

University of Pittsburgh
Institutional Review Board

3500 Fifth Avenue
Ground Level
Pittsburgh, PA 15213
(412) 383-1480
(412) 383-1508 (fax)
<http://www.irb.pitt.edu>

Memorandum

To: Howard Aizenstein
From: IRB Office
Date: 3/15/2018
IRB#: [MOD18010096-02](#) / PRO18010096
Subject: Neural mechanisms of monoaminergic engagement in late-life depression treatment response (NEMO - 2.0)

The University of Pittsburgh Institutional Review Board reviewed and approved the requested modifications by expedited review procedure authorized under 45 CFR 46.110 and 21 CFR 56.110.

Modification Approval Date: 3/15/2018
Expiration Date: 2/5/2019

For studies being conducted in UPMC facilities, no clinical activities that are impacted by the modifications can be undertaken by investigators until they have received approval from the UPMC Fiscal Review Office.

Please note that it is the investigator's responsibility to report to the IRB any unanticipated problems involving risks to subjects or others [see 45 CFR 46.103(b)(5) and 21 CFR 56.108(b)]. Refer to the IRB Policy and Procedure Manual regarding the reporting requirements for unanticipated problems which include, but are not limited to, adverse events. If you have any questions about this process, please contact the Adverse Events Coordinator at 412-383-1480.

The protocol and consent forms, along with a brief progress report must be resubmitted at least one month prior to the renewal date noted above as required by FWA00006790 (University of Pittsburgh), FWA00006735 (University of Pittsburgh Medical Center), FWA00000600 (Children's Hospital of Pittsburgh), FWA00003567 (Magee-Womens Health Corporation), FWA00003338 (University of Pittsburgh Medical Center Cancer Institute).

Please be advised that your research study may be audited periodically by the University of Pittsburgh Research Conduct and Compliance Office.



[\[reviewer notes→\]](#)

Provide a short title for this study (200 characters or less):

Neural mechanisms of monoaminergic engagement in late-life depression treatment response (NEMO - 2.0)

T1.0

Select the type of application:

New Research Study

T2.0

Is the proposed research study limited to the inclusion of deceased individuals?

* No

T2.1

Are any research activities being conducted at the VA Pittsburgh Healthcare System or with VA funds?

* No

[\[reviewer notes→\]](#)

T3.0

What is the anticipated risk to the research participants?

Greater Than Minimal Risk

[\[reviewer notes-\]](#).

CS1.0 What is the reason for this submission?

New Research Protocol Submission

CS1.1

Has this research study been approved previously by the University of Pittsburgh IRB?

* No

CS1.1.1

Has this research study (or a substantially similar research study) been previously disapproved by the University of Pittsburgh IRB or, to your knowledge, by any other IRB?

* No

[\[reviewer notes-\]](#)

CS2.0

Title of Research Study:

Neural mechanisms of monoaminergic engagement in late-life depression treatment response (NEMO - 2.0)

CS2.0.1

Requested approval letter wording:

CS2.1

Research Protocol Abstract:

In this competing renewal (Year 11) of our R01 using fMRI to study late-life depression (LLD) pharmacotherapy (R01MH076079), the primary aim is to characterize functional connectivity changes associated with initial medication exposure (12-hour challenge). Our preliminary data suggests that these initial fMRI changes reflect monoaminergic engagement, regardless of monoaminergic class, and predict later treatment response. In the proposed study we test a neural systems level model that response in LLD is mediated by acute pharmacologically-induced changes in cognitive and affective large scale network. Depression in older adults is frequently disabling and is often resistant to first-line treatments, requiring more prolonged treatment trials than in younger adults, mainly due to its heterogeneous pathophysiology (e.g. vascular and degenerative brain changes). Currently, there is little neurobiological data to guide changing or augmenting antidepressant medications. Thus, there has been a heightened focus on tailoring treatment to optimize outcome as described in the 2015 NIMH draft strategic plan (strategy 3.2). While antidepressant clinical response may take up to 8 weeks, recent studies suggest that physiologic changes, as measured with pharmacologic fMRI (phMRI) are seen within 12 hours of starting a new monoaminergic antidepressant (32). For this proposal, we focus on three major Cognitive and Affective Networks (CAN): the Default Mode Network (DMN), the Salience Network (SN) and the Executive Control Network (ECN). The proposed model suggests that monoaminergic engagement leads to core CAN changes, changes that subsequently are related to overall clinical response as well as response in specific symptom clusters such as negative bias, somatizations/anxiety and cognitive control. The same networks that are functionally connected while individuals are at rest, are also selectively engaged during tasks. Our prior work shows that pharmacotherapy – regardless of type of antidepressant used – engages these specific networks at rest and during standard cognitive and affective tasks. Given the role of cerebrovascular disease in LLD treatment response, we will also explore the moderating role of vascular burden on the proposed association between CAN engagement and treatment response. We will recruit 100 older adults with LLD who will be randomized to receive treatment with either a very specific serotonin reuptake inhibitor (escitalopram) or a norepinephrine reuptake inhibitor (levomilnacipram). A pair of fMRI scans one day apart will be used to measure FC associated with medication titration. We propose to use a very early (12 hours after initiation of treatment) biomarker of treatment response, which, when validated, would decrease substantially the waiting time between medication changes. Additionally, our study will further our understanding of the acute neural system changes associated with monoaminergic antidepressants; this knowledge of mechanism is essential for both guiding LLD treatment research, and serving as an engagement target in LLD treatment research.

CS2.2

Select the category that best describes your research:

Hybrid - includes aspects of BOTH types of research (check this option if your research is mainly social/behavioral but also involves specimen collection or blood draws to look at biological measures)

[\[reviewer notes-\]](#)

CS3.0

Name of the Principal Investigator:

[Howard Aizenstein](#)

Note: Adjunct faculty of the University, including lecturers and instructors, are not permitted to serve as a PI or Faculty Mentor but may serve as co-investigators. Refer to [Chapter 4](#) on the HRPO website for more information.

CS3.1 Affiliation of Principal Investigator:

UPitt faculty member

If you chose any of the **Pitt options**, please indicate the specific campus:

[Main Campus - Pittsburgh](#)

If you chose the UPitt faculty member option, provide the PI's **University Faculty Title**:

Professor of Psychiatry, Bioengineering, and Clinical and Translational Science

CS3.2 Address of Principal Investigator:

[REDACTED]

CS3.3 Recorded Primary Affiliation of the Principal Investigator:

U of Pgh | School of Medicine | Psychiatry

CS3.4 Identify the School, Department, Division or Center which is responsible for oversight of this research study:

[U of Pgh](#) | [School of Medicine](#) | [Psychiatry](#)

CS3.5 Telephone Number of Principal Investigator:

[REDACTED]

CS3.6 Recorded Current E-mail Address of Principal Investigator to which all notifications will be sent:

[REDACTED]

CS3.7 Fax Number:

[REDACTED]

CS3.8 Does this study include any personnel from Carnegie Mellon University, and/or use any CMU resources or facilities (e.g., Scientific Imaging and Brain Research Center (SIBR))?

* No

CS3.9 Is this your first submission, as PI, to the Pitt IRB?

* No

[\[reviewer notes→\]](#)

CS4.0**List of Co-Investigators:**

Last	First	Organization
Andreescu	Carmen	U of Pgh School of Medicine Psychiatry
Butters	Meryl	U of Pgh School of Medicine Psychiatry
Kim	Tae	U of Pgh School of Medicine Radiology
Tudorascu	Dana	U of Pgh School of Medicine Medicine

[\[reviewer notes-\]](#)**CS5.0 Name of Primary Research Coordinator:**[Rachel Berta](#)**CS5.1 Address of Primary Research Coordinator:****CS5.2 Telephone Number of Primary Research Coordinator:****CS6.0 Name of Secondary Research Coordinator:**

Dana Williams

CS6.1 Address of Secondary Research Coordinator:**CS6.2 Telephone Number of Secondary Research Coordinator:**

412-246-5924

CS6.3 Key Personnel/Support Staff (Only list those individuals who require access to OSIRIS):

Last	First	Organization
Bednar	Samantha	UPMC Hospital Divisions WPIC
Buente	Kara	UPMC Hospital Divisions WPIC
Cyphers	Hayley	UPMC Hospital Divisions WPIC
DeLozier	Isaac	UPMC Hospital Divisions WPIC
Devine	David	UPMC Hospital Divisions WPIC
Frye	Catherine	UPMC Hospital Divisions WPIC
Green	Jasmine	U of Pgh College of General Studies General Administration
Krystek	Jeffrey	UPMC Hospital Divisions WPIC
Lagattuta	Sally	U of Pgh School of Medicine Psychiatry
Lakis	Angela	UPMC Other
Rogers	Shannon	U of Pgh School of Medicine Psychiatry
Runk	Ashlyn	UPMC Hospital Divisions WPIC
Tamburo	Erica	UPMC Hospital Divisions WPIC
Tozzie	Caitlin	UPMC Other
Truong	Cecile	U of Pgh Faculty of Arts and Sciences Psychology
Zmuda	Michelle	UPMC Hospital Divisions WPIC

[\[reviewer notes-\]](#)

CS7.0 Will this research study use any [Pediatric PittNet](#) or Clinical and Translational Research Center (CTRC) resources?

No

[\[reviewer notes-\]](#)

CS8.0 Select the entity responsible for scientific review.

WPIC SRC - Western Psychiatric Institute and Clinic Scientific Review Committee. Note: Please upload the Research Committee approval notification in the "Supporting Documentation" section.

[\[reviewer notes-\]](#)

CS9.0 Does this research study involve the administration of an investigational drug or an FDA-approved drug that will be used for research purposes?

* Yes

CS9.1 Do you plan to utilize the Investigational Drug Service (IDS) to dispense the drug?

* Yes

CS10.0 Is this research study being conducted under a University of Pittsburgh-based, sponsor-investigator IND or IDE application?

* No

If YES, you are required to submit the IND or IDE application and all subsequent FDA correspondence through the Office for Investigator-Sponsored IND and IDE Support (O3IS). Refer to applicable University policies posted on the O3IS website (www.O3IS.pitt.edu).

[\[reviewer notes→\]](#)

CS11.0

Use the 'Add' button to upload one or more of the following:

- the sponsor protocol (including investigator initiated studies) and/or other brochures
- the multi-center protocol and consent form template, *if applicable*

Name Modified Date

Is this research study supported in whole or in part by industry? This includes the provision of products (drugs or devices).

* No

Is this a multi-centered study?

* No

[\[reviewer notes→\]](#)

CS12.0

Does your research protocol involve the evaluation or use of procedures that emit ionizing radiation?

* No

CS13.0

Does this research study involve the deliberate transfer of recombinant or synthetic nucleic acid molecules into human subjects?

* No

Upload Appendix M of NIH Guidelines:

Name Modified Date

CS14.0

Are you using UPMC facilities and/or UPMC patients during the conduct of your research study?

* Yes

If Yes, upload completed Research Fiscal Review Form:

Name Modified Date

[NEMOUPMCFiscal_Form_Updated2-21-2018.docx](#)

2/21/2018 2:11 PM

[\[reviewer notes→\]](#)

CS15.0

Indicate the sites where research activities will be performed and/or private information will be obtained.

Choose all sites that apply and/or use **Other** to include sites not listed:

Sites:

[University of Pittsburgh](#)

UPMC

University of Pittsburgh

Campus: _____

Main Campus - Pittsburgh

List university owned off-campus research sites if applicable:

UPMC

Sites: _____

UPMC Presbyterian

UPMC Western Psychiatric Institute & Clinic

If you selected **School**, **International** or **Other**, list the sites:

***For research being conducted at non Pitt or UPMC sites, upload a site permission letter granting the researcher permission to conduct their research at each external site:**

Name Modified Date

CS15.1 Have you, [Howard Aizenstein](#), verified that all members of the research team have the appropriate expertise, credentials, and if applicable, hospital privileges to perform those research procedures that are their responsibility as outlined in the IRB protocol?

* Yes

CS15.2 Describe the availability of resources and the adequacy of the facilities to conduct this study:

* This study brings together a highly experienced research team with experience in study coordination, recruitment, psychiatric evaluations, administration of research quality assessments and tools, and the actual implementation and conduct of studies. There is sufficient private office space available for investigators and project staff.

Geriatric Psychiatry Neuroimaging Lab (GPN) (Director: Howard Aizenstein, M.D., Ph.D. http://www.gpn.pitt.edu/GPN/About_Us.html): GPN uses structural and functional magnetic resonance imaging (fMRI) to study the brain changes associated with aging. On-going functional magnetic resonance imaging (fMRI) studies aim to relate the cognitive and affective symptoms in the elderly to the functional neuroanatomy. The GPN Lab is located in Thomas Detre Hall, the main building of Western Psychiatric Institute and Clinic (WPIC), and is fully equipped to conduct neuroimaging analyses and data management. The GPN image processing lab consists of 25 multi-processor Macintosh workstations connected on a GB local area network to a Mac Pro server. The computers share access to an array of RAID drives containing a total of 35 terabytes of storage. The data are backed up monthly to multiple tape sets using an LT05 Quantum Tape Drive and Retrospect, tapes, which are stored both on and off-site. The workstations have all necessary software for structural and functional neuroimaging analysis, including Matlab, AFNI, NIS, ITK, VTK, MIPAV, ImageJ, and FSL. Additionally, the computers

run the Microsoft Office software suite, including Word, PowerPoint, and Excel. All computers are connected (via a 100 MB line) to the UPMC network (in addition to the GB LAN). All computers utilize the WPIC office of Academic Computing (OAC) Network.

The GPN office space includes twelve offices and a computer lab, which contains networked image processing workstations. Office space is provided for faculty, research staff, post-doctoral fellows, and graduate and undergraduate students.

Magnetic Resonance (MR) Research Center

The MR Research Center (MRRRC) is a state of the art facility located [REDACTED] UPMC Presbyterian supporting an MR Research Program. The Program is built around development and application of acquisition and image reconstruction schemes for clinical as well as research MRI studies. The Center opened September 1994. The center has access to medical support facilities and staff. All scanners are equipped with MRI-compatible cardiac EKG equipment and blood oxygen monitors. The scanners are operated by registered MR Technologists..

