Study Protocol with Statistical Analysis Plan

Study Title: Brain Aging and Treatment Response in Geriatric Depression

PI: Helen Lavretsky, M.D.

NCT #: NCT01902004

Date of Document: 9/19/2018 (approved, current version)

1/24/2013 (approved, original version)

9/20/2019 (date of access)

Date: Friday, September 20, 2019 10:39:47 AM

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ID: IRB#12-001714 View: NEW 1.1 - Study Title and Key Personnel

This view has been locked by amendment(s)

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Study Title and Key Personnel

All items marked with a red asterisk (*) are required. Items without an asterisk may or may not be required depending on whether the items are applicable to this study.

1.0 ***Full Title of the Submission:**
Brain aging and treatment response in geriatric depression

1.1 **Protocol Version Date and/or Number:**

2.0 ***Working or Lay Title:**
Aging Brain and Depression

3.0 **Principal Investigator:**

3.1 ***Name:** HELEN LAVRETSKY
Degree(s): If degrees are not shown here, please add them to the next section, Section 1.1a/Item 1.0, which will then update the Principal Investigator's webIRB account information.
MD, MS

3.2 **UCLA Title:** Professor

3.3 ***Will the Principal Investigator conduct the informed consent process with potential study participants?**

- (●) **Yes**
- ( ) No
- ( ) Not Applicable

3.4 ***Is the Principal Investigator an undergraduate student, graduate student, post-doctoral fellow, or resident physician?**

( ) Yes (●) **No**

3.4.1 **If you answered "yes" to the above question, indicate the Faculty Sponsor for this study.**

3.5 **UCLA Policy 900 defines types of UCLA employees who may be eligible to serve as a Principal Investigator. Check the policy to see if the Principal Investigator for this study needs an exception to the eligibility requirements.**

If an exception is needed, either attach the letter of exception here, or indicate a Faculty Sponsor in the above item.

Document Name	Document Version #
There are no items to display	

4.0 **Study Contact Person: Indicate the person, in addition to the Principal Investigator, who should receive all of the study correspondence.**
JILLIAN YEARGIN

5.0 **List the key personnel and study staff below.**

Note: All personnel listed below are required to complete CITI training courses (except for Fund Managers and Regulatory Coordinators). Please verify CITI training completion for all personnel prior to submitting a New Study application or Amendment application to add personnel. Verify using the Training Log tab in the application workspace (accessible by clicking the Exit button at the bottom of this page). HIPAA training is also required if personnel will be accessing protected health information.
Please make sure to have all personnel update their webIRB profile and contact information.
Instructions on how to update the webIRB profile are available here.

	Name	Department	Role	Other Role (if applicable)	Will Obtain Consent?	Manage device accountability?	Access to personally identifiable info?	Access to code key?
View	ASHLYN APPLEGATE	SEMEL INSTITUTE	Study Coordinator		no	Not Applicable	Yes	Yes
View	JORGE BARRIO	MOLECULAR & MEDICAL PHARMACOLOGY	Co-Investigator		no	Yes	No	No
View	THOMAS BELIN	BIOSTATISTICS	Co-Investigator		no	No	No	No
View	LINDA ERCOLI	PSYCHIATRY/BIOBEHAVIORAL SCI	Co-Investigator		yes	Yes	No	No
View	CHRISTIE FANOUS	SEMEL INSTITUTE	Research Assistant		no	Not Applicable	Yes	Yes
View	BRANDON HEIMBERG	SEMEL INSTITUTE	Study Coordinator		no	Not Applicable	Yes	Yes
View	RAQUEL HERNANDEZ SOTOMAYOR	SEMEL INSTITUTE	Research Assistant		no	Not Applicable	Yes	Yes
View	JASON JALIL	PSYCHIATRY/BIOBEHAVIORAL SCI	Co-Investigator		yes	Yes	Yes	Yes
View	LISA KILPATRICK, PhD	MEDICINE-GASTROENTEROLOGY	Statistician or Data Analyst		no	Yes	Yes	Yes
View	BEATRIX KRAUSE	SEMEL INSTITUTE	Study Coordinator		no	Yes	Yes	Yes
View	KELSEY LAIRD	SEMEL INSTITUTE	Study Coordinator		no	Not Applicable	Yes	Yes
View	MICHAELA MILILLO	SEMEL INSTITUTE	Study Coordinator		no	Not Applicable	Yes	Yes
View	KATHERINE NARR, PhD	NEUROLOGY	Co-Investigator		no	Yes	No	No
View	PRABHA SIDDARTH	SEMEL INSTITUTE	Statistician or Data Analyst		no	No	No	No
View	GARY SMALL, MD	PSYCHIATRY/BIOBEHAVIORAL SCI	Co-Investigator		no	Yes	No	No
View	NATALIE ST. CYR, BA	SEMEL INSTITUTE	Study Coordinator		no	Yes	Yes	Yes

