline is meant to be a guide for you to use while considering the study and reading the consent form. It is not meant to replace the consent form, which you will have to sign if you decide to participate in the study. The consent form contains detailed information about the study and about the risks which you will need to consider before making your decision. Read the consent form carefully and discuss it with others before deciding to take part. And remember that, even if you agree to participate, you can change your mind at any time.

## VOLUNTARY

As with all research, this is a voluntary study, and you do not have to participate if you do not want to. Also, you may stop participating at any time.

## ALTERNATIVE TREATMENTS/ALTERNATIVES TO PARTICIPATION

The alternative to participating in this study is to seek treatment outside the research project. Other medications in the same family as escitalopram are available (e.g., fluoxetine (Prozac), sertraline (Zoloft), etc.) as well as in different families of medications, such as duloxetine. In addition, psychotherapy may be helpful with depression, whether on its own or combined with medication.

## PROCEDURES

- You have a 50/50 chance (like flipping a coin) of being assigned to one of two tracks: RFM Track, weekly study visits or CFM, monthly study visits, both tracks being antidepressant medication vs. placebo and for 8 weeks in duration
- If you still have depressive symptoms after four weeks on the pills you are given, the dose will be increased to two pills (either 20mg of escitalopram of 2 placebo pills, depending on the group to which you are assigned)
- If you previously have not tolerated or had an adverse reaction to escitalopram, you will be started on 30 mg of duloxetine. After 4 weeks, if you have not responded to the medication, you will be increased to 60 mg of duloxetine vs placebo.
- If you respond, you will come monthly to our research clinic for three months after Week 8 to continue the double-blind study
- At the end of the study you will be informed whether you received medication or placebo, and you are entitled to 3 months of free doctor visits in the clinic and at least 1 month of free medication.

## RISKS AND INCONVENIENCES

This study includes some risks and discomforts (please refer to the consent form for further details and explanations of these risks). These include the risk that your depression may worsen if you are assigned to placebo and do not receive actual medication for your condition until after the 2 to 5-month study is over. For the duration of the study, you may also continue taking medication which is not effective for you before trying another medication. The most common side effects reported for escitalopram are nausea, insomnia,

and inability to have an orgasm. The most common side effects reported for duloxetine are insomnia, constipation or diarrhea, dry mouth, sweating, nausea, and a small increase in blood pressure.

Furthermore, specifically for any potential in person visits to NYSPI, individuals are at increased risk for exposure to COVID-19 both in transit to NYSPI as well as during their time at NYSPI. Procedures are in place to minimize this risk. We plan to offer car transportation subject to a maximum of $50 each way, which minimizes exposure to public transportation for those participants. At NYSPI, personal protective equipment such as masks will be utilized at all times both by staff and participants, and social distancing will be adhered to when possible (exceptions exist for procedures such as blood draws and EKGs). Screen shields between patient and staff will be used during neuropsychological testing to further minimize exposure risk.

BENEFITS

This research study is not meant to benefit you directly.

QUESTIONS

You may contact the study doctor, Bret Rutherford, MD at 646-774-8660 with any questions.

NEW YORK STATE PSYCHIATRIC INSTITUTE DEVELOPING NEW CLINICAL MANAGEMENT STRATEGIES FOR ANTIDEPRESSANT TREATMENTS

The following outline is meant to serve as a guide to help you learn about this research study and decide whether you want to take part. It does not replace the consent form that you will be asked to read and sign. The consent includes much more information you'll need to make a decision. Read the consent form carefully, ask questions, and take your time or speak to others if you want to before you make your choice. Remember, even if you agree to take part in research you can change your mind at any time.