Instrumentation: The MR Research Center houses three Siemens Medical Systems 3 Tesla Magnetom TIM Trio scanners. TIM, Total Imaging Matrix, is an innovative RF system and coil design that allows for whole body scanning without coil changes and subject repositioning. These systems are dedicated to research studies, primarily focused on the development of functional MRI, investigation of novel contrast mechanisms, and applications in Neuroscience, Psychology, and Neurosurgery. The magnet rooms are magnetically, acoustically and RF shielded. The compact superconducting magnet (198cm or 6' 6" long) can accommodate a 50cm field of view and has excellent homogeneity, typically 1.2 ppm, based on 24 plane plt, 50cm Diameter Sphere Volume. The Audiocomfort feature combines hardware and software to reduce acoustic noise up to 20 dB (A) compared to conventional 3T systems. The system has a top of the line gradient system with 45mT/m maximum amplitude, and a slew rate of 200T/m/sec with a 100% duty cycle. It also includes up to 102 seamlessly integrated coil elements with up to 32 RF channels and PAT up to 16. All conventional and echo planar MR imaging and MR angiographic functions (both phase contrast and time-of-flight methods) are supported. Two of the scanners operate under version VB15 software that provides multi-nuclear capabilities not previously available under the TIM platform. The third scanner was recently upgraded to the TIM platform with version VB17 software and is dedicated to the Osteoarthritis Initiative, or OAI, a multicenter, longitudinal, prospective observational study of knee osteoarthritis (OA).

The fifth scanner, a Siemen's Biograph mMR scanner, was installed in the MR center on May 2012 and is now operational. This state-of-the-art scanner allows simultaneous acquisition of whole-body MR and PET. The mMR utilizes a 3T niobium-titanium magnet (length: 163 cm; bore: 60 cm), an actively shielded whole-body gradient coil (length: 159 cm; amplitude: 45 mT/m; slew rate: 200 T/m/s), and a radiofrequency body coil (peak power: 35 kW; transmitter bandwidth: 800 kHz). The MR system can acquire a 0.5–50 cm FOV, with a 2D slice thickness of 0.1 - 200 mm, 3D slab thickness from 5 - 500 mm, maximum matrix size of 1,024 elements, and maximum resolution of 9 mm. A PET detector assembly exists between the gradient and radiofrequency coils: 8 rings of 56 detector blocks, 8x8 LSO crystals (4x4x20 mm) per block, coupled to an array of 3x3 APDs for a total of 4,032 channels. The PET system (127 planes; transaxial FOV: 59.4 cm; axial FOV: 25.8 cm) can acquire static multibed and list-mode data in 3D mode. (Delso et al., JNM 2011; 52:1914–1922).

Radiofrequency Coils:

- A 32-channel receiver array head-coil for parallel imaging capabilities is available on both 3T systems.
- A 32-channel receiver array head-coil with 20-ch transmit array

Mock Scanner/MRI Simulator: The Center houses a mock MRI scanner that can be used to acclimate adults and children to the MRI scanner environment. The mock scanner includes a mock head coil, Motrak head motion monitoring system that tracks participant movement during a simulated scan, and a computer running Eprime software for visual and auditory stimulus presentation and recording of subject feedback.

Eye Tracker: Two of the 3.0T scanners are fitted with MRI-compatible eye tracking monitoring and recording systems (ASL, Bedford, Massachusetts). The EYE-TRAC®6 series uses optics that provide optimum pupil image contrast in most indoor environments. The systems include control units with long-range remote optics and multi-speed camera with telephoto lens needed for the MRI environment, two 9 inch black and white monitors, one 5 inch LCD monitor for the MRI scan room, and the EYEPOS package for real-time conversion of the eye movements into numerical pupil position and diameter data streams. The system includes a custom PC with two frame grabbers, one capable of supporting 240 Hz eye imaging, and the other capable of recording to disk the entire image of the eye during the MRI scan.

Physiological Monitoring Equipment: A Veris MR compatible physiological monitor (MEDRAD, Indianola, PA), is available with one of the 3T scanners. The system includes a variety of blood pressure cuff sizes, flexible grip pulse oximeter probes, two channels of skin surface temperature utilizing fiber optic technology and is capable of analyzing mixed gases and anesthetic agents.

Computing, Networking And Data Transfer: Three independent, but interconnected, LAN's support the operation of the MRRRC: a research network, an administrative network and a scanner network. All systems are interfaced to a high-speed (Gigabit) local area network for data transfer to workstations for analysis. The scanner network operates on a combination of thin-wire Ethernet and 1Gb/s switched router. This network provides low latency access to all computers supporting the different subsystems for the scanners and is connected through a router to the research and administrative networks. The computational power for the research network is supplied by an 8 CPU Silicon Graphics Power Challenge L serve, a 32 CPU Linux server a Linux cluster (4x2.0GHz dual-core opterons). The SGI servers have 2GB of RAM and the Linux servers have 4GB of RAM. Together they provide over 12TB of online data storage. Access to the servers is performed through multiple Linux PC workstations. A 1Gb/s LAN interconnects all computers on the research network. Commercial software for image analysis (AVS, SAGE, IDL, Analyze, MATLAB) as well as freeware packages (FSL, SPM) complements the development of customized software for individual projects. The administrative LAN operates on a 100Mb/s Ethernet and is connected by router to the other two LAN's. The administrative LAN includes Apple Macintosh OS X, Windows XP and PC's, 3 high-speed 600dpi laser printers and one color laser printer. Available software includes packages for word processing, relational database, image display and processing, presentation graphics and communications. The administrative and research LAN's can communicate through a router to the Radiology Department's Novell Netware-based Ethernet LAN. The administrative LAN system has access to Novell file server and e-mail systems permitting file sharing and communication with other department members. This connection also provides access to the University of Pittsburgh computer networks and from there to the worldwide Internet network for intra- and extra-mural collaboration, respectively.

Quality Assurance: MRRRC defined quality assurance procedures are in place for all scanners. These include daily signal stability scans for echo planar imaging (1% maximum RMS over a continuous 30 minute acquisition with a 64x64 matrix size) and daily signal-to-noise measurements with the standard RF head coil. One of the 3T Scanners is

accredited by the American College of Radiology. The MR Research Center has maintenance agreements with the scanner manufacturers that guarantee service in less than 12 hours whenever daily stability scans fail to meet the required specifications.

Radio Frequency Research Facility (Director: T.S. Ibrahim, Ph.D.)

The RF Research Facility (BST3 building at University of Pittsburgh) contains all the necessary equipment for electromagnetic testing including 3 network analyzers, RF and LF impedance analyzers, frequency synthesizer and oscilloscopes. The associated mechanical workshop has a lathe and milling machine with accessories for fabrication of metal, fiberglass and plastic supports for antennas, coils and phantoms.

Equipment pertinent to this project in the RF Research Facility includes:

- 12-channel network analyzer
- Access to a 3D printer
- RF conductivity and dielectric constant meter
- DAK: high-precision dielectric measurement system for fast and reliable evaluation of liquids, solids and semi-solids
- 8-channel fiber optic thermometry
- Chemistry kits for designing biological phantoms

Computational Capabilities in RF Research Facility:

There are advanced computing resources that are available for the PI's research group including:

- Super computer cluster dedicated to Dr. Ibrahim's research
- +352-Core/1.3TB (RAM) 64-bit Opteron Architecture

Office: Dr. Ibrahim has an office (~150 Sq. ft.) in Biomedical Science Tower 3 (where the RF Research Facility is located.) Dr. Ibrahim's research group includes post-doc/student office space in BST3.

Bioengineering 7T Research Program

The Departments of Bioengineering and Radiology have longstanding financial and operational agreement in place regarding the 7 Tesla (7T) Human MRI system. Dr. Ibrahim's Research Lab occupies the 7T Human MRI scanner two full days per week (Tues and Weds).

7T human MRI scanner is housed in the basement of the Biomedical Science Tower in the same building and floor as the RF Research Facility. This 7T system is a Siemens retrofit of a GE magnet. As part of this retrofit, the scanner was upgraded to 32 independent receive channels, each of them with multi-nuclear capabilities. To achieve high slew rate, the scanner is fitted with a head only, removable, gradient set capable of 80mT/m gradients and 800mT/m/s slew rate. Finally, the 7T supports parallel transmission capabilities with the addition of a parallel transmission unit from Siemens Medical Systems. This unit provides 8 independent transmission channels as well as support for additional gradient controllers that could be used for dynamic shimming applications.

The Geriatric Neuropsychology Research Program (Director: Meryl A. Butters, Ph.D.)

The Geriatric Neuropsychology Research Program (GNRP), located within Department of Psychiatry and the Western Psychiatric Institute and Clinic (WPIC), is a suite of six offices and two testing rooms. These offices are occupied by Dr. Butters, a post-doctoral scholar, a program coordinator, two project coordinators and four full-time research specialists/neuropsychology examiners. The GNRP also occupies a full-time testing room and office in the Late-Life Mood Disorders clinic located in Bellefield Tower.

The GRNP research specialists are well-trained neuropsychological examiners. The GNRP maintains a full library of neuropsychological tasks including traditional paper and pencil and newer computerized tests. The

GNRP typically serves from 15-20 funded research studies, including those on which Dr. Butters serves as PI and all studies affiliated with the GPN as well as ancillary studies being conducted throughout the UPMC. The examiners administer neuropsychological assessments to geriatric participants in a number of settings, including the GNRP, PCP offices, participants' homes and institutions such as nursing homes. Staff of the GNRP regularly train neuropsychological examiners who work on studies both within the University of Pittsburgh and elsewhere. GNRP staff monitor both their own performance and that of other examiners working in separate studies through regular inter-rater reliability assessment. The GNRP has numerous computers (including 9 PCs and 3 lap tops for general use, 5 tablet PCs for computerized tests, and 4 iPads for NIH Toolbox.

[\[reviewer notes→\]](#).

CS16.0 Special Research Subject Populations:

Categories

None

[\[reviewer notes→\]](#).

CS17.0 Does your research involve the experimental use of any type of human stem cell?

* No

NIH Definition of a Clinical Trial

A research study¹ in which one or more human subjects² are prospectively assigned³ to one or more interventions⁴ (which may include placebo or other control) to evaluate the effects of those interventions on health related biomedical or behavioral outcomes.⁵

¹ See Common Rule definition of research at [45 CFR 46.102\(d\)](#) .

² See Common Rule definition of human subject at [45 CFR 46.102\(f\)](#) .

³ The term “prospectively assigned” refers to a pre-defined process (e.g., randomization) specified in an approved protocol that stipulates the assignment of research subjects (individually or in clusters) to one or more arms (e.g., intervention, placebo, or other control) of a clinical trial.

⁴ An intervention is defined as a manipulation of the subject or subject’s environment for the purpose of modifying one or more health-related biomedical or behavioral processes and/or endpoints. Examples include: drugs/small molecules/compounds; biologics; devices; procedures (e.g., surgical techniques); delivery systems (e.g., telemedicine, face-to-face interviews); strategies to change health-related behavior (e.g., diet, cognitive therapy, exercise, development of new habits); treatment strategies; prevention strategies; and, diagnostic strategies.

⁵ Health-related biomedical or behavioral outcome is defined as the pre-specified goal(s) or condition(s) that reflect the effect of one or more interventions on human subjects’ biomedical or behavioral status or quality of life. Examples include: positive or negative changes to physiological or biological parameters (e.g., improvement of lung capacity, gene expression); positive or negative changes to psychological or neurodevelopmental parameters (e.g., mood management intervention for smokers; reading comprehension and /or information retention); positive or negative changes to disease processes; positive or negative changes to health-related behaviors; and, positive or negative changes to quality of life.

CS18.0 * Based on the above information, does this study meet the NIH definition of a clinical trial?

☒ Yes ☐ No

If Yes, click Save and then [Click Here For Study Team's CITI Training Records](#) . Please ensure all personnel's training is up to date

[\[reviewer notes-\]](#)

1.1 Objective: What is the overall purpose of this research study? (Limit response to 1-2 sentences.)

The primary aim is to characterize functional connectivity changes associated with initial medication exposure (12-hour challenge). In the proposed study we test a neural systems level model that response in late life depression (LLD) is mediated by acute pharmacologically-induced changes in cognitive and affective large scale network.

1.2 Specific Aims: List the goals of the proposed study (e.g., describe the relevant hypotheses or the specific problems or issues that will be addressed by the study).

We will recruit 100 older adults with late life depression (LLD) who will be randomized to receive treatment with either a very specific serotonin reuptake inhibitor (escitalopram) or a norepinephrine reuptake inhibitor (levomilnacipram). PhMRI (a pair of fMRI scans one day apart) will be used to measure FC associated with medication titration.

Aim 1: Responders versus non-responders: Compare how phMRI probe relates to later treatment response.

Hypo 1.1: Across the whole group (both medications), the change in functional connectivity (FC) associated with a 1-day pharmacologic probe will differ in responders compared to non-responders. Compared to non-responders, treatment responders will have a decrease in Default Mode Network (DMN) and an increase in Salience network and Executive Control Network (ECN) FC at rest and during task.

Hypo 1.2: The relationship between early FC change at rest and during task and response group is independent of medication class.

Aim 2: Associations of Networks with Symptom Clusters: Characterize how monoaminergic engagement of Cognitive and Affective Networks (CAN) is associated with specific clinical components of LLD response.

Hypo 2.1: Changes in FC associated with a 1-day pharmacologic probe in each of the three canonical networks will predict improvement from baseline to 12 weeks in overall depression severity as well as in a specific symptom cluster: DMN changes at rest -- negative bias; ECN changes during cognitive challenge -- cognitive control; Salience network changes during affective regulation -- somatization/anxiety.

Hypo 2.2: Increase of dACC centrality from baseline to 12 weeks will predict overall improvement in depression severity.

Aim 3: Integration with established clinical and biological markers of LLD treatment response.

Hypo 3.1: Early CAN engagement is a better predictor of treatment response compared to other biological (cerebrovascular burden) or clinical markers (depression severity, comorbid anxiety, early clinical response).

IMPACT: The study will test a mechanistic model that describes the treatment-related dynamic changes of the core cognitive and affective networks (CAN) at rest and during standard behavioral tasks. If proven that treatment response may be identified very early during a medication trial, our study results would have a notable clinical impact, as they would allow for earlier strategizing of treatment plans in LLD.

1.3 Background: Briefly describe previous findings or observations that provide the background leading to this proposal.

Very recent data has shown that brain's intrinsic connectivity can be altered by acute serotonergic(1),(2, 3) or noradrenergic(4) 1- or 7-day challenge in healthy subjects(5). No data is so far available for LLD subjects. The data reflecting early FC changes are consistent with PET (6) and - more recent ASL(7) - studies reporting differences in monoaminergic occupancy and cerebral blood flow(8) after a single dose of SSRI. This opens the way for investigating connectivity changes induced by pharmacological modulation(1). However, as this is a new area of research much is still unknown. The data reported so far is promising enough to warrant a change in the approach to treatment-induced neural changes from the classic pre/post-treatment fMRI analysis. If confirmed, these very early markers of treatment response could be a guide in clinical decision-making. Given the widespread distribution of the monoaminergic projections, a network-based approach offers a more realistic picture of serotonin/ norepinephrine impact on CNS compared with a region-based approach.