	Name	Department	Role	Other Role (if applicable)	Will Obtain Consent?	Manage device accountability?	Access to personally identifiable info?	Access to code key?
View	PAULINE WU	PSYCHIATRY/BIOBEHAVIORAL SCI	Co-Investigator		yes	Yes	Yes	Yes
View	JILLIAN YEARGIN	SEMEL INSTITUTE	Study Coordinator		no	Not Applicable	Yes	Yes

ID: IRB#12-001714

View: NEW 1.1a - Other Personnel

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Other Personnel

All items marked with a red asterisk (*) are required. Items without an asterisk may or may not be required depending on whether the items are applicable to this study.

1.0 Principal Investigator

1.1 **Name:** HELEN LAVRETSKY
***Please type the Degree(s):** MD, MS

1.2 **Principal Investigator's UCLA Department:** PSYCHIATRY/BIOBEHAVIORAL SCI

1.3 ***Protocol's UCLA Home Department:** PSYCHIATRY/BIOBEHAVIORAL SCI

This response defaults to the PI's payroll department. If you wish to affiliate this protocol with another department, please select the department from the list above.

For tips on effective search, please see guidance to the right.

2.0 If there will be other types of personnel working directly under the PI's supervision on aspects of the study, provide their name, title and institution, indicate their responsibilities, training and qualifications and complete Item 2.1.

Please also indicate, if applicable, whether that person will obtain consent, manage device accountability, have access to personally identifiable information and/or have access to the code key.

Please use a new entry to add each individual unless describing a class of individuals who rotate through the study team (see guidance area to the right).

Note: If there will not be other types of personnel go to Item 3.0.

	Name, title, institution	Study role(s): e.g., conduct interviews/surveys, recruit participants, obtain consent, review records, etc.
View	Rotating volunteers, Volunteer Services, UCLA	review records, data entry, recruitment, and conduct surveys with participants.

For existing protocols: Item 2.0 has been modified and this item cannot be edited. When submitting an amendment please use the information found in the text box below to complete Item 2.0 above.
Briefly describe the other study personnel.

2.1 **Indicate the human subjects research training these personnel have or will receive. If training is required in a language other than English or if research is occurring in a location where research personnel do not have access to the internet (e.g., rural community without internet capability), please describe how human subjects training requirements will be fulfilled.**

Check all that apply:

- [x] **CITI Training**
- [x] **UC HIPAA Training**
- [ ] Other

2.2 **If you indicated "Other" to item 2.1, describe:**

3.0 ***Will any of the study procedures or analyses be contracted to a consultant or an organization?**

○ Yes ◉ **No**

3.1 **If yes, specify the consultant(s) and/or organization(s) and the work that they will do for the study.**

ID: IRB#12-001714 View: NEW 1.1b - Type of Study Review

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Type of Study Review

1.0 ***Indicate the level of risk involved with this study.**

(if there are multiple groups or phases associated with this study, select the highest level of risk.)