- This is a research study in which you may receive treatment with escitalopram (Lexapro), duloxetine (Cymbalta) or placebo. Escitalopram and duloxetine are FDA approved medications indicated for the treatment of major depressive disorder. A placebo is a sugar pill.
- The purpose of this study is to investigate whether individuals who have study visits with a doctor once per month respond to treatment differently from individuals who have study visits with a doctor once per week.
- At the beginning of the study, you will be given a physical examination, an electrocardiogram (EKG), have your blood drawn, and fill out some psychological tests.
- The first phase of the study lasts 8 weeks, and participants in this study will return to our clinic for visits either weekly or monthly. Individuals being seen on a monthly visit schedule will speak to members of the research team between monthly study visits.
- The second phase of the study lasts three months and is only for those who respond to their assigned medication. Individuals in the second phase will return to our clinic for monthly visits and speak with members of the research staff by telephone between monthly study visits.
- The main risk of participating in this study is that your depression may worsen if you are assigned to placebo and do not receive actual medication for the duration of the study.
- The most common side effects reported for escitalopram are nausea, insomnia, and inability to have an orgasm.
- The most common side effects reported for duloxetine are insomnia, constipation or diarrhea, dry mouth, sweating, nausea, and a small increase in blood pressure.
- You will not be charged for any procedures that are a part of this study including the study medication and the clinical interviews.
- You do not have to participate in this study to receive treatment for your depression. The alternative to participating in this study is to seek treatment outside the research project.

NEW YORK STATE PSYCHIATRIC INSTITUTE DEVELOPING NEW CLINICAL MANAGEMENT STRATEGIES FOR ANTIDEPRESSANT TREATMENTS

PURPOSE OF STUDY

The purpose of this study is to investigate whether individuals who have in-person visits with a doctor once per month respond to treatment differently from individuals who have in-person visits with a doctor once per week. If you are eligible and decide to participate in the study, you have a 50/50 chance (like flipping a coin) of being assigned to one of two groups. You are being asked to participate in this study because you have been diagnosed with Major Depressive Disorder and you are between the ages of 18 and 75.

This research study is a medication trial. Participants in this study will be randomly assigned to either treatment medication or a sugar pill. Escitalopram is an FDA approved medication indicated for the treatment of major depressive disorder. It is the default medication for the study. If you previously have not tolerated or had an adverse reaction to escitalopram, you will be treated with duloxetine. A placebo is a sugar pill. You may receive treatment for depression with FDA approved medications, escitalopram (Lexapro) or duloxetine (Cymbalta), or placebo (a sugar pill). Escitalopram is a Selective Serotonin Reuptake Inhibitor (SSRI) medication that appears to help with symptoms of depression by increasing the availability of specific chemicals in the brain. Duloxetine is selective serotonin and norepinephrine reuptake inhibitor (SSNRI) that are thought to work by increasing the amount of mood enhancing chemicals in the brain. Participants in this study will **return to our clinic for visits** either weekly or monthly. Individuals being seen on a monthly visit schedule will speak with members of the research staff by telephone between monthly study visits.

The source of funding for this study is the Binational Science Foundation.

VOLUNTARY

Participation in this research study is voluntary. If you decide not to participate, or if you later decide to stop participating, you will not lose any benefits to which you are otherwise entitled. A decision not to participate or withdraw your participation will not affect your current or future treatment at the New York State Psychiatric Institute of Columbia University Irving Medical Center.

ALTERNATIVE TREATMENT

You do not have to participate in this study to receive treatment for your depression. The alternative to participating in this study is to seek treatment outside the research project. Other medications in the same family as escitalopram are available (e.g., fluoxetine (Prozac), sertraline (Zoloft), etc.) as well as in different families of medications, such as duloxetine. In addition, psychotherapy may be helpful with depression, whether on its own or combined with medication.

STUDY PROCEDURES

During COVID-19 pandemic:

In an effort to decrease direct contact and abide by social distancing guidelines, some of your visits may be conducted remotely using the telephone or WebEx, a HIPAA-compliant video teleconferencing. The consent discussion process will include discussion and explanation of WebEx, a HIPAA-compliant video communication platform. The study team will address any concerns you may have, such as access to a private space in which to take calls, or accessibility—access at home to adequate devices, cell signal, or WIFI. The evaluation procedures will consist of two separate visits: a virtual visit followed by an in-person visit. During the virtual component of the evaluation, you will be interviewed (via video conference call or phone call) by a doctor and a research assistant from the Clinic for Aging, Anxiety, and Mood Disorders. You will be asked to complete several assessments that ask about your psychological and physical health. If you may be eligible based on the virtual evaluation, you will then be scheduled for an in-person evaluation at the clinic in order to complete the remaining assessments that are necessary to determine study eligibility. During the in-person visit, you may be asked to complete additional measures of physical functioning, such as a physical exam, a cardiogram, provide a blood sample, about four tablespoons, for routine testing, and/or provide a urine sample for routine testing and a drug screen. If you are not eligible, you will be referred to appropriate options for further treatment. If you are eligible and continue to wish to participate, you will proceed with the next part of the study.

If you are eligible and decide to participate in the study, you have a 50/50 chance (like flipping a coin) of being assigned to one of two groups. This study utilizes design randomizing patients to "Research Frequency Management" (RFM Track, weekly study visits) vs. "Community Frequency Management" (CFM Track, every 4 weeks study visits) and antidepressant medication vs. placebo. If you are assigned to the RFM group, you will return to our research clinic for weekly in-person visits (at the beginning of the study and then Weeks 1-8). If you are assigned to the CFM group you will return to our research clinic for in-person visits every 4 weeks (at the beginning of the study, Week 4, and Week 8) with every 2-week telephone check-ins in between clinic visits (Weeks 2 and 6). If you respond to the treatment, we will continue the double-blind study for three months. After Week 8, you will return to our research clinic for in-person visits every 4 weeks with 2-week telephone check-ins in between clinic visits. Questionnaires and assessments will be administered using Qualtrics, a HIPAA-compliant online application. Regardless of which study group you are assigned to, you will be randomly assigned to receive treatment with the antidepressant medication escitalopram (or duloxetine, if you previously have not tolerated or had an adverse reaction to escitalopram) or pill placebo (a sugar pill). At the end of the study you will be informed whether you received medication or placebo.

If you are assigned to the study group having a monthly visit schedule, you will be asked to participate in a telephone check-in between clinic appointment. Each check-in will involve speaking with the doctor treating you as well as other members of our research staff for about 30 minutes. You may request to arrange an additional in-person visit to our clinic at any time during the study. We will automatically schedule an additional in- person visit for you if you are experiencing a significant new medication side effect or if your condition worsens substantially. You should also know that you will be provided with the beeper number of a physician who is available to speak with you 24hrs per day for emergencies.

At the beginning of the study, you will be given a physical examination, an electrocardiogram (EKG), have your blood drawn, and fill out some psychological tests. The total amount of blood taken for this study is

about two tablespoons. You will be asked to return once a week if you are assigned to the RFM Track, or once a month if you are assigned to the CFM Track to see one of the study doctors and talk about how you are feeling. These meetings will last about 30 minutes. If you still have depressive symptoms after four weeks on the pills you are given, the dose will be increased to two pills (either 20mg of escitalopram or 60 mg duloxetine) or 2 placebo pills, depending on the group to which you are assigned). You will receive free medication for the duration of the study.

During the study, if your doctor feels your condition worsens significantly, the current treatment will be stopped, and you will be offered different treatments for your depression. Your doctor may stop your participation in the study at any time without your consent if you do not comply with the study procedures or for other reasons. The research study will end after 8 weeks if you do not respond to treatment (either medication or placebo). If you respond, you will come monthly to our research clinic for three months to continue the double-blind study.

Following your participation in the study, you will receive 3 months of free doctor visits in the clinic and at least 1 month of free medication. Every effort will be made to provide free medication for 3 months total, but we cannot guarantee the availability of free medication beyond 1 month. Video Recording if you agree, your study visits will be video recorded. The purpose of video recording the interview is to check the characteristics of the interview being delivered and to evaluate the reliability of our interviewers. You do not have to agree to be video recorded in order to be evaluated. A separate consent form will document whether you agree to be video recorded.