The functional signal measured with phMRI reflects a combination of acute

pharmacodynamic effects on the monoaminergic neurons targeted by the antidepressants, and acute compensatory responses, due in part to auto-receptor and inter-neuron feedback. These secondary effects maintain a balance between 5-HT₂ and NE post-synaptic activity, and may explain the similar efficacy pattern across these medication classes(9). The acute effects are believed to induce the longer-term changes necessary for clinical response(9, 10).

We hypothesize that acute FC changes are similar regardless of medication class. In order to test this, subjects will take a SSRI (escitalopram) or a (relatively) selective norepinephrine reuptake inhibitor (levomilnacipram). Unlike venlafaxine, desvenlafaxine or duloxetine, in vitro studies of levomilnacipram have shown that, although it inhibits the reuptake of both serotonin and norepinephrine, it is a three-fold more potent inhibitor of norepinephrine reuptake from initial doses(11, 12). There are several other antidepressant medications, with different profiles, such as bupropion, a medication with a combined dopaminergic/noradrenergic/serotonergic effect, mirtazapine or vortioxetine - both medications with partial serotonergic agonist effects, or more non-specific monoamine inhibitors such as tricyclic antidepressants and monoamine oxidase inhibitors. We chose these two molecules as 1) they represent relatively specific serotonergic and noradrenergic drugs, 2) they have safe side-effect profiles for the geriatric population (compared to other medications such as nortriptyline) and 3) they capture the spectrum of the most frequently used drugs in the geriatric population, thus increasing the clinical translation potential of our study.

1.4 **Significance: Why is it important that this research be conducted? What gaps in existing information or knowledge is this research intended to fill?**

The results of this study will have two potential outcomes. First, from a clinical translation perspective, very early changes associated with treatment response may alter the current treatment decision-making process, which relies entirely on clinical changes seen several weeks after the treatment initiation. The results of our study would help validate a treatment-decision process based on biomarkers of response. fMRI has not yet been incorporated into LLD treatment guidance, likely because of limited effect sizes and the challenge of operationalizing pre-treatment markers of response prediction into pharmacotherapy heuristics. Nevertheless, the number of studies using rsfMRI is reaching a critical mass and this technique may develop into an effective tool for personalized medicine⁵². Rather than waiting 3-6 weeks to determine if an intervention is effective, fMRI markers of treatment response will allow for faster and more efficient pharmacologic titration. Second, from a disease mechanism perspective, the results would help characterize the early neural system changes associated with typical antidepressant treatment, and thus clarify our understanding of the mechanisms of treatment response in LLD. This is essential for development of improved prevention and treatment strategies. Moreover, the study will describe markers that can be used to accelerate drug discovery through their use as an early marker of target engagement, much as amyloid imaging is serving as a primary end-point in identifying effective anti-amyloid therapies for Alzheimer's disease⁷⁸.

[\[reviewer notes→\]](#).

2.1 Does this research study involve the **use** or evaluation of a drug, biological, or nutritional (e.g., herbal or dietary) supplement?

* Yes

2.1.1 Does this research study involve an evaluation of the safety and/or effectiveness of one or more marketed nutritional (e.g., herbal or dietary) supplements for the diagnosis, prevention, mitigation or treatment of a specific disease or condition or symptoms characteristic of a specific disease or condition?

* No

[\[reviewer notes→\]](#).

2.1.2 Does this research study involve the use or evaluation of one or more drugs or biologicals **not** currently approved by the FDA for general marketing?

* No

[\[reviewer notes-\]](#)

2.1.3 Does this research involve the use or an evaluation of the effectiveness and/or safety of one or more drugs or biologicals currently approved by the FDA for general marketing?

* Yes

2.1.3.1 Are the FDA-approved drugs or biologicals being evaluated in this research study for a new clinical indication, different population, or route of administration and/or dosage level that is not currently specified in the FDA-approved product labeling?

Drugs are often used **Off-Label** during routine practice. Before answering this question, review the FDA product labeling (<http://labels.fda.gov>) for the approved "Indications and Usage." If being used off-label, answer **Yes** to this question. You are required to provide information and/or upload the package insert for each drug that is administered for research purposes.

* No

If you respond **YES**, an IND number or the FDA written concurrence of IND exemption may be required.

Upload information on FDA approved indications/doses and FDA exemption letter if applicable:

Name	Modified Date
Fetzima_label.pdf	1/8/2018 9:51 AM
escitalopram_label.pdf	1/8/2018 9:31 AM

[\[reviewer notes-\]](#)

2.2 Will this research use or evaluate the safety and/or effectiveness of one or more devices?

* No

[\[reviewer notes→\]](#)

2.3 Summarize the general classification (e.g., descriptive, experimental) and methodological design (e.g., observational, cross-sectional, longitudinal, randomized, open-label single-blind, double-blind, placebo-controlled, active treatment controlled, parallel arm, cross-over arm) of the proposed research study, as applicable.

The proposed pHMRI study will use a randomized clinical trial (RCT) of escitalopram versus levomilnacipran.

2.3.1 Does this research study involve a placebo-controlled arm?

* No

[\[reviewer notes-\]](#)

2.4 Will any research subjects be withdrawn from known effective therapy for the purpose of participating in this research study?

* Yes

2.4.1 Provide a **justification for discontinuing** subjects from known effective therapy for the purpose of study participation.

The only way participants will be tapered off of their current medication and subsequently allowed into the study is if their depression is non-remitting, despite current use of medication.

High doses of benzodiazepines (>2 mg of lorazepam daily, or equivalent) are known to affect brain function, so we will work with patients to lower their daily dosage to be equal to or below this range. Participants will be required to switch from longer acting benzodiazepines (e.g. clonazepam) to lorazepam (if the equivalent dose of other longer acting benzodiazepines is less than 2 mg lorazepam/day). Participants on high doses of benzodiazepines (e.g., greater than or equivalent to 2 mg of lorazepam/day) will be excluded given the complexity and potential complications of benzodiazepine taper/withdrawal. Close clinical monitoring will occur during this time. Patients will be told that they can choose to discontinue the tapering at any time, or may choose to not taper at all. These patients will be referred for appropriate psychiatric care.

2.4.2 Describe the **risks** to subjects associated with discontinuing them from known effective therapy for the purpose of study participation.

There is a chance that the subject's depression could worsen if they are in the process of tapering from one antidepressant so that they can safely begin this study. The tapering process will be directed by the medical physicians and will be slow and steady to minimize symptoms.

Abrupt termination of benzodiazepine use may be accompanied by withdrawal symptoms. We will mitigate this risk by providing participants with a gradual taper with close clinical monitoring. Patient education will be provided along with supportive care and available psychiatric consultation.

Symptoms reported following rapid discontinuation of benzodiazepines include headache, anxiety, tension, depression, insomnia, restlessness, confusion, irritability, sweating, rebound phenomena, dysphoria, dizziness, derealization, depersonalization, hyperacusis, numbness/tingling of extremities, hypersensitivity to light, noise, and physical contact/perceptual changes, involuntary movements, nausea, vomiting, diarrhea, loss of appetite, hallucinations/delirium, convulsions/seizures, tremor, abdominal cramps, myalgia, agitation, palpitations, tachycardia, panic attacks, vertigo, hyperreflexia, short-term memory loss, and hyperthermia.

[\[reviewer notes-\]](#)

2.5 Will screening procedures (i.e., procedures to determine research subject eligibility) be performed specifically for the purpose of this research study?

* Yes

2.5.1 List the **screening** procedures that will be performed for the purpose of this research study. Do NOT include the inclusion/exclusion criteria in this section as

they will be addressed in section 3; questions 3.13 and 3.14.

Screening procedures will take place following informed consent in Western Psychiatric Institute and Clinic in a private office.

Clinical Assessments (3-5 hours):

- Participants will complete a Structured Clinical Interview for DSM-IV Disorders (SCID). The SCID assesses current and lifetime depression and other psychiatric disorders. It will be used to clarify psychiatric inclusion and exclusion criteria.
- The Montgomery-Asberg Depression Rating Scale (MADRS) will be used to assess current depressive symptoms.
- The Modified Mini-Mental State (3MS) test along with the SCID will be used to assess presence of dementia.
- The Cumulative Illness Rating Scale for Geriatrics (CIRS-G) will be used to rule out any unstable medical conditions or medication contraindications. The Personal Medical History form will be used to assist in completing the CIRS-G.
- The Suicidal Ideation Scale (SIS) will be administered to assess presence and severity of suicidal ideation.
- The Antidepressant Treatment History Form (ATHF) will be administered to assess history of treatment response/resistance.

NDA ID Assignment Form:

- Study staff will administer this form to obtain the personally identifiable information (PII) necessary to create a GUID for the National Institute of Mental Health Data Archive (NDA). This information includes (as per the participant's birth certificate): full name, date of birth, sex at birth, city/municipality of birth, and twin status at birth. We also need to ask if the participant has a twin. This form will be stored in paper form only, separate from research data. While the PII is needed to assign and/or locate the GUID, the PII is not sent to the NDA. There is nothing about a GUID that would allow someone to infer the identity of the individual to whom it belongs.
- This data is collected as part of the NIMH data sharing requirement. De-identified data is uploaded to a database where other researchers will have access to the data.

The specific steps in the GUID ID assignment process will be as follows:

- 1) Study staff will enter participant PII into the NDA website using the GUID Tool
- 2) The tool uses the PII, without it ever leaving our computers, to generate a series of one-way hash codes.
- 3) The hash codes are encrypted and sent to the GUID system at NDA.
- 4) If the codes match an existing GUID, this GUID is sent back to the researcher.
- 5) If they do not, a new one is created and sent back.
- 6) Study staff will record the GUID in a secure database, separate from the research records
- 7) Participant's research data will later be uploaded to the NDA website, using only the recorded GUID as the identifier.

Simulation MRI Scan (up to 1 hour)

- Participants will be asked to complete a simulation MRI as part of their screening visit. The simulation scan may last up to 1 hour. Participants will be introduced to the MRI environment as well as introduced to the tasks that they will complete during the actual scan.

Labs/Vitals (blood draws and electrocardiogram):

Participants who remain eligible after completing clinical evaluations will complete lab testing, including a basic metabolic panel, urine analysis, an EKG, and vital signs including blood pressure, heart rate, height, and weight. The basic metabolic panel will allow us to exclude participants with hyponatremia.

As the clinical assessments can be lengthy the participant may choose to complete screening procedures in one day or in multiple visits. Ideally, we will complete the visits in three visits over a span of up to one month.

Medication Tapering:

Individuals who present on antidepressant/anti-anxiety medication (including, but not

limited to SSRI/SNRI) and wish to participate will undergo a thorough assessment once we determine that he/she is eligible based on the clinical assessments and labs. The assessment to determine appropriateness to taper will include a focused review of factors that could influence the decision about whether to discontinue medication: a list of current medication(s) with start date, current dose, and side effects, a summary of the course of their depression and co-occurring symptoms, before and after medication use, assessment of medication treatment history with information about medication type and effectiveness, reasons for discontinuing medication in the past, method and consequences of any prior experience with antidepressant discontinuation, a summary of current and past suicidal ideation and any past attempts, and information about where these occurred in relation to starting or stopping antidepressant medication. We will note any current psychosocial stressors that might lead to worsening depression upon antidepressant discontinuation and provide a brief summary of pros and cons of discontinuation.

Any participant experiencing a robust response to medication in the current episode will NOT be tapered off medication for study participation. With the patient's consent, we will proceed with medication taper after it is determined to be clinically appropriate. Given the potential long-lasting effects of psychopharmacology on the central nervous system (CNS) receptors and neural circuits (6-9), participants eligible to taper the antidepressant medications, such as SSRIs, will be required to be medication-free for 1 week prior to their first MRI scan (4 weeks for fluoxetine). The full taper process typically takes about 2 weeks for most antidepressants (6 weeks for fluoxetine).

A study physician will oversee the taper procedure. During the tapering and discontinuation of medication, we will maintain close contact with the participant either in person or by phone (at least once weekly) to monitor clinical state. With the participant's consent, we may also communicate with a family member/close friend. If the secondary contact person is unaware of the participant's well-being, we will ask him/her to attempt to contact the participant and then we will follow up to ascertain their well-being. If the secondary contact person is also unable to reach the participant, if we have any reason to suspect that the participant is at risk of hurting themselves or someone else, we will contact the appropriate authorities (ReSolve Crisis Center and/or [if necessary] the police).

We will also have 24/7 access to a study clinician and physician to assist with clinical guidance regarding medication after typical working hours.

MRI Screening

Should the participant have any history of surgeries involving implants, we will obtain a copy of any medical records related to the procedure/s to confirm whether he/she may safely complete the MRI scans.

Study staff may access medical records after a subject has signed consent to get a complete list of medications that the person is currently taking (if applicable) as well as to assess medical history to address any unstable medical conditions or exclusionary diagnoses.

[\[reviewer notes-\]](#)

2.6 **Provide a detailed description of all research activities (e.g., all drugs or devices; psychosocial interventions or measures) that will be performed for the purpose of this research study.**

This description of activities should be complete and of sufficient detail to permit an assessment of associated risks.

At a minimum the description should include:

- **all research activities**
- **personnel (by role) performing the procedures**
- **location of procedures**
- **duration of procedures**
- **timeline of study procedures**

PRIOR TO MEDICATION START

Participants will be required to be medication free at the time of baseline scan (e.g., anti-anxiety and anti-depressant medications). Participants will also be asked to reduce benzodiazepine use in cases where their usual dosage exceeds 2 mg of lorazepam daily (or equivalent). We will work with these participants to taper their benzodiazepine use to a maximum daily equivalent dose of 2 mg of lorazepam. Participants will be instructed to taper gradually to minimize the chances of side effects and may resume their usual medication schedule once the first three scans are completed. In cases where the usual medication schedule is resumed, we will again work with the participant to taper their dose to an equivalent of 2 mg of lorazepam daily as their final week 12 MRI scan (or repeat baseline and first dose scans) approaches. We will review participants' lists of medications at their clinical visit and will inform them whether it will be necessary for them to taper from any of their usual medications. Participants will be told (as per the consent form) that they may decide that they do not wish to taper from relevant medications prior to their scans. If so, they will be considered ineligible for the study.

BASELINE CLINICAL MEASURES:

- 1) The Hamilton Anxiety Rating Scale- A standard measure of anxiety symptoms
- 2) Rumination Subscale of Response Style Questionnaire (RSQ)- A 22-item scale that assesses ruminative thoughts
- 3) The Antidepressant Side Effect Checklist (ASEC) will be administered to assess baseline side effects to allow investigators to better determine if symptoms that develop throughout treatment could be result of the study antidepressant.
- 4) The Montgomery Asberg Depression Rating Scale (MADRS) will be repeated at baseline, prior to the first MRI scan
- 5) Suicidal Ideation Scale (SIS) will be administered to assess baseline suicide risk in the participant.