- ○ Minimal risk or no known risks - Click here for the OHRPP tip sheet on minimal risk.
- ◉ **Greater than minimal risk**

2.0 ***Indicate the type of review that you are requesting for this study.**

- ◉ **IRB Review: Expedited or Full Board**
- ○ Certification of Exemption from IRB Review

2.1 **If you indicated "IRB Review: Expedited or Full Board" as the type of review in item 2.0, select the IRB that you think best matches your research.**

	Name	Description
○	Medical Institutional Review Board 1	MIRB1 reviews general and internal medicine, infectious diseases and ophthalmologic research.
○	Medical Institutional Review Board 2	MIRB2 reviews oncology and hematology research.
◉	**Medical Institutional Review Board 3**	MIRB3 reviews neuroscience, neurology, psychiatric, drug abuse and dental research.
○	North General Institutional Review Board	NGIRB reviews research from the College of Letters & Science and the Professional Schools.

	Name	Description
○	South General Institutional Review Board	SGIRB reviews social-behavioral research from the Schools of Public Health, Nursing, and Medicine.

***Please note**: The above requests are for initial routing purposes only. The final decision as to committee assignment and type of review, rests with OHRPP and/or the IRBs.*

ID: IRB#12-001714 View: NEW 1.2 - Conflict of Interest Information

This view has been locked by amendment(s)

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Conflict of Interest Information

1.0 * **Does the Principal Investigator, any of the key personnel, or their spouses, registered domestic partners, or dependent children, have a financial interest in the sponsor (profit, non-for-profit) of the research?**

○ Yes ◉ **No**

1.1 **If yes, attach a completed copy of the Financial Interests Form for each person who indicates a financial or related interest:**

Document Name	Document Version #
There are no items to display	

2.0 * **Does the Principal Investigator, any of the key personnel, or their spouses, registered domestic partners, or dependent children, have any financial interests related to the research sponsored by a government agency?**

○ Yes ◉ **No**

2.1 **If yes, attach a completed copy of the Financial Interests Form:**

Document Name	Document Version #
There are no items to display	

3.0 * **Indicate whether any of these financial interests have been submitted to or reviewed by the UCLA campus Conflict of Interest Review Committee (CIRC):**

◉ **Yes** ○ No

3.1 **If you have received a response from CIRC, attach it here:**

Document Name	Document Version #
Barrio 2013-0209 2011.pdf	0.02
CIRC Case 2015-0021.pdf	0.01
Small 2013-0208 0210.pdf	0.02

ID: IRB#12-001714 View: NEW 1.3 - Study Locations

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Study Locations

1.0 ***Indicate the locations where any research activities will be performed by the UCLA research team with participants and/or private information obtained.**

Check all that apply:

- [x] **a. UCLA Sites or UCLA Health System Sites**
- [ ] b. Off Campus (in California)
- [ ] c. Outside California (in the U.S.)
- [ ] d. Outside the United States ***See note at right**
- [ ] e. Internet

1.1 **If you selected b, c or d above, please provide your assurance that documentation of each site's permission to conduct the research at the site(s) will be obtained and maintained by the UCLA PI as applicable:**

Agree ☐

2.0 ***Is this a multi-institutional study (i.e., a collaborative project with other sites that have their own IRBs or principal investigators)?**

(Includes but not limited to UC MOU and CTSI MOU collaborations where UCLA IRB review is requested.)

○ Yes ◉ **No**

If no, please skip directly to the next page, do not complete the questions below.
If yes, please answer items 2.1-2.3:

2.1 **Will UCLA be responsible for the overall direction of the study at the other institutions?**

○ Yes ○ No

2.1.1 **Indicate the measures that will be taken to assure regulatory compliance at each site and that the following types of information will be communicated to the other sites: study procedures; modifications to the protocol and related documents; and safety updates, interim results and other information that may impact risks to study participants.**

Check all that apply:

- [ ] Conference calls or meetings with minutes distributed to each site
- [ ] Timely e-mail communications
- [ ] Postings on the study website
- [ ] Other

2.1.1.1 **If you chose "other", describe.**

2.1.2 **If you answered "yes" to item 2.1 above, please provide your assurance that the current IRB approval for each site(s) will be obtained and maintained by the UCLA PI as applicable:**

Agree ☐

2.2 **Will the UCLA principal investigator specified on this application be responsible for the data coordinating center?**

2.3 **Indicate the anticipated total number of study participants that will be enrolled across all of the institutions.**

Warning: Save your work at least every 15 minutes by clicking "Save" or "Continue."