RISKS

The main risk of the study is that your depression may worsen if you are assigned to placebo and do not receive actual medication for your condition until after the 2 to 5-month study is over. If you need to be tapered off (dose gradually reduced to zero) of your current medication before taking the study drug or placebo, the amount of time during which you are not receiving actual or enough medication could be one additional month. You may also be assigned to the study group having monthly doctor visits, meaning that you could receive placebo (no medication) and have 4 weeks between in person doctor visits. For the duration of the study, you may also continue taking medication which is not effective for you before trying another medication.

The most common side effects reported for escitalopram are nausea, insomnia, and inability to have an orgasm. Less common side effects reported for escitalopram include constipation or diarrhea, dry mouth, dizziness, headache, and sedation. The most common side effects reported for duloxetine are insomnia, constipation or diarrhea, dry mouth, sweating, nausea and small increases in blood pressure. The less common side effects of duloxetine are abnormal orgasm, fainting, and headache. The Food and Drug Administration (FDA) has concluded that antidepressants increase the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. No suicides occurred in any of these studies. It is unknown whether the suicidality risk in children and adolescents extends to longer-term use, i.e., beyond several months. It is also unknown whether the suicidality risk extends to adults, although the FDA has concluded that suicidality risk extends to individuals up to age 24. Please contact a study team member immediately if you are feeing worse or suicidal.

You cannot participate in the study if you abuse alcohol or drugs. In any case, you should be careful about drinking alcohol, since it may have a greater effect on you in combination with medication. You must not take monoamine oxidase inhibitor (MAOI) drugs (tranylcypromine or Parnate, phenelzine or Nardil) during the study or within five weeks of ending the study (after the study). Serious reactions, including death, have been reported when MAOIs are co-administered with medications like escitalopram (the study drug). When your blood is drawn, there is a small risk you may be left with a bruise that will resolve within a few days. Blood taken for research purposes will remain confidential.

The FDA has directed the manufacturers of all antidepressant medications to add a "black box" warning that describes the increased risk of suicidality related to antidepressant use in children and adolescents (but not in adults). The warning urges that adults with MDD or co-morbid (two illnesses occurring together) depression in the setting of other psychiatric illness being treated with antidepressants should be observed closely for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The procedures of this study involving medication with escitalopram or duloxetine are low risk during pregnancy or breastfeeding, especially compared to the risk of depression in the mother. Still, these medications cannot be considered safe during pregnancy or breast-feeding, because there is concern about causing permanent damage to a developing fetus or young infant. Therefore, you should not participate in this research if you are pregnant, or breast feeding a baby, or if you plan to become pregnant during the time you are in the study.

Should you decide to attempt to have a child or feel there is any possibility you may be pregnant, you should notify your study physician immediately. If the pregnancy test is positive, you will not be able to participate in the study. It is important to understand that even if a pregnancy test is negative, you could still be pregnant, because these tests cannot detect very early pregnancies (that is, within the first few days). If you are sexually active, it is very important that you use an effective form of birth control before and throughout your study participation. Methods of birth control considered to be effective include double barrier methods (condom plus spermicide, or diaphragm plus spermicide), IUDs, and oral contraceptive pills. It is important to understand that even if you use an effective birth control method, there is still a chance you could become pregnant. Also, if you do not use the birth control method consistently (for example if you don't use condom/spermicide some of the time) you may become pregnant. If you think you might be pregnant, it is important to let the study team know right away. The study team will conduct a pregnancy test and help you decide what to do next

Furthermore, specifically for any potential in person visits to NYSPI, individuals are at increased risk for exposure to COVID-19 both in transit to NYSPI as well as during their time at NYSPI. Procedures are in place to minimize this risk. We plan to offer car transportation subject to a maximum of $50 each way, which minimizes exposure to public transportation for those participants. At NYSPI, personal protective equipment such as masks will be utilized at all times both by staff and participants, and social distancing will be adhered to when possible (exceptions exist for procedures such as blood draws and EKGs). Screen shields between patient and staff will be used during neuropsychological testing to further minimize exposure risk.

BENEFITS

You may not benefit from this study, and no benefit is in any way guaranteed as a result of your participation.