NEUROPSYCHOLOGICAL TEST BATTERY:

Participants will complete a neuropsychological testing battery in order to determine the presence and severity of any Axis I disorder as well as the presence and severity of cognitive impairment. The neuropsychological testing battery, developed and applied by Co-I Meryl Butters, PhD, includes components of the Delis-Kaplan Executive Function Scale (D-KEFS) (10), and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (11). We will also administer the E-Cog (short form) (13). This measure, which detects decline in daily function, will require phone contact with a family member that can provide input regarding the participant's ability to perform certain tasks. This will be described during the consent process. At times, we will be unable to complete this measure due to an inability to contact the participant's informant. We will use the Performance Assessment of Self-Care Skills (PASS) which detects deficits in the cognitive instrumental activities of daily living (e.g., paying bills, medication management, appliances repair (14). Finally, we will use the Wide Range Achievement Test (WRAT)—Reading Subtest to assess premorbid verbal IQ.

fMRIs AND MEDICATION START:

Participants will complete at least 4 fMRIs while participating in this research study. The first three fMRIs will take place in the first two weeks of participation. The baseline fMRI visit will take place prior to the administration of the study medication. Physiological data (EKG and skin conductance) may be collected with each MRI scan.

The purpose of the scans in between the first and last is to examine functional changes in the brain throughout different periods of pharmacotherapy, as follows:

ALL PARTICIPANTS:

Will take their first dose of medication the evening prior to their 2nd MRI scan, which will

take place within 24 hours of the baseline MRI scan. The day of their baseline MRI scan, participants will receive this first dose of escitalopram (5 mg) or levomilnacipran (20mg) to take that evening. The medication assignment will be double-blinded and determined randomly (using a permuted block design, stratified by gender, with each group containing 50 individuals). The third MRI scan will take place after approximately one week. Participants will increase their dose of study medication one day before their third scan.

Participants will be scanned at the MRRC using the Siemens 3-Tesla PRISMA in UPMC Presbyterian Hospital, or the 7-Tesla scanner located in the Biomedical Science Tower building. Study staff will escort participants from desired parking location to the location of the scanner. The decision to scan at 3-Tesla versus 7-Tesla will be made on a case by case basis, dependent upon scheduling availability as the the priority will always be to get the participant started with scanning and on the study medication as soon as possible. Also, participants who have implants that cannot be cleared for safety on the 7-Tesla scanner will be scanned at 3-Tesla. For example, many stents are not tested at 7-Tesla, but have been tested and cleared for safe scanning at 3-Tesla.

In our experience with elderly participants, the table set-up time is increased due to age-related psychomotor slowing. Therefore, participants will be asked to arrive up to an hour prior to table-time in order to ensure they have enough time to gain familiarity with functional tasks, complete the safety screening, and change clothes (if necessary). A secure locker will be provided to participants for personal items during the scan. Any premenopausal women will have a urine pregnancy test prior to the scan. The baseline, repeat baseline, and follow up fMRIs will last approximately 60-75 minutes and include structural and functional imaging. Other MRI scans will last approximately 30-45 minutes and will include functional imaging only. For the first portion of each of the structural scans, we will gather structural data, and participants will be doing nothing more than lying on the MRI table. The second portion involves functional imaging, which involves looking at pictures and/or words on a computer screen. All participants will be trained on the functional tasks prior to beginning the scan. A study staff member will be present throughout the fMRI and will be communicating with the participant at different intervals. A trained MR technologist will run the scanner. If a participant is claustrophobic or needs to come out of the machine for any reason, the scan will be immediately aborted. Participants will be instructed to either alert us verbally at times when staff is checking in with the participant, or via the emergency squeeze ball which participants may activate at any time throughout the scanning sessions.

We may measure physiological response (blood pressure, heart rate, and respiration rate) using an MR-compatible physiological monitoring system to explore the correlation between networks' activation and physiological response. Electrodermal activity (also called galvanic skin response) and the electrocardiogram will be monitored and analyzed for signs of sympathetic nervous system activity changes as a result of the experimental procedures. These waveforms will be digitized and recorded on a PC that also logs trigger signals for when stimuli are presented. In this fashion, the timing of changes in electrodermal activity (rise above baseline), or in heart rate variability (HRV, measured by the RR interval, which is the time elapsed between consecutive R waves) can be linked to preceding events in the experiment. These additional monitors pose no additional risk to subjects.

FUNCTIONAL TASKS:

Faces Affective Reactivity Task. Participants are asked to match pictures of faces that have emotional expressions (angry or afraid). They are not asked to attend to or regulate their affect during this task, thus the task only involves affective reactivity, rather than affect regulation. Matching geometric shapes is used as a control task.

Digit Symbol Substitution Task (DSST). The fMRI DSST task is based on the validated computerized version of the DSST (30, 31). The participant sees on a screen one number-symbol matching pair (cue). After the cue disappears, an answer key (probe) appears containing a grid of four number-symbol matching pairs. The participant is instructed to push the right-finger button if the probe contains one number-symbol that matches the cue, and to push the left index finger button if the probe does not contain any number-symbol that matches the cue. Instructions are to respond "as fast as you possibly can".

INCOMPLETE SCANS:

In the case where the participant is unable to complete their first scan due to their own reservations (anxiety, claustrophobia), s/he will be deemed ineligible, will not complete any remaining fMRI scans, and will be removed from the study. If the participant is unable to complete any scan due to problems at the MR Research Center (scanner malfunctions, etc), s/he will NOT be removed from the study. In this case, we will either reschedule the scanning session or skip the scan altogether, depending on which is appropriate. We will do our best to reschedule as many scans as possible should this situation arise. Regardless of whether a scan time-point is aborted or rescheduled, the subject will continue with the protocol. Participants will be compensated for each visit, regardless of whether or not they were able to complete the fMRI.

TREATMENT MONITORING/MEDICATION TITRATION:**OVERVIEW:**

Participants will have weekly appointments lasting 30-60 minutes with study staff for the first 6 weeks (considered Phase I) of the medication trial. Dr. Aizenstein, Dr. Andreescu, or one of the other physicians will always be available by pager or cellular phone. To reduce the risk of adverse outcome by suicide, the GPN Lab has both a psychiatrist and staff on call 24 hours/daily, seven days/weekly, so professional guidance is always available for high-risk situations. In addition, one staff member will be unblinded regarding study randomization. Should the need ever arise, the blind can be instantly broken for the participant's safety and well-being.

Participants will receive an initial dose of 5mg blinded escitalopram or 20mg blinded levomilnacipran of study medication (initial low doses are chosen to limit potential side effects in a geriatric population). We will use a permuted block randomization, which will prevent guessing the allocation of the participants to the experimental groups. Since there will be two groups with a 1:1 randomization, the block size can be 2, 4. Thus within each of two conditions there will be 50 persons. Due to the small sample size, we will use a stratified randomization by gender only. The block sizes will be kept confidential from the research staff that will be randomizing the participants.

At day 7, the doses will be titrated to 10mg of escitalopram/40 mg of levomilnacipran. Further titrations (maximum dose of 20mg of escitalopram or 120mg of levomilnacipran) will be decided based on clinical response and tolerability, but will not involve additional MR scanning. Dosing will be based on medication tolerability and will be based on a standard clinical approach.

Participants who do not show signs of response to treatment by week 6 (defined as either a MADRS score of greater than 12 or less than a 30% reduction in MADRS score to be deemed a non-responder) will continue with weekly visits and further medication titrations, if applicable. Participants who are deemed a responder will continue with bi-weekly clinic visits and further medication titrations, if applicable.

MONTHLY ASSESSMENTS:

We will repeat the basic metabolic panel and the EKG monthly. We will also ask participants to complete the RSQ monthly.

CLINICAL ASSESSMENTS:

The following measures will be repeated at each medication visit to assess response and assure safety:

- 1) MADRS
- 2) SIS
- 3) HARS
- 4) ASEC
- 5) VITALS
- 6) PROTOCOL ADHERENCE

BLOOD TESTING:

Blood levels for escitalopram or levomilnacipran will be drawn by trained personnel after each titration to test pharmacokinetics as well as adherence to treatment.

Blood samples will be also be obtained to assess biomarkers. Upon signing consent,

participants will be given the option to decline the additional blood taken to examine biomarkers, and this will not impact their ability to continue with the rest of the study.

The samples collected to examine blood biomarkers will be kept in a locked and secured laboratory area at WPIC. While the specific analyses performed will be determined based on emerging models and methods in the field at the time this study is completed, we will have the ability to measure serum levels of various cytokines, growth factors, and DNA.

FOLLOW UP PROCEDURES:

In addition to the week 12 MRI scan and the weekly assessments completed for treatment monitoring, follow-up assessments will also include repeat neuropsychological testing, which will again take up to 1.5 hours.

All participants will be offered referrals for treatment once study participation has ended to specialized clinics such as the Benedum Geriatric Center from the University of Pittsburgh Medical Center.

Participants may be offered transportation to and from their MRI visits via Corporate Sedan/VauxCo Limousines or a taxi service. Subject name and address will be given to the driver, but no description of the research study will be made available. At times, participants may be unable to afford transportation to and from Oakland for all of their study visits. We would like to offer transportation for all visits in these rare occurrences. This will be reviewed on a case by case basis.

2.6.1

Will blood samples be obtained as part of this research study?

* Yes

*If submitting a protocol for expedited review, it should be clear that the planned blood draws are within the parameters described here:
<http://www.hhs.gov/ohrp/policy/expedited98.html> (see Expedited Research Category #2)

If **Yes**, address the frequency, volume per withdrawal, the total volume per visit, and the qualifications of the individual performing the procedure:

At screening, approximately 18 mL (~4 teaspoons) of blood will be collected for the blood tests (basic metabolic panel, CBC, thyroid panel, B12 testing).

Throughout the 12 week medication trial, trained personnel will draw 10-20 mL (2-4 teaspoons) of blood per visit (the upper end when sodium and medication levels need to be assessed at the same time).

Participants who opt to complete the blood draws for inflammatory biomarkers will have 10 mL (~2 teaspoons) of blood drawn at both baseline and follow-up. At follow-up, this will result in a total of up to 24.5 mL (~5 teaspoons) of blood as the Week 12 blood test may also include medication levels and the basic metabolic panel.

Blood will be collected at the WPIC laboratory by trained personnel.

Study Flow Chart:

Name

[Flow Chart](#)

Modified Date

2/21/2018 11:14 AM

[\[reviewer notes-\]](#)

2.7 Will follow-up procedures be performed specifically for research purposes? Follow-up procedures may include phone calls, interviews, biomedical tests or other monitoring procedures.

* Yes

See study flow chart in question 2.6

[\[reviewer notes-\]](#)

2.8 Does this research study involve the use of any questionnaires, interview or survey instruments?

* Yes

Upload a copy of all materials except for the SCID or KSADS which are on file at the IRB. The use of all instruments must be addressed in question 2.6 and/or question 2.7 (except for an exempt submission where they should be addressed on the appropriate uploaded exempt form).

Name	Modified Date
hars.doc	1/8/2018 1:09 PM
MADRS.doc	1/9/2018 1:44 PM
ATHF.doc	1/9/2018 1:34 PM
ECog.doc	1/9/2018 1:35 PM
protocol adherence	1/26/2018 7:03 AM
DKEFS_CWI.pdf	1/11/2018 11:23 AM
3 item PASS.pdf	1/9/2018 1:44 PM
Personal Medical HX.doc	1/9/2018 1:36 PM
3MS 07 2011.pdf	1/9/2018 1:36 PM
WRAT-4 Reading	1/23/2018 10:55 AM
cirs_g.pdf	1/8/2018 1:20 PM
RBANS.PDF	1/11/2018 11:22 AM
DKEFSTMT5.pdf	1/9/2018 1:35 PM
DKEFSTMT4.pdf	1/11/2018 11:22 AM
Side Effect Scale (ASEC).pdf	1/11/2018 11:23 AM
NDA ID Assignment Form - NEMO.docx	1/11/2018 11:22 AM
SIS.doc	1/11/2018 11:23 AM
rsq_rumination.docx	1/11/2018 11:21 AM

Previously the name and publisher for commercially available materials were listed in the textbox below but effective 9/1/2015, all materials (except for the SCID and KSADS) must be uploaded using the Add button above.

SCID-IV: American Psychiatric Association Publishing

[\[reviewer notes→\]](#)

2.9 If subjects are also patients, will any clinical procedures that are being used for their conventional medical care also be used for research purposes?

* no

If **Yes**, describe the clinical procedures (and, if applicable, their frequency) that will be used for research purposes:

2.10 The blood sample question was moved to 2.6.1.

[\[reviewer notes→\]](#)

2.11 What is the total duration of the subject's participation in this research study across all visits, including follow-up surveillance?

* Up to 14 weeks (if no taper needed), up to 20 weeks for those tapering off of fluoxetine, and up to 18 weeks for those tapering off of other anti-depressant medication

[\[reviewer notes→\]](#)

2.12 Does this research study involve any type of planned deception?

If Yes, you are required to request an alteration of the informed consent process (question 4.7)

* No

[\[reviewer notes→\]](#)

2.13 Does this research study involve the use of UPMC/Pitt protected health information that will be de-identified by an IRB approved "honest broker" system?

* No

[\[reviewer notes→\]](#)

2.14 Will protected health information from a UPMC/Pitt HIPAA covered entity be accessed for research purposes or will research data be placed in the UPMC/Pitt medical record?

* Yes

If you answer **Yes**, you are required to submit this study to the Center for Assistance in Research using e-Record (CARE). Per UPMC Policy HS-RS0005, all research projects that access or involve UPMC electronic protected health information (e-PHI) must be submitted

to CARE, with the exception of clinical trials that are contracted through the UPMC Office of Sponsored Programs and Research Support (OSPARS).

Complete the online submission form at <https://care.upmc.com/request.aspx>. After the study is submitted in OSIRIS, a CARE representative will conduct a review. You will be notified once your CARE review is complete or if anything further is needed.

Studies that will access only paper-based medical records (not in combination with any electronic records) do not need to be submitted to CARE.

For additional information, please see <https://care.upmc.com>.

Describe the medical record information that will be collected from the UPMC/Pitt HIPAA covered entity and/or the research-derived information that will be placed in the medical records.

In addition to a "research chart" that contains hard copies of assessments, all research subjects will have a "clinic chart" that contains any pertinent clinic notes, laboratory values, demographic information, pharmacy orders, neuropsychological assessment with identifiable information, and outside correspondence consistent with good clinical care practices. According to the preferences of collaborating primary care physicians (PCP), when care is delivered at a primary care site, if the PCP desires, we will generate a progress note to be included in the subject's medical record to assist their PCP with their routine care. No structured assessments (e.g., data assessments) will be placed in the subject's medical record.