UCLA Sites or UCLA Health System Sites

*Please complete this section if you indicated that your study is greater than minimal risk **AND** that research activities will be performed at UCLA Sites or UCLA Health System Sites.*

1.0 ***Indicate where study procedures or data collection procedures - that are greater than minimal risk - will be conducted.**

Check all that apply:

- [x] **Clinical & Translational Research Center (CTRC)**
- [ ] Inpatient Medical Facility
- [ ] Outpatient Treatment Facility/Private Office
- [ ] Public Area
- [x] **Research Laboratory**
- [ ] Other

1.1 **If you indicated "other", specify.**

2.0 ***Indicate the resources available to handle potential emergencies related to study procedures that are greater than minimal risk.**

Check all that apply:

- [ ] This item is not applicable to this study
- [ ] Basic Life Support (BLS) certified personnel
- [ ] Advanced Cardiac Life Support (ACLS) certified personnel
- [x] **Code Blue Team (hospital emergency response team)**
- [ ] Emergency crash cart
- [x] **Paramedic Emergency Response Team (911)**
- [x] **Suicide Protocol**
- [ ] Other

2.1 **If you indicated "other", specify.**

This view has been locked by amendment(s)

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Project Identification Information

1.0 ***Type of Submission (Select one)**

- (●) **Research Study**
- ( ) Application for Approval of "Research Participant Pool" or recruitment database only

2.0 ***Type of Submission (Select one)**

For Amendments, do not undo the response below. Undoing the response may remove sections of the original application.

- (●) **New Submission**
- ( ) Transfer of Ongoing Research from Another Site from Investigator moving to UCLA. Please complete Item 2.1.

2.1 **If you selected "Transfer of Ongoing Research" in Item 2.0 indicate the current status of the study and a brief summary of the work to date.**

3.0 ***Who developed this study?**

Check all that apply:

- [x] **UCLA investigator**
- [ ] Investigator from another institution
- [ ] Industry/Pharmaceutical Company
- [ ] Cooperative Group (e.g., Children's Oncology Group, AIDS Clinical Trial Group)
- [ ] Other

3.1 **If other, specify.**

4.0 **Review For and Reliance Upon External IRBs.**

***Indicate if one of the following applies to this study. (Select one)**

- (●) **None of the options apply.**
- ( ) UCLA IRB to serve as IRB of record for another institution.
- ( ) UCLA to RELY on another IRB.
  This includes reliance using UC MOU, CTSI, NCI, RAND, and Western IRBs.

5.0 ***Is this study cancer related,** including the recruitment of individuals with cancer, collection of cancer human biological samples, specimens or data, or the recruitment of individuals because they are cancer survivors or at risk of developing cancer?

( ) Yes (●) **No**

Note: If you answered "Yes", you must submit an application to the Jonsson Comprehensive Cancer Center (JCCC) Internal Scientific Peer Review Committee (ISPRC). Click here for instructions for submitting to the ISPRC. The ISPRC approval notice or letter of exemption should be attached in Section 2.1/Item 7.2 of the webIRB application.

6.0 ***Nurse Involvement:** Does this study involve any nursing time, effort, and/or resources at UCLA Health System sites, including as subjects, investigators, clinical care providers or data or specimen collectors?