CONFIDENTIALITY

Your records will be stored in a locked file and will be available to research staff, and to Federal, State and Institutional regulatory personnel (who may review records as part of routine audits). Representatives of the state and institutional regulatory personnel may review your records to ensure compliance with study design. There are legal advocacy organizations that have the authority under State Law to access otherwise confidential records, though they cannot be redisclosed without your consent. All records will be kept confidential to the extent permitted by law. Your name and other personal identifying information will be stored in an electronically secure database at New York State Psychiatric Institute. Electronically stored data will be accessible only by password known to the study investigators and research assistants. Patient questionnaires and some assessments at Week 0 and for the duration of the study will be administered using Qualtrics, an application accessible by smart phone or computer, by which raters and participants can access and complete online surveys. Qualtrics is an online application that allows patients to complete online surveys and assessments in a data-secure platform while maintaining compliance with existing health privacy laws. These virtual visits will be conducted through Zoom which is a HIPAA-compliant platform or through secure Facetime call.

There may be future analyses of all the research data conducted by the study investigators, yet unplanned, dealing with other aspects of illnesses of late-life. Additionally, research data may also be shared and provided to other investigators for the purpose of secondary analyses or distributed to another investigator for future research studies. The results of this study may also be published or presented at professional meetings. In each of these instances, all personal identifiers (such as your name, birth date) will have been removed (de-identified) and replaced with a specific code number. The information linking this code number to your identity will be kept in a separate, secure location.

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.

COMPENSATION AND ECONOMIC CONSIDERATIONS

Due to the COVID-19 pandemic, we will not be using cash as a form of compensation until further notice. We will be using visa gift cards (either physical or virtual) instead, along with the option of a lump-sum check.

You will not be charged for any procedures that are a part of this study including the study medication and the clinical interviews.

To compensate you for the time required for each weekly study visit, we offer $20 at the Week 0 visit and $20 for each in person visit thereafter. This money will be paid by cash at the conclusion of each of these visits. For the RFM track, compensation is up to $180 for the Acute Phase and up to $60 for the Continuation Phase for a total of $240. For the CFM track, compensation is up to $60 for the Acute Phase and up to $60 for the Continuation Phase for a total of $120.

IN CASE OF INJURY

Federal regulations require that we inform participants about our institution's policy with regard to compensation and payment for treatment of research-related injuries.

If you believe that you have sustained an injury as a result of participating in a research study, you may contact the Principal Investigator at (646) 774-8660 so that you can review the matter and identify the medical resources that may be available to you.

In case of injury, New York State Psychiatric Institute, Columbia University and New York Presbyterian Hospital will furnish that emergency medical determined to be necessary by the medical staff of this hospital. Please be aware that you will be responsible for the cost of such care, either personally or through your medical insurance or other form of medical coverage. No monetary compensation for wages lost as a result of injury will be paid to you by Research Foundation for Mental Hygiene, the New York State Psychiatric Institute, Columbia University, or by New York Presbyterian Hospital. However, you should be aware that by signing this consent form, you are not waiving any of your legal rights to seek compensation through the courts.

QUESTIONS

If you have further questions about the research procedures, or about your response to the procedures, research staff members are available to answer them to the best of their ability. You can reach Dr. Bret Rutherford at 646-774-8660 during general business hours. In an emergency, you may reach the on-call doctor at 917-786-6940, 24 hours per day. If you have general questions, you may contact the research coordinator at 646-774-8677.

We will notify you of any significant new findings that may relate to your willingness to continue to participate.

If you have any questions about your rights as a research participant, want to provide feedback, or have a complaint, you may call the NYSPI Institutional Review Board (IRB). (An IRB is a committee that protects the rights of participants in research studies). You may call the IRB Office at (646)774-7155 during regular office hours.

You will be given a copy of this consent form to keep.

DOCUMENTATION OF CONSENT

I voluntarily agree to participate in the research study described above

Signature Date

Print Name

I have discussed the proposed research with this participant [or patient], and, in my opinion, this participant [or patient] understands the benefits, risks and alternatives (including nonparticipation) and is capable of freely consenting to participate in this research.

Signature of Person Obtaining Consent Telephone Date

Print Name