We will access the participant's medical record after consenting to participation but before he/she is randomized. We want to ensure that it is medically safe for the participant to enter this clinical trial. Should participants have any history of surgeries involving implants, we will also review any records related to the procedure/s to confirm whether he/she may safely complete the MRI scan

2.14.1 Will protected health information from a non-UPMC/Pitt HIPAA covered entity be obtained for research purposes or will research data be placed in the non-UPMC/Pitt medical record?

* Yes

If Yes, describe how the HIPAA requirements will be met:

For participants that have had surgeries involving implants outside of the UPMC system, we will ask participants to sign a release of information form. We will then request paper copies of medical records from the facility that performed the surgery. The paper copies will be kept separately from the research data, since records will contain identifiers. The medical records will be used to determine whether participants can safely complete fMRI procedures. We will not be placing research data into participants' medical records.

I, Howard Aizenstein, certify that any member of my research team accessing, reviewing and/or recording information from medical records have completed the CITI Privacy & Information Security course or, if completed within the past year, the Internet-Based Studies in Education and Research (ISER) HIPAA for Researchers (Formerly RPF Module 6). The HIPAA certificates must be available for review if audited but do not need to be uploaded into this OSIRIS application.

* Yes

2.14.2

Are you requesting a waiver of the requirement to obtain written HIPAA authorization for the collection of the PHI?

* No

[\[reviewer notes→\]](#)

2.15 Does this research study involve the long-term storage (banking) of biological specimens?

* Yes

2.15.1 Broadly describe the intended future use of the banked biological specimens:

The blood sample we obtain will be kept for an indefinite period of time. This blood is to examine markers of inflammation and growth factors potentially involved in mood regulation. The reason that we will keep this blood is so that we may examine new markers of inflammation that may be discovered in the future that relate to depression.

2.15.2 Indicate the planned length of storage of the banked biological specimens:

* indefinitely

2.15.3 Will biological specimens be stored **without identifiers or linkage codes?**

* Yes

[\[reviewer notes→\]](#)

2.15.3.1 Identify the honest broker system or describe the process that will be used to de-identify the specimens:

The samples will be labeled with an identification number, participant initials, visit date, and study name. There is nothing about the identification number that would allow someone to infer the identity of the individual. The linkage between study ID number and the participant's identity is kept in a table in our password-protected database.

2.15.3.2 If applicable, specify the IRB approved honest broker number (e.g., HB123456):

N/A

2.15.3.3 Identify the specific individual(s) who will be de-identifying the specimens:

The research staff who will be accompanying participants for their blood draws will be labeling the tubes and the accompanying lab request form.

[\[reviewer notes-\]](#)

2.16 Will research participants be asked to provide information about their family members or acquaintances?

* Yes

2.16.1

Describe what information about the third party will be obtained from the participant:

We request that the participant provide the name, address and phone number of an emergency contact; someone whom the research team may contact to ensure their safe participation. The research team may contact this person if they have questions about or are concerned about the health of the participant or if they are unable to reach the participant. Participants who are unable/unwilling to provide an emergency contact are ineligible to participate.

We also ask participants to designate a close friend or family member whom the study treatment team can contact to complete a questionnaire (E-Cog) about the participant's thinking and memory. We ask participants to provide the name, relationship, and phone number(s) for this individual.

2.16.2

If the information about the third party is of a private nature, can the identity of the third party be readily ascertained or associated with this information?

*

Not applicable - The information about the third party is not of a private nature

[\[reviewer notes-\]](#)

2.17 What are the main outcome variables that will be evaluated in this study?

Across the whole group, the change in functional connectivity associated with a 1-day pharmacologic probe will be compared between responders and non-responders. We will use the established endpoint for response, defined as a MADRS score of 10 or less (21) as our primary marker of response.

Changes in FC associated with a 1-day pharmacologic probe in each of the three canonical networks may predict improvement from baseline to 12 weeks in overall depression severity as well as in a specific symptom cluster: DMN changes at rest -- negative bias; ECN changes during cognitive challenge -- cognitive control; SN changes during affective regulation -- somatization/anxiety. To assess this, we are interested in looking at changes in connectivity (FC at rest for DMN, during faces-shapes for SN, during DSST for ECN) in predicting symptom cluster improvement (baseline-week 12). Symptom clusters will be defined by using MADRS (for overall depression), RSQ-Rumination (for negative bias), HARS (for anxiety/somatization) and a composite score from the neuropsych evaluations.

2.18 Describe the statistical approaches that will be used to analyze the study data.

* Addressed below:

Aim 1: Responders Versus Non-Responders.

Hypo 1.1: Across the whole group (both medications), the change in FC associated with a 1-day pharmacologic probe will differ in responders compared to non-responders. Compared to non-responders, treatment responders will have a decrease in DMN and an increase in Salience network and ECN FC at rest and during task.

Our primary analysis will consist of linear mixed effects models with FC (for each ROI) as the outcome measure and group (R [responder]/NR[non-responder]), time and their interaction.

We will control these models for other covariates (e.g. pre-treatment connectivity measures). The interaction between group and time will be a test of the effect over time and will indicate if the change in the FC measure over time is non-constant across the two groups. Models with different covariance structures of the longitudinal outcomes will be examined for goodness of fit using Akaike Information Criteria and Schwartz's Bayesian Criterion (23).

Hypo 1.2: The relationship between networks FC change at rest and during task and response group is independent of medication class.

Secondary analysis of longitudinal data component consisting of mixed effects models will also be used to assess changes in FC across time between groups, with and without the inclusion of medication group in the models. An interaction term between the two grouping factors will be added and its significant will be determined using likelihood ratio tests.

Aim 2: Associations of Networks with Symptom Clusters.

Hypo 2.1: Changes in FC associated with a 1-day pharmacologic probe in each of the three canonical networks will predict improvement from baseline to 12 weeks in overall depression severity as well as in a specific symptom cluster: DMN changes at rest -- negative bias; ECN changes during cognitive challenge -- cognitive control; SN changes during affective regulation -- somatization/anxiety. For this aim we are interested in looking at changes in connectivity (FC at rest for DMN, during faces-shapes for SN, during DSST for ECN) in predicting symptom cluster improvement (baseline-week 12). Symptom clusters will be defined by using MADRS (for overall depression), RSQ-Rumination (for negative bias), HARS (for anxiety/somatization) and an EF composite score for cognitive control (see C3). Linear mixed effects models will be used to investigate the associations between overall depression severity or each symptom cluster improvement and changes in in each of the three defined outcomes (FC at rest for DMN, during faces-shapes for SN, during DSST for ECN). For each of these outcomes, change will be computed as the difference in connectivity between two time-points (T3-T2), where T2 and T3 represent the time-points before and after initiation of medication. The mixed models will include time and connectivity change as variable of interest, we will control for baseline/pre-treatment measures of connectivity, and we will fit models with random intercept and time slope to account for the fact that not all individuals will change at the same rate. We will also explore quadratic effects of time and higher order polynomials and use quadratic smoothers if needed (24).

Hypo 2.2: Increase of dACC centrality from baseline to 12 weeks will predict overall improvement in depression severity. The outcome variable for this aim is depression severity (as measured by MADRS), and the predictor of interest is dACC centrality (which will be measured across time). If dACC centrality varies greatly between participants, appropriate transformations will be performed. Correlation between dACC centrality and depression severity will first be examined as well as spaghetti plots to visualize individual variations across time. The dACC centrality will be used in grand mean centered form such that the intercept of the model will represent the depression severity for participants with average dACC centrality. We will use a random intercept and slope mixed effects model to examine the association between dACC centrality and time. We will also explore quadratic effects of time as well as higher order polynomials. Quadratic smoothers will be considered if needed (24). The covariance structure will be examined in a similar manner as in our Aim 2.1.

Aim 3: Integration with Established Clinical and Biological Markers of LLD Treatment Response.

Hypo 3.1: Early CAN engagement is a better predictor of treatment response compared with other biological (cerebrovascular burden) or clinical markers of response (baseline depression severity, baseline comorbid anxiety, early clinical response, history of non-response). The outcome variable (treatment response) will be categorized into responders and non-responders based on the MADRS score at 12 weeks. We will fit to our data a linear logistic regression model to predict treatment response and we will use CAN engagement as the first predictor. CAN engagement will be defined as T3-T2 FC in each network-of-interest at rest and during task. We will compute the area under the receiver operating characteristic (ROC) curve. We will then add the cerebrovascular burden to the model and test the difference between the ROC curves for the model that contains CAN engagement alone to them model that contains CAN engagement and the cerebrovascular burden. Then, we will examine the predictive contribution of each clinical marker of response separately through the use of a comparison of the ROC curves for the series of models containing individual.

Early treatment response will be operationalized as a decrease in MADRS of >20% in the first two weeks of treatment (5). Additional clinical predictors to be tested: gender, duration of current episode, history of treatment response (by use of the ATHF), medical burden, sleep disturbance, executive dysfunction, and poor social support. As the ultimate goal of this aim is to develop a prediction model, we will use other model-fitting approaches as well. We will consider models based on LASSO (25) as the variable selection technique to identify the best model. We will also use alternative measures of the predictiveness of the model, including the Net Reclassification Index and predictiveness curves (26). We will fit generalized additive logistic regression models (27) to assess the relationship between treatment response and each of the main predictors.

Power Analysis. Based on our experience with previous longitudinal studies, a 20% attrition rate will account for unusable scans and for the longitudinal design. Thus, power analysis is computed on the final sample of 80 participants. We will compute effect sizes based on the following assumptions: a two-sided significance level of 0.05, a power of 0.80 and measurements at four time-points for a repeated measures model. Based on these assumptions, we are powered to observe an effect size of 0.48 when the observations are correlated at a level of 0.5 across time (H1.1). For the linear regression analysis (H1.2), with an N=80, the study will be adequately powered to detect an R² of 7.5% when a new variable is added to the model that contains two covariates accounting for 20% of variability. For H2.1, we assume that there are four measurements over time with a fixed correlation between the repeated measurements of 0.5, a two-sided significance level of 0.05, and an effect size of 0.49 resulting in an estimated power of 80% (28). Models will be limited to 2-3 covariates to insure that a minimum of 5-10 observations is available for each parameter estimated. If we assume a correlation of 0.4 between the repeated measures, we will be able to achieve 80% power to detect an effect size of 0.44.

If we consider a more conservative alpha level (0.01) due to the multiple ROI connectivity measures that will be investigated for the linear regression analysis, with the proposed sample size, the study will be adequately powered to detect an R² of 10.5% when a new variable is added to the model that contains two covariates accounting for 21% of variability. For H 2.1, we assume that there are four measurements over time, a fixed correlation between the repeated measurements of 0.5, a two-sided significance level of 0.05, and an effect size of 0.60 resulting in an estimated power of 80%. If we assume a correlation of 0.4 between the repeated measures, we will be able to achieve 80% power to detect an effect size of 0.56 (half standard deviation difference between groups across time in the outcome variable).

H3.1: Sample Size and Power: Based on previous literature, we will assume a 60/40 distribution in responders and non-responders (29). A sample of 48 from the responders group and 32 from the non-responders group achieve 82% power to detect a difference of 0.17 between two area under the ROC curve (AUC) of 0.68 and another with AUC of 0.80 using a two-sided z-test at a significance level of 0.05. Power computations were performed using SAS software, 9.4 and R 3.1.4.

Additional Exploratory and Secondary Analyses. We will also perform full-brain seed-to-voxel secondary analyses to explore network connectivity beyond the ROIs that are the focus of this project. Additional exploratory analyses will include: a) medication plasma levels; b) duration of illness (current episode and number of previous episodes); c) age of onset (early vs. late onset LLD, e.g., onset before/after age 60 (18); and d) prior use of medications (as measured by ATHF (22)). The rich data set acquired as part of this study will also allow for data-driven biomarker identification using multivariate approaches, such as machine learning.

[\[reviewer notes→\]](#)

2.19

Will this research be conducted in (a) a foreign country and/or (b) at a site (e.g., Navajo Nation) where the cultural background of the subject population differs substantially from that of Pittsburgh and its surrounding communities?

* No

Note that copies of training records, licenses, certificates should be maintained in the study regulatory binder and are subject to audit by the Research Conduct and Compliance Office (RCCO).

In addition, individuals planning to conduct human subject research outside the United States must complete an optional module on the CITI training website: International Studies. [Click here](#) to access the instruction sheet for accessing optional CITI modules.

[\[reviewer notes→\]](#)

2.21

Will this research study be conducted within a nursing home located in Pennsylvania?

* No

[\[reviewer notes→\]](#)

Section 3 - Human Subjects

3.1 What is the age range of the subject population?

60 years and older

3.2 What is their gender?

* Both males and females

Provide a justification if single gender selected:

3.3 Will any racial or ethnic subgroups be explicitly excluded from participation?

* No

If **Yes**, identify subgroups and provide a justification:

3.4 For studies conducted in the U.S., do you expect that all subjects will be able to comprehend English?

* Yes

[\[reviewer notes→\]](#)

3.5 Participation of Children: Will children less than 18 years of age be studied?

* No

If **No**, provide a justification for excluding children:

Children, adolescents, and young adults will not be enrolled because we are studying individuals who may suffer from depression in late-life (age 60 and above).

[\[reviewer notes→\]](#)

3.6 Does this research study involve prisoners, or is it anticipated that the research study may involve prisoners?

* No

[\[reviewer notes→\]](#)

3.7 Will pregnant women be knowingly and purposely included in this research study?

* No

[\[reviewer notes→\]](#)

3.8 Does this research study involve neonates of uncertain viability or nonviable neonates?

* No

[\[reviewer notes→\]](#)

3.9 Fetal Tissues: Does this research involve the use of fetal tissues or organs?

* No

[\[reviewer notes→\]](#)

--->

3.10 What is the total number of subjects to be studied at this site, including subjects to be screened for eligibility?

Note: The number below is calculated by summing the data entered in question 3.11. Any additions or changes to the values entered in 3.11 will be reflected in 3.10.

* 140

3.11 Identify each of the disease or condition specific subgroups (include healthy volunteers, if applicable) that will be studied.

Click on the "Add" button and specify for each subgroup:

1) how many subjects will undergo research related procedures at this site; and

2) if applicable, how many subjects will be required to undergo screening procedures (e.g., blood work, EKG, x-rays, etc.) to establish eligibility. **Do Not include subjects who will undergo preliminary telephone screening.**

*

Subgroup	Number to undergo research procedures	Number to undergo screening procedures
View levomilnacipram	50	70
View escitalopram	50	70

3.12 Provide a statistical justification for the total number of subjects to be enrolled into this research study at the multicenter sites or this site.