(●) **Yes** ( ) No

Note: If you answer "Yes", please submit an application to the Nursing Practice Research Council (NPRC). For contact information or for more information about NPRC and how to apply, click here. ***IRB approval is not contingent on NPRC approval and you do not need to upload documentation of approval from the NPRC into webIRB.***

7.0 ***Federal regulations (45 CFR 46.111) require scientific review before an IRB approves a study. For the majority of studies being reviewed and approved by the UCLA IRB, the IRB performs this review. See http://ora.research.ucla.edu/OHRPP/Documents/Policy/4/Scientific_Review.pdf for additional details.**

Do you want the IRB to consider external scientific or scholarly review?

(●) **Yes** ( ) No

7.1 **If yes, indicate the source of scientific or scholarly review for the study.**

Check all that apply.

- [x] **National Institutes of Health (NIH)**
- [ ] The funding agency (other than NIH)
- [ ] Faculty Sponsor
- [ ] JCCC – Internal Scientific Peer Review Committee (ISPRC)
- [ ] Clinical Translational Research Center (CTRC)
- [ ] UCLA Department
- [ ] Other

7.1.1 **If you checked "other", describe.**

7.2 **Attach a copy of the scientific or scholarly review, if applicable.**

Document Name	Document Version #
There are no items to display	

ID: IRB#12-001714 View: NEW 2.2 - Lay Summary and Keywords

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Lay Summary and Keywords

Please provide the following information about your study.

1.0 ***Provide a brief lay summary describing this study. (limit 500 words).**

This study is designed to conduct a double-blind placebo-controlled trial of Namenda (Memantine) as an augmentation to Lexapro (Escitalopram) in depressed older adults 60 years of age and older with mild cognitive impairment. Throughout the course of the study, we anticipate screening about 400 subjects to recruit 134 participants in the first four years. This study will require that the subjects complete up to 20 (twenty) visits in 12 (twelve) months to the study site during their participation.

The purpose of this study is to determine whether Namenda® (memantine) when taken in combination with Lexapro® (escitalopram), may improve the quality of treatment response by making it faster and more complete, and also by improving thinking and memory in comparison to Lexapro taken with a placebo. Enrolled subjects will be provided with 10-20 mg of escitalopram for 12 months, and concurrently randomly assigned to either memantine or placebo groups. We will also examine the safety and tolerability (how well the treatment works and the side effects) of a combination of Namenda and Lexapro as compared to placebo and Lexapro in subjects with major depressive disorder and mild cognitive impairment who are at least 60 years of age. Individually, Namenda and Lexapro have been tested for safety and efficacy in younger and older adults and are approved by the United States Food and Drug Administration (FDA) for use in human subjects, including people older than 60 years old. However, the combination of Namenda and Lexapro for the treatment of depression with mild cognitive impairment is experimental and different from the FDA approved use for each drug. Namenda is not FDA approved for depression in any age group.

The proposed project will also evaluate the role of neuroimaging biomarkers of brain aging (i.e., neurodegenerative and vascular brain changes) and mild cognitive impairment in the patterns of treatment response to memantine combined with escitalopram compared to escitalopram and placebo. Memantine is likely to accelerate and enhance antidepressant response to escitalopram and improve cognitive performance. Subjects with amnestic mild cognitive impairment or biomarkers of brain aging at baseline are likely to have preferential response to the combination of memantine and escitalopram compared to escitalopram and placebo.

We will conduct neuroimaging using two functional and structural magnetic resonance imaging (MRI) scans and a positron emission tomography (PET) scan. The purpose of the imaging procedure is to measure the amyloid and tau protein in the brain using the identified substance called [18F]FDDNP to predict the response to depression and memory treatments.

Additionally, we will explore the levels of telomerase and NFkappaB as correlates of depression as predictors of response to the interventions directed toward improvement in the severity of depression, quality of life and resilience. We will examine the role of 2 candidate genes involved in the regulation of mood and memory, and evaluate telomerase and NFkappaB activity before and after the intervention. This proposal is a continuation of our ongoing work in this area.