* Described below:

We intend to screen 140 participants in order to have 100 participants who complete research procedures. We expect that up to 40 participants may be ineligible. Based on our experience with previous longitudinal studies, a 20% attrition rate will account for unusable scans and for the longitudinal design. Thus, power analysis is computed on the final sample of 80 participants. We will compute effect sizes based on the following assumptions: a two-

sided significance level of 0.05, a power of 0.80 and measurements at four time-points for a repeated measures model. Based on these assumptions, we are powered to observe an effect size of 0.48 when the observations are correlated at a level of 0.5 across time (H1.1). For the linear regression analysis (H1.2), with an $N=80$, the study will be adequately powered to detect an R^2 of 7.5% when a new variable is added to the model that contains two covariates accounting for 20% of variability. For H2.1, we assume that there are four measurements over time with a fixed correlation between the repeated measurements of 0.5, a two-sided significance level of 0.05, and an effect size of 0.49 resulting in an estimated power of 80% (28). Models will be limited to 2-3 covariates to insure that a minimum of 5-10 observations is available for each parameter estimated. If we assume a correlation of 0.4 between the repeated measures, we will be able to achieve 80% power to detect an effect size of 0.44.

If we consider a more conservative alpha level (0.01) due to the multiple ROI connectivity measures that will be investigated for the linear regression analysis, with the proposed sample size, the study will be adequately powered to detect an R^2 of 10.5% when a new variable is added to the model that contains two covariates accounting for 21% of variability. For H 2.1, we assume that there are four measurements over time, a fixed correlation between the repeated measurements of 0.5, a two-sided significance level of 0.05, and an effect size of 0.60 resulting in an estimated power of 80%. If we assume a correlation of 0.4 between the repeated measures, we will be able to achieve 80% power to detect an effect size of 0.56 (half standard deviation difference between groups across time in the outcome variable).

H3.1: Sample Size and Power: Based on previous literature, we will assume a 60/40 distribution in responders and non-responders (29). A sample of 48 from the responders group and 32 from the non-responders group achieve 82% power to detect a difference of 0.17 between two area under the ROC curve (AUC) of 0.68 and another with AUC of 0.80 using a two-sided z-test at a significance level of 0.05. Power computations were performed using SAS software, 9.4 and R 3.1.4.

[\[reviewer notes-\]](#)

3.13 Inclusion Criteria: List the specific criteria for inclusion of potential subjects.

- Age greater than or equal to 60 years old
- Major Depressive Disorder and current Major Depressive Episode
- Montgomery-Asberg Depression Rating Scale (MADRS) greater than or equal to 15
- 3MS score greater than or equal to 84.

3.14 Exclusion Criteria: List the specific criteria for exclusion of potential subjects from participation.

- 3MS less than 84
- History of Mania or Psychosis
- Current suicidal ideation that cannot be safely managed within the confines of a clinical trial.
- Alcohol or Substance Abuse (current or past 3 months) endorsed via phone screening interview or diagnosed by SCID
- Dementia of any etiology endorsed via phone screening interview or diagnosed by SCID
- Medical conditions with known significant effects on mood (e.g., stroke, current hypothyroid state) as well as unstable medical illness, including delirium, uncontrolled diabetes mellitus, hypertension, hyperlipidemia, or cardiovascular risk factors that are not under medical management.
- Unwilling or clinically determined to be unable to taper from high doses of benzodiazepines (equivalent to > 2 mg lorazepam/day) or other anti-depressant/anti-anxiety medications at time of screening
- Inability to complete required assessments including brain MRI and blood draw
- Hearing/vision impairment precluding neuropsychological testing
- Difficulty conversing in English
- Clinical contraindication to use of escitalopram or levomilnacipran or history of treatment resistance to escitalopram or levonilnacipran
- Unable or unwilling to provide a secondary/emergency contact person
- Confirmed history of stroke, current epilepsy, or current post-concussive symptoms
- Impaired renal function defined as a glomerular filtration rate (GFR) of 60 or lower

3.15 Will HIV serostatus be evaluated specifically for the purpose of participation in this research study?

* No

If **Yes**, provide a justification:

[\[reviewer notes-\]](#)

- 4.1** Select all recruitment methods to be used to identify potential subjects:
 Advertisements
[Pitt + Me](#)

Advertisements

Upload the advertisements for review:

Name	Modified Date
NEMO commercial narrative	1/11/2018 1:03 PM
NEMO flyer	3/5/2018 2:41 PM
NEMO audio clip	1/11/2018 12:52 PM
NEMO screen ad	2/16/2018 1:43 PM

- 4.2** **Provide a detailed description of your recruitment methods, including identifying and initiating contact with participants:**

Participants will be recruited from the community from primary care practices, tertiary care centers, and research centers (referrals and research registries). Providers will be informed of the study and will approach potential participants. If a physician's patient expresses interest in the study, the physician will forward the contact information to the PI and/or study coordinator (with permission of the patient). Alternatively, study contact information will be provided to the patient.

Participants may also be recruited from advertisements (posters and audio clips) in the community. Word of mouth referrals are also an option for inclusion into the study.

The CTSI (Pitt+Me) Registry connects community members and UPMC patients with researchers at the University of Pittsburgh and UPMC. Registry Participants will receive a periodic newsletter that describes research study findings and details of research process and a list of research studies based on their health interests and/or medical condition(s). Names will be given to the research coordinator and s/he will follow up with the registry participants within two weeks of notification.

Potential subjects will be administered a phone screening (see Section 4.6.3) by the PI or research staff to ensure eligibility. If the participant is interested and eligible, the PI or research staff will fully describe and explain the research procedures to the participant and will schedule the visit(s). Participants will be questioned to ascertain that the procedures are clearly understood prior to beginning any study procedures. Written informed consent will be obtained prior to any research activities from the participant during the initial visit.

Note: Questions jump from 4.2 to 4.6 as questions 4.3-4.5 have been removed and the information is now captured in 4.1

[reviewer notes-],

4.6 Are you requesting a waiver to document informed consent for any or all participants, for any or all procedures? (e.g., a verbal or computerized consent script will be used, but the subjects will not be required to sign a written informed consent document. *This is not a waiver to obtain consent.*

* Yes

4.6.1 Identify the specific research procedures and/or the specific subject populations for which you are requesting a waiver of the requirement to obtain a signed consent form.

Addressed below:

If not all, identify the specific procedures and/or subject populations for which you are requesting a waiver:

We have requested a waiver of the requirement to obtain signed informed consent for the screening process, which will take place over the phone. We believe we meet the following criteria: The respective research procedures present no more than minimal risk of harm to the involved participants and involve no procedures for which written consent is normally required outside of the research context. We believe the information being obtained during the screening phone call is the same type of information that would be collected on patients setting up an appointment for their condition.

4.6.2 Indicate which of the following regulatory criteria is applicable to your request for a waiver of the requirement to obtain a signed consent form.

45 CFR 46.117(c)(2)

45 CFR 46.117(c)(1) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or

45 CFR 46.117(c)(2) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

4.6.2.1 Address why the specific research procedures for which you are requesting a waiver of the requirement to obtain a signed consent form present no more than minimal risk of harm to the research subjects:

The screening questions present no more than minimal risk of harm to the involved participants and involve no procedures for which written consent is normally required outside of the research context. The information being obtained during the screening phone call is the same type of information being collected on patients setting up an appointment for their depression. If the participant is deemed not to be eligible, all the information collected during the screening process will be destroyed. In addition, written informed consent will be obtained at the screening visit prior to any research activities.

4.6.2.2 Justify why the research listed in 4.6.1 involves no procedures for which written informed consent is normally required outside of the research context:

The phone screening will act as documentation of verbal consent for the phone screening interview. We will first read the screening script followed by (with permission from the participant) the screening questions. The script will then be reviewed and a determination would be made as to whether the participant is appropriate for a 3T and/or 7T MRI study or whether s/he are ruled out of the study for safety reasons. If s/he is ruled out, the specific screening information will be destroyed and a simple form that states only that the participant failed the screening for the MRI scan will be retained so we can avoid contacting that participant for MRI studies in the future. At this point, if s/he is eligible and interested in enrolling in this research study, s/he will be invited to come in for further evaluation at which time the formal study consent form will be signed.

4.6.3

Address the procedures that will be used and the information that will be provided (i.e., script) in obtaining and documenting the subjects' verbal informed consent for study participation:

The phone screening will act as documentation of verbal consent for the phone screening interview. After the phone script is reviewed and all of the participant's questions/concerns are answered, if the participant is interested in participation, the study staff will explain that to determine eligibility, we will need to ask him/her some screening questions. The research staff member will explain that he/she may choose not to answer any questions that make him/her feel uncomfortable and may end the phone call at any time. The questions will ascertain that the participant is currently experiencing symptoms of depression and is eligible to safely undergo an MRI.

Upload Scripts:

Name	Modified Date
NEMO_phone_screen.docx	1/25/2018 3:35 PM

[\[reviewer notes~\]](#)

4.7 Are you requesting a waiver to obtain informed consent or an alteration of the informed consent process for any of the following?

* No

4.7.1 If Yes, select the reason(s) for your request:

There are no items to display

General Requirements: The Federal Policy [45 CFR 46.116 (d)] specifies in order for a waiver of consent to be approved, the request must meet four criteria. For each request, you will be asked to provide a justification addressing how each of these criterion is met.

[\[reviewer notes~\]](#)

4.8 Are you requesting an exception to the requirement to obtain informed consent for research involving the evaluation of an 'emergency' procedure?

Note: This exception allows research on life-threatening conditions for which available treatments are unproven or unsatisfactory and where it is not possible to obtain informed consent.

* No

[\[reviewer notes-\]](#)**4.9****Upload all consent documents for watermarking:**

Draft Consent Forms for editing:

Name	Modified Date
Consent Form	3/1/2018 11:28 AM

Approved Consent Form(s):

Name	Modified Date
Consent Form	3/1/2018 11:28 AM

[\[reviewer notes-\]](#)**4.10****Will all potential adult subjects be capable of providing direct consent for study participation?**

*

Yes

[\[reviewer notes→\]](#)

4.11

At what point will you obtain the informed consent of potential research subjects or their authorized representative?

After performing certain of the screening procedures, but prior to performing any of the research interventions/interactions

4.11.1

Address why you feel that it is acceptable to defer obtaining written informed consent until after the screening procedures have been performed.

The phone screenings will allow the investigators to determine the potential subject's eligibility as well as his or her safety in undergoing an MRI scan (e.g. metal in body). Conducting this interview with brief screening would reduce participant burden by eliminating an extra visit to the research site should they not be eligible to participate. The telephone screening script will include obtaining verbal consent prior to asking the screening questions.

4.11.2

Taking into account the nature of the study and subject population, indicate how the research team will ensure that subjects have sufficient time to decide whether to participate in this study. In addition, describe the steps that will be taken to minimize the possibility of coercion or undue influence.

Participants will be allowed as much time as they need to consider participation after the consent form is reviewed. They will be encouraged to voice any questions or concerns at that time, prior to signing the consent form. Subjects will be provided with a clear explanation of the objectives, procedures, risks and benefits of the study and all questions will be answered. Because we believe that consent is an ongoing process in any study, we will continue to educate subjects about the nature of the research and address any questions that may arise throughout the course of the study. All members of our research team who have contact with potential participants will receive training in the importance of not coercing or otherwise unfairly influencing individuals to participate in this study.

[\[reviewer notes→\]](#)

4.12

Describe the process that you will employ to ensure the subjects are fully informed about this research study.

* Addressed below:

This description must include the following elements:

- who from the research team will be involved in the consent process (both the discussion and documentation);
- person who will provide consent or permission;
- information communicated; and
- any waiting period between informing the prospective participant about the study and obtaining consent

In addition, address the following if applicable based on your subject population:

- process for child assent and parental permission
 - continued participation if a child subject turns 18 during participation
- process for obtaining proxy consent and assent for decisionally impaired subjects
 - continued participation if subject regains capacity to consent

Drs. Aizenstein or Andreescu will review the consent form with the participant. The purpose

of the research study, the procedures involved in the conduct of the study, potential risks and benefits, and the rights of study participants will be discussed with the potential subject prior to the attainment of written informed consent. Questions will be asked of subjects to ensure they understand the nature of the research, the risks and potential benefits of participation, and their rights as research subjects. Participants will be given as much time as needed to decide whether they wish to sign the consent form. Participants will also be informed that signing the consent form does not bind them to complete any part of the study- they can always change their mind.

We believe that consent is an ongoing process in any study, and we will continue to educate subjects about the nature of the research and address any questions that may arise throughout the course of the study. We are not planning proxy consent.

Subjects who require re-consent will be given ample time to review the consent form. Study staff will review the changes made to the consent form and any applicable study procedures that were revised. A note to file will be attached to the re-consent outlining the reason for the additional consent form.

4.13

Are you requesting an exception to either IRB policy related to the informed consent process?

- For studies involving a drug, device or surgical procedures, a listed physician investigator is required to obtain the written informed consent unless an exception to this policy has been approved by the IRB
- For all other studies, a listed investigator is required to obtain consent (Note: In order to request an exception to this policy, the study must be minimal risk)

* No

If **Yes**, provide a justification and describe the qualifications of the individual who will obtain consent:

4.14

Will you inform research subjects about the outcome of this research study following its completion?

* No

If **Yes**, describe the process to inform subjects of the results:

[\[reviewer notes-\]](#)

5.1 Describe potential risks (physical, psychological, social, legal, economic or other) associated with screening procedures, research interventions/interactions, and follow-up/monitoring procedures performed specifically for this study:

*

View	Research Activity:	Breach of Confidentiality
	Common Risks:	<i>No Value Entered</i>
	Infrequent Risks:	There is a potential risk of breach of confidentiality that is inherent in all research protocols. There is a possibility that if research data were to become generally known, this knowledge could potentially impact a subject's future insurability, employability, or reproduction plans, or have a negative impact on family relationships, and/or in paternity suits or stigmatization.
	Other Risks:	<i>No Value Entered</i>
View	Research Activity:	Electrocardiogram (EKG)
	Common Risks:	<i>No Value Entered</i>
	Infrequent Risks:	Risks associated with the electrocardiogram (EKG) can include skin irritation, chaffing, and redness.
	Other Risks:	<i>No Value Entered</i>
View	Research Activity:	Fetzima (levomilnacipran)
	Common Risks:	5% of people (5 out of 100 people) may experience nausea, constipation, hyperhidrosis, heart rate increase, erectile dysfunction, tachycardia, vomiting, and palpitations
	Infrequent Risks:	Occurring in < 2% of MDD patients treated with FETZIMA (2 out of 100 people) may experience angina pectoris; supraventricular and ventricular extrasystoles; dry eye; Vision blurred; Conjunctival hemorrhage; chest pain; thirst; abdominal pain; flatulence; blood cholesterol increased; liver function test abnormal; migraine; paraesthesia; syncope; extrapyramidal disorder; agitation; anger; bruxism; panic attack; tension; aggression; pollakiuria; hematuria; proteinuria; yawning; dry skin; pruritus; urticaria; low levels of salt (sodium) in the blood Serotonin syndrome occurs when people take medications that cause high levels of serotonin to accumulate in the body. Symptoms of this include high body temperature, agitation, increased reflexes, tremor, sweating, dilated pupils, and diarrhea.
	Other Risks:	Bruising and gastrointestinal bleeding are increased in older individuals taking serotonergic antidepressants

[View](#)

Research Activity:	Lexapro (Escitalopram)
Common Risks:	10-25% of people (10 to 25 out of 100 people) may experience nausea
Infrequent Risks:	Occurring in 1-10% of people include sleepiness, fatigue, yawning, trouble sleeping, dizziness, flu-like symptoms, feeling anxious, sweating, shaking, not feeling hungry, dry mouth, runny nose, sinus congestion, sexual problems, urinary tract infection, and gastrointestinal symptoms such as constipation, abdominal pain, diarrhea, and indigestion. Serotonin syndrome occurs when people take medications that cause high levels of serotonin to accumulate in the body. Symptoms of this include high body temperature, agitation, increased reflexes, tremor, sweating, dilated pupils, and diarrhea.
Other Risks:	Occurring in less than 1% of people include suicidal thoughts or actions, severe allergic reactions, abnormal bleeding or bruising, seizures or convulsions, manic episodes (feeling unusually energetic, happy and/or irritable), low levels of salt (sodium) in the blood, and visual problems. Bruising and gastrointestinal bleeding are increased in older individuals taking serotonergic antidepressants

[View](#)

Research Activity:	MRI
Common Risks:	<i>No Value Entered</i>
Infrequent Risks:	Some subjects experience discomfort associated with confinement and remaining stationary for a long period of time. Since the MRI is very noisy, there is the risk of hearing impairment. There is also the risk of injury related to metal attraction, since the MRI machine is a giant magnet. There is an increased risk of dizziness and nausea associated with being in the 7-Tesla scanner.
Other Risks:	<i>No Value Entered</i>

[View](#)

Research Activity:	Rating scales, questionnaires, and cognitive assessments
Common Risks:	<i>No Value Entered</i>
Infrequent Risks:	Some inconvenience and or anxiety may occur due to time required to complete formal rating scales and questionnaires. The cognitive assessments impose some risk of emotional discomfort.
Other Risks:	<i>No Value Entered</i>

[View](#)

Research Activity:	Skin conductance
Common Risks:	<i>No Value Entered</i>
Infrequent Risks:	Some subjects experience discomfort related to the cuff. We are able to loosen the cuff to a certain extent to make more comfortable.
Other Risks:	<i>No Value Entered</i>

[View](#)

Research Activity:	Tapering off of anti-anxiety medication
Common Risks:	There is a risk of withdrawal symptoms in individuals who are asked to reduce their dose of benzodiazepines. Potential withdrawal symptoms include an increase in anxiety symptoms as well as symptoms of withdrawal, such as feeling nauseous, achy, having diarrhea, or beginning to sweat. .
Infrequent Risks:	<i>No Value Entered</i>
Other Risks:	<i>No Value Entered</i>

View	Research Activity:	Tapering off of antidepressant medication
	Common Risks:	There is a risk of withdrawal symptoms in individuals who stop taking another antidepressant medication before starting the study medication. Potential withdrawal symptoms include an increase in depressive symptoms as well as symptoms of withdrawal, such as feeling nauseous, achy, having diarrhea, or beginning to sweat. Participants who decide to abruptly discontinue the study antidepressant medication (not advised) may also experience symptoms of withdrawal.
	Infrequent Risks:	<i>No Value Entered</i>
	Other Risks:	<i>No Value Entered</i>
View	Research Activity:	Venipuncture blood draw
	Common Risks:	<i>No Value Entered</i>
	Infrequent Risks:	Risks of venipuncture blood draws may include mild discomfort and bruising at the venipuncture site and a chance of bleeding, fainting, and/or infection.
	Other Risks:	<i>No Value Entered</i>

5.1.1 Describe the steps that will be taken to prevent or to minimize the severity of the potential risks:

The venipuncture blood draws will be performed by properly trained personnel.

Rating scales will be performed by experienced research clinicians. If subjects experience emotional distress or undue burden during the administration of the assessments, collection of data will be postponed or minimized for that subject. With respect to minimizing the discomfort that may result from the interview, raters have been or will be selected on the basis of personal attributes and interpersonal skills as well as substantive knowledge. They will be further trained and periodically observed to ensure that they are respectful and sensitive to the needs and feelings of the subjects. Furthermore, they are trained to recognize signs of significant stress or irritability and will be instructed that they should gently terminate the interview whenever distress is observed.

Risks associated with MR imaging include claustrophobia, ringing in the ears, and the magnetic field which can attract ferromagnetic objects toward the magnet. Care will be taken to minimize distress due to claustrophobia by thoroughly training all project staff who come in contact with subjects, to ensure that they are sensitive to a subject's distress and will be capable of dealing with them in a courteous manner. In addition, subjects will be screened for potential contraindications for MR scanning, including metal in their body and claustrophobia, and will be excluded from the study when appropriate. Trained MR technologists will complete a thorough secondary safety screen about medical history to insure there is no metal in the participant's body that could potentially be attracted by the scanner. The presence of such metal is exclusionary. All subjects are required to wear ear plugs in the scanner to protect their hearing. Despite all preparation, some subjects experience discomfort associated with confinement and remaining stationary for a long period of time. Testing or scanning of any subject who becomes distressed will be terminated immediately. We will mitigate this risk by opting to scan participants on 3-Tesla machine when there is any doubt that it could be unsafe to scan them at 7-Tesla

Physiologic signals will be recorded using MR-safe equipment and disposables. For EKG and SGR, we will be using specially designed carbon fiber electrode leads and carbon fiber electrodes, designed to be used within the MRI suite. The physiologic signals will then be carried thorough the penetration panel into the MRI control room on MRI cables designed by Biopac Systems Inc to provide isolated and RF filtered interfacing between the subject and the control room. In the control room, Biopac Systems Inc amplifiers with signal

processing circuitry to remove spurious MRI artifact from the source physiological data will be used. This system is nearly identical to Bipoac systems in use in the MRI suite in both Children's Hospital and the McGowan Institute.

There is a potential risk of breach of confidentiality that is inherent in all research protocols. Procedures have been established, and will be followed, to minimize the risk of breach of confidentiality. Data will be entered into password-secured databases by staff authorized by the PI to do this, and they will abide by confidentiality regulations of the IRB. These data are password-secured for accessibility only by authorized personnel associated with the study. Subject anonymity will be preserved by the use of a code number (not related to name, social security number, or date of birth) on all questionnaires and reports. A list of subject names will be kept in a separate locked cabinet with access only to study personnel authorized by the PI. No subject will be identified by name in any published reports.

Recruitment procedures will protect subject confidentiality and no cold-calling will occur. No individually identifiable health information will be shared with the researchers until a potential subject signs a HIPAA authorized consent form.

The PI will have primary responsibility for the monitoring of subjects during the entire time they participate in the study. Subjects will be reviewed at baseline with the PI or physician co-investigators; exclusion criteria will reduce the risk to subjects.

The risk of withdrawal symptoms associated with abrupt discontinuation of the study antidepressant medication will be mitigated by warning participants of the necessity to gradually decrease their dosage under the supervision of a physician if they decide that they no longer wish to remain on the study medication. For those entering the study who either wish to discontinue an ineffective antidepressant medication or are asked to reduce their dosage of a benzodiazepine medication, the risk of withdrawal symptoms will be mitigated by careful (at least weekly) monitoring. Tapering plans will also be sufficiently gradual to minimize the risk of withdrawal symptoms. Participants will also be instructed to let the study physician know if he/she experiences withdrawal symptoms, so that the taper can be adjusted to decrease the withdrawal symptoms.

The risks of worsening of depressive or anxiety symptoms and an increase in suicidal thinking and suicidal behavior or psychotic thinking will be mitigated by systematic and careful assessment of depressive, and anxiety symptoms, and for suicidality throughout the protocol. Subjects who are psychotic or whose suicidality is deemed too severe to be managed in the context of the protocol will be withdrawn from the study and offered (or when necessary, involuntarily given) appropriate treatment. If a subject is thought to be suicidal or psychotic, a physician investigator will immediately be contacted, and the severity of the suicidal ideation or psychosis will be further probed, imminent risks assessed, and an immediate plan of care implemented, such as increased frequency of outpatient assessments, further evaluation at the psychiatric emergency room, or immediate psychiatric hospitalization via emergency services. If a participant is found to be at high risk for suicide via the phone screen, he/she will be immediately referred to services, and we may initiate a 3-way call to Re:Solve with the participant's cooperation. A study physician will be contacted for guidance with the referral and to conduct a more in-depth evaluation. We have a detailed suicide/depression management flowchart which has been attached in "Other Attachments".

One of the study physicians will always be available by pager or cellular phone to discuss and assume management of suicidal patients with the clinician-therapist. To reduce the risk of adverse outcome by suicide, there will be a physician on call 24 hours/daily, seven days/weekly, so professional guidance is always available for high-risk situations.

Another protection against risk in this study is the standardization of assessment, treatment, and follow-up that will be provided by the study. In other words, the study will provide a safety net for patients and a source of information, education, and reassurance for family members and caregivers that can reach project staff on a 24/7/365 basis (with physician back-up). Adequate measures have been taken to ensure that the occurrence of illness or injury will be detected and treated. In addition to procedures established to protect confidentiality, careful monitoring of side effects, careful monitoring of dosage throughout the study, careful assessment of suicidality throughout the study, the 24 hour

answering service, and the Data and Safety Monitoring plan. Patients will be informed of the possible side effects from the study medication. Vital signs will be monitored regularly. Similarly, sodium levels and EKG will be monitored throughout the study. A study physician will be available by pager at all times for prompt assessment of any concerns (e.g., clinical worsening) or potential adverse reactions. Subjects are asked to identify a family member or other person who can be contacted by research staff to discuss depressive symptoms and concerns about subject's clinical status. Specific endpoints that will result in removal of a subject from the study include: if a subject develops side effects or medical complications that cannot be satisfactorily treated by a decrease in dosage, if a subject develops incident psychopathology (such as psychosis, delirium, or severe agitation) that requires treatment with another psychotropic (such as an antipsychotic agent), or if a subject's suicidality is deemed too severe to be managed in the context of the study. These subjects will be referred for appropriate follow up care based on their needs and preferences.

5.2

What steps will be taken in the event that a clinically significant, unexpected disease or condition is identified during the conduct of the study?

*** Addressed below:**

During screening, if a clinically significant and/or unexpected disease or condition is detected, the individual will be encouraged to follow-up with their primary care physician or report to an emergency room. The PI of the study will always be on call to assist the screening clinician with 1) further evaluation of the detected disease/condition and 2) assuring that appropriate referrals for safe follow-up care are provided to the individual. If a person is deemed to be suicidal, we will follow our internal suicide assessment plan.

Should anything previously unknown be found on the MRI that is of clinical relevance, it will be reviewed immediately by a radiologist. The PI will review the findings with the patient and give an appropriate referral. A copy of the MRI will be burned to a disc and provided to the patient if requested.

5.3

All the risk questions (screening, intervention/interaction, follow-up) have been merged into one question (5.1).

[\[reviewer notes-\]](#)

5.4

Do any of the research procedures pose a physical or clinically significant psychological risk to women who are or may be pregnant or to a fetus?

* No

[\[reviewer notes-\]](#)

5.5

Do any of the research procedures pose a potential risk of causing genetic mutations that could lead to birth defects?

* No

[\[reviewer notes→\]](#)

5.6

Are there any alternative procedures or courses of treatment which may be of benefit to the subject if they choose not to participate in this study?

* Yes - Describe below:

If **Yes**, describe in detail:

Subjects can choose to not participate or choose to seek a second opinion to receive alternative treatment for their depression symptoms.

[\[reviewer notes→\]](#)

5.7

Describe the specific endpoints (e.g., adverse reactions/events, failure to demonstrate effectiveness, disease progression) or other circumstances (e.g., subject's failure to follow study procedures) that will result in discontinuing a subject's participation?

* Describe below:

Endpoints related to depression treatment: If subjects are determined by the research team to be unable to follow study requirements, such as attend appointments, or participate in research assessments. If a subject develops side effects or medical complications that cannot be satisfactorily treated by a decrease in dosage, or if a subject develops incident psychopathology (such as psychosis, delirium, or severe agitation) that requires treatment with another psychotropic (such as another antipsychotic agent), or if a subject's suicidality is deemed too severe to be managed in the context of the study. These subjects will be referred for appropriate follow up care based on their needs and preferences.

Endpoints related to the MRI include: inability to return for the post-treatment scan, any adverse reaction to the pre-treatment scan, and the presence of any exclusion criteria (e.g., metal in body).

[\[reviewer notes→\]](#)

5.8

Will any individuals other than the investigators/research staff involved in the conduct of this research study and authorized representatives of the University Research Conduct and Compliance Office (RCCO) be permitted access to research data/documents (including medical record information) associated with the conduct of this research study?

* Yes

5.8.1

Identify the 'external' persons or entity who may have access to research data/documents and the purpose of this access:

The National Institute of Mental Health (the sponsor of this study) may choose to audit and review our research data.

Authorized representatives or other affiliated health care providers (such as lab personnel, pharmacy staff, neuropsychological staff) may also have access to identifiable information related to individuals' participation in this research study for the purpose of (1) fulfilling orders, made by the investigators, for hospital and health care services (e.g., laboratory tests, diagnostic procedures) associated with research study participation; (2) addressing correct payment for tests and procedures ordered by the investigators; and/or (3) for

internal hospital operations (i.e., quality assurance).

Participants may need transportation through Corporate Sedan/VauxCo Limousines or a taxi service. Subject name and address will be given to the driver, but no description of the research study will be made available.

We may also release deidentified research records to the National Institute of Mental Health Data Archive (NDA).

To protect participant confidentiality, all personal identifiers (such as your name, social security number, birth date) will be removed (de-identified) and replaced with a specific code number. The information linking this code number to participant identity will be kept in a separate, secure location. The investigators on this study will keep the data indefinitely.

Secondary investigators who may be interested in depression in the older population may receive data for analysis that is de-identified.

5.8.2

Will these 'external' persons or entity have access to identifiable research data/documents?

*

No; the research data/documents will be coded and subject identifiers removed prior to access by the external persons

If **Yes**, describe how they will protect the confidentiality of the research data:

5.9

Has or will a Federal Certificate of Confidentiality be obtained for this research study?

* Yes

5.10

Question has been moved to 5.17

5.11

Question has been moved to 5.16

[\[reviewer notes→\]](#)

5.12 Does participation in this research study offer the potential for direct benefit to the research subjects?

Yes - Describe the direct benefit that subjects may receive as a result of study participation. Indicate if all, or only certain, of the subjects may derive this potential benefit.

Describe the benefit:

There is no guarantee that a subject will benefit from participation in this research study. Symptoms may improve but there is no guarantee that they will. Subjects may benefit from the comprehensive diagnostic assessments and on-going close monitoring provided in the study. They will receive treatment by skilled clinicians and treatment with a medication with proven safety and efficacy for major depressive disorder. Subjects may benefit from careful assessment of cognition if areas of impairment are detected that could be improved by other forms of treatment.

5.13 Describe the data and safety monitoring plan associated with this study. If the research study involves multiple sites, the plan must address both a local and central review process.

The basic protection against risk in this study is the standardization of assessment, treatment, and follow-up that will be provided by the study. In other words, the study will provide a safety net for patients and a source of information, education, and reassurance for family members and caregivers that can reach project staff on a 24/7/365 basis (with physician back-up). The study investigators, study coordinator, study staff, and data manager will meet weekly (or at times bi-weekly) to review accrued data, data confidentiality, adherence to protocol design, recruitment and subject complaints. During this meeting, subjects in the study will be clinically reviewed, including discussion of clinical presentation, changes in clinical symptoms, concurrently prescribed medications, side effects, and any possible adverse events, and subjects with suicidal risk. During these discussions, any possible changes to the protocol or risk-benefit level will be discussed.

Adverse events, assessment of changes to the risk/benefit ratio, acceptability of study continuation, breaches in confidentiality, and subject complaints will be reviewed by the principal investigator. The PI will meet with study team on a weekly or bi-weekly basis to discuss study conduct and study safety. This can happen more frequently if clinically indicated. Summaries of these data and safety monitoring activities will be provided to the IRB at the time of protocol renewal. Any change in risk-to-benefit ratio will be provided to currently active subjects and once a modified consent form is approved by the IRB, active subjects will be re-consented if they decide to continue, and any new subjects will be consented with the new consent form.

[\[reviewer notes→\]](#)

Section 5 - Potential Risks and Benefits of Study Participation

5.14

What precautions will be used to ensure subject privacy is respected? (e.g. the research intervention will be conducted in a private room; the collection of sensitive information about subjects is limited to the amount necessary to achieve the aims of the research, so that no unneeded sensitive information is being collected, drapes or other barriers will be used for subjects who are required to disrobe)

All data collection and intervention sessions in this study will be conducted in private rooms. The collection of sensitive information about subjects in this study is limited to the amount necessary to achieve the aims of the research, so that no unneeded sensitive information is being collected. Drapes will be used to provide privacy when participants disrobe for the EKG exam.

The experimental procedures including during the MRI occur at the MR research center which is specifically equipped for research studies in order to maintain the confidentiality of subjects. Participants are provided with a locked, private room in which they can change their clothing and store their belongings in individually padlocked lockers. Furthermore, the

collection of sensitive information about subjects is limited to the amount necessary to achieve the aims of the research, so that no unneeded sensitive information is being collected.

5.15

What precautions will be used to maintain the confidentiality of the research data during collection, transmission and storage? It is important that you indicate the data security measures for all data types.

Go to the [A-Z Guidance](#), download the Data Security Assessment Form, complete, and upload using the Add button below. Depending on the data type, you may need to consult with your data manager to address some of the sections. Email irb@pitt.edu if you have any questions.

* Upload Data Security Form:

Name	Modified Date
Data Security AssessmentForm_new NEMO Jan 2018.docx	1/16/2018 8:21 AM

Address what precautions will be used to maintain the confidentiality of the research data collected in paper format if applicable:

Data will be entered into password secured data bases by staff authorized by the principal investigator to do this, and they will abide by confidentiality regulations of the IRB. These data are password secured for minimal access to authorized personnel associated with the study. No research documents will contain the names of participating subjects. Subject anonymity will be preserved by the use of a code number. Research records will be kept in a locked file. No subject will be identified by any published report.

Study staff will assign NDA GUIDs through the NDA website (GUID Tool) using certain identifiers (full name at birth, date of birth, twin status at birth, sex, and city or municipality at time of birth). These identifiers will only be used by study staff for the purposes of searching for an existing GUID or to creating a new GUID. The identifiers will never be sent to or stored by the NDA, and will be stored by study staff in paper form in a locked filing cabinet, behind locked doors, separate from research data. The GUID will be stored electronically in a secured, password-protected database table. This table, which will contain the subject's initials, DOB, sex, and race, will be separate from the research data. Before uploading any data to the NDA repository, we will ensure that all data is deidentified using the GUID.

5.15.1

Does your research study require a data security review? Answer Yes if any of the following conditions are met:

- Identifiable or *coded data will be collected, stored, or transmitted using any of the following technologies: mobile app, web-based site or survey, wearable device, text messaging, electronic audio, photographic, or video recording or conferencing **and/or**
- The IRB requested a data security review during their review of the study

* No

***Coded:** Identifying information (such as name) that would enable the investigator to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a code (number, letter, symbol, or any combination) and a key to decipher the code exists, enabling linkage of the identifying information to the private information or specimens

5.16

If the subject withdraws from the study, describe what, if anything, will happen to the subject's research data or biological specimens.

Any identifiable research or medical information which is recorded, which results from subject participation in this research study prior to the date that subject formally withdrew consent may continue to be used and disclosed by investigators.

5.17

Following the required data retention period, describe the procedures utilized to protect subject confidentiality. (e.g., destruction of research records; removal of identifiers; destruction of linkage code information; secured long-term retention)

Data will be entered into password secured databases by staff authorized by the PI to do this and they will abide by confidentiality regulations of the IRB. These data are password secured for accessibility only by authorized personnel associated with the study. Subject confidentiality will be preserved by the use of a code number on all questionnaires and reports. Research records will be kept in a locked file accessible to only research personnel. A list of subject names will be kept in a separate locked file with access only to study personnel authorized by the PI. No subject will be identified in any published report. After the retention period, we will maintain the deidentified data in a password-secured database.

[\[reviewer notes-\]](#)**6.1**

Will research subjects or their insurance providers be charged for any of the procedures (e.g., screening procedures, research procedures, follow-up procedures) performed for the purpose of this research study?

*

No

[\[reviewer notes-\]](#)**6.2 Will subjects be compensated in any way for their participation in this research study?**

* Yes

6.2.1

Describe the amount of payment or other remuneration offered for complete participation in this research study.

Participants will receive up to \$20 for completing clinical assessments (regardless of whether they are excluded prior to the completion of all assessments) and \$10 for the simulator (Total: \$30)

Participants will receive \$75 for each hour long scan and \$50 each for each 1/2 hour scan. (Total: \$250)

Travel-related reimbursement of \$10 for every in-person visit.

Total compensation of up to \$450 may be paid to each participant.

6.2.2 Describe the amount and term of payment or other remuneration that will be provided for partial completion of this research study.

Participants will be paid upon completion of each activity (screening visit, simulator, MRI). If a participant is unable to complete the activity (e.g., scanner issue, claustrophobia, etc), they will be compensated in full for that particular activity.

[\[reviewer notes~\]](#)

7.1 Summarize the qualifications and expertise of the principal investigator and listed co-investigators to perform the procedures outlined in this research study.

Howard J. Aizenstein, M.D., Ph.D., is a Professor of Psychiatry, Bioengineering, and Clinical and Translational Science at the University of Pittsburgh. Dr. Aizenstein is a geriatric psychiatrist and has research experience in the cognitive neuroscience and functional MRI of memory and learning systems. He has carried out studies of implicit learning using behavioral measures and also functional brain imaging.

Carmen Andreescu, M.D., is an Assistant Professor of Psychiatry and geriatric psychiatrist who carries out research on anxiety and depression in elderly persons.

Meryl A. Butters, Ph.D., is an Associate Professor of Psychiatry at the University of Pittsburgh. Dr. Butters is a neuropsychologist with extensive expertise in evaluating and examining cognitive function in the context of depression, mild cognitive impairment, dementia, and normal aging.

Tae Kim, Ph.D., is Assistant Professor of Radiology at the University of Pittsburgh, whose research focuses on MRI methodology for quantitative measurement of cerebrovascular changes that are associated to the cerebrovascular-induced alterations in the brain as well as other quantifications related to neurodegenerative diseases, such as Alzheimer's disease. He possesses an excellent background in MRI physics and data processing.

Dana Tudorascu, Ph.D. is Assistant Professor of Medicine, Biostatistics, Psychiatry, and Clinical and Translational Science at the University of Pittsburgh. As a biostatistician, Dana has over six years of experience working with investigators in different areas of clinical research (neuroimaging, health research outcomes, cognitive markers, etc).

[\[reviewer notes~\]](#)**7.2 Indicate all sources of support for this research study.**

*

Selections

Federal: Upload a copy of the entire grant application (**including the cover sheet**) if our site is the awardee institution; for federal contracts, upload a copy of the research plan

If **Federal** support, provide the sponsor information:

Federal sponsor	Grant Title	Grant number	Awardee institution	Federal grant application
View NIH/NIMH	Neural Mechanisms of Monoaminergic Engagement in late-life depression treatment response (NEM)	R01 MH076079	University of Pittsburgh	NEMO Grant Application(0.01)

For projects not supported by a federal grant, upload the research plan that was submitted for funding:

Name Modified Date

If **Industry** support, provide the sponsor information and level of support:

If **Foundation** support, provide the sponsor information:

If **Other** support, provide the support information and level of support:

[\[reviewer notes-\]](#)

7.3

Is this study funded in part or whole by a PHS Agency?

* No

Does any investigator* involved in this study (select all that apply):

Name

- ☐ **A.** Have equity in a **publicly-traded entity** that either sponsors** this research or owns the technology being evaluated or developed that exceeds a **5% ownership interest** or a current value of **\$10,000**?
- ☐ **B.** Have equity in a **non-publicly-traded entity** that either sponsors this research or owns the technology being evaluated or developed?
- ☐ **C.** Receive salary, consulting fees, honoraria, royalties or other remuneration from an entity that either sponsors this research or owns the technology being evaluated or developed that is expected to exceed **\$10,000** during the past or next 12 months?
- ☐ **D.** Have rights as either the author or inventor of **intellectual property** being evaluated or developed in this research that is the subject of an issued patent or has been optioned or licensed to an entity?
- ☐ **E.** Have an officer or management position**** with a **Licensed Start-up Company** overseen by the COI Committee that either sponsors this research or owns the technology being evaluated or developed?
- ☐ **F.** Receive compensation of any amount when the value of the compensation would be affected by the outcome of this research, such as compensation that is explicitly greater for a favorable outcome than for an unfavorable outcome or compensation in the form of an equity interest in the entity that either sponsors this research or owns the technology being evaluated or developed?
- ☒ **None of the above options apply and there are no other financial conflicts of interest in the conduct of this research.**

***Investigator** means the PI, co-investigators, and any other member of the study team, regardless of title, who participates in the design, conduct, or reporting of this research, as well as his/her spouse, registered domestic partner, dependents, or other members of his/her household. **The PI is responsible for ensuring that s/he and all other relevant members of the study team review the above questions describing Significant Financial Interests.**

******through the provision of funds, drugs, devices, or other support for this research

********Such as serving on the Board of Directors or Board of Managers or a position that carries a fiduciary responsibility to the company (e.g., CEO, CFO, CTO, or CMO).

[\[reviewer notes→\]](#)

Supporting Documentation Section

References and Other Attachments

Additional documents:

Name	Modified Date	Version
Benzo Equiv Table	1/5/2018 1:45 PM	0.01
GPN Lab Protocol for Suicide Risk	1/5/2018 1:45 PM	0.01
NEMO IRB Refs	1/5/2018 1:46 PM	0.01
Over the phone suicide assessment	2/21/2018 12:41 PM	0.01
WPIC Research Committee Approval Letter	1/5/2018 1:44 PM	0.01

Please use the Add button to the left to upload additional documents if needed.

[\[reviewer notes→\]](#)

ClinicalTrials.gov is a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world.

"[Applicable clinical trials](#)" are required **by federal law** to be registered in [ClinicalTrials.gov](#).

Applicable Clinical Trials (ACTs) are studies that meet the following criteria:

- The study is an interventional study AND
- The study intervention is a drug, biologic, medical device, radiation or genetic AND
- The Study is not Phase 0 or 1 AND
- The study has at least one site in the United States or is conducted under an investigational new drug application or investigational device exemption

NIH Policy

Effective January 18, 2017, revised [NIH](#) Policy requires that all [clinical trials](#) funded in whole or in part by the NIH be registered and results information posted on ClinicalTrials.gov.

As defined by the NIH, a [clinical trial](#) is:

A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health related biomedical or behavioral outcomes.

The NIH Policy extends beyond the Food and Drug Administration Amendment Act (FDAAA 801) requirements in that it requires registration and results reporting of:

- clinical trials of behavioral, surgical and other types of health and medical interventions
- phase 1 studies of drugs and biological products
- small feasibility studies of device products

Failure to submit all required registration and results information requested on ClinicalTrials.gov can jeopardize University grant funding, the future funding of the grantee and subject the University of Pittsburgh to future monetary penalties.

In addition, to promote transparency of the clinical trials process, the [International Committee of Medical Journal Editors \(ICMJE\)](#) has established a policy requiring the entry of clinical trials in a public registry, such as ClinicalTrials.gov, prior to subject enrollment as a condition of consideration for publication of the trial results.

*** Based on the above information, will this study be registered in ClinicalTrials.gov?**

Yes

Who will serve as the Responsible Party? UPMC/Pitt Investigator or IND/IDE Pitt Sponsor

Why are you registering your study? (Check all that apply)

It is an **ACT** (*Registration must be no later than 21 days after the enrollment of the first participant*)

If you are not yet registered and need to establish an account for the PI or other research staff that may need to access the record, please send an email to the University of Pittsburgh PRS administrator at ctgov@pitt.edu with the following information for each individual:

- Full name
- Telephone number
- Pitt or UPMC email address

If you have any questions or concerns, please email us at ctgov@pitt.edu.

To find out additional information about how to register your study go to:
<https://www.clinicaltrials.gov/ct2/manage-recs/how-register>