2.0 ***List three to five keywords describing this study (separate the words with commas). The keywords may be used for identifying certain types of studies.**
geriatric depression, MCI, neuroimaging, biomarkers, memantine

3.0 ***Is this study conducted or supported by HHS (e.g., the National Institutes of Health, Centers for Control and Prevention, etc.)?**
(●) **Yes** ( ) No

3.1 ***Is NIH the HHS agency supporting or conducting the study?**
(●) **Yes** ( ) No

3.2 ***Please choose one:**

- (●) **I acknowledge that my study is automatically covered by a Certificate of Confidentiality and I understand the responsibilities associated with that Certificate.**
- ( ) The NIH Certificate of Confidentiality policy does not apply to my study (see guidance at right and explain below)

4.0 ***Is this study regulated by the Food and Drug Administration (FDA)?**
(●) **Yes** ( ) No

4.1 **If yes, check all that apply:**

- [x] **Human Drugs**
- [ ] Medical Devices
- [ ] Biological Products
- [ ] Mobile Medical Applications
- [ ] Food Additives
- [ ] Color Additives
- [ ] Other

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Methods/Procedures - Descriptors

Note: The items listed below are not an inclusive list of methods and procedures that may be used in research studies. The list only includes items that will trigger additional questions related to the research or are needed for the review process

1.0 ***Indicate all that apply to this study.**

- [ ] Audio, Visual or Digital Recordings
- [ ] Certificate of Confidentiality for research not supported by NIH
- [x] **Clinical Trial of a Drug, Biologic, Device or a Behavioral Intervention**
- [ ] Community Based Research

- [ ] Controlled Substances (Schedule I or II)
- [ ] Deception or Partial Disclosure
- [ ] Devices/Diagnostics (including Humanitarian Devices - HUD)
- [x] **Drugs/Biologics/Dietary Supplements**
- [ ] Expanded Access to Drug, Device or Biologic for Treatment Purposes (aka Compassionate Use, Treatment Use)
- [x] **Genetic Analyses/Genotyping**
- [ ] Human Embryonic Stem Cells and/or Induced Pluripotent Stem Cells
- [ ] Human Gene Transfer/ Recombinant DNA
- [ ] Infectious Agents
- [ ] Non-FDA approved medical equipment used with UCLA hospital patients or research participants that operate under the UCLA Hospital License.
- [x] **Radiation (Standard of Care or Investigational Use of radioactive materials, radiation producing machines or ionizing radiation)**
- [ ] Substance Abuse Research (with Medication)
- [ ] Treatment in an Emergency Setting (with request to waive consent)
- [ ] **None of the above**

2.0 ***Will the study require services or resources owned/rented/operated or provided by the UCLA Health System (e.g. clinic and/or hospital visit(s), CTRC, professional medical services, clinical treatment, diagnostics, labs, medical supplies, etc.)?**

Please direct any questions about this to The Financial Coverage & Activation Team at coverageanalysis@mednet.ucla.edu.

◉ **Yes** ○ No

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Coverage Analysis

1.0 ***Will <u>all</u> protocol-required items and services that produce data for the study be funded by intramural or extramural funding/support?**

- ◉ **Yes - we will <u>not</u> bill participants or their insurers for any protocol-required items or services**
- ○ No - we will bill one or more protocol-required items or services to participants or their insurers
- ○ Not Applicable – this is a non-interventional study (e.g., observational/registry/retrospective study without active treatment) that <u>does not require</u> additional visits, labs, items or services performed solely due to study participation

<u>Note:</u>

*If "**Yes**" is selected to the question above, then the corresponding "Research Only" cost language in the guidance to the right should be included in the ICF, and an abbreviated coverage analysis review is indicated.*

*If "**No**" is selected to the question above, then the "Mixed Cost" language in the guidance to the right should be included in the ICF, and a full coverage analysis review is indicated.*

*If "**Not Applicable**" is selected to the question above, then coverage analysis may not be applicable, and the corresponding "All Standard of Care" cost language in the guidance on the right should be included in the ICF.*

2.0 ***Is your study any of the following?**

- **Treatment Use (Expanded Access, Compassionate Use, or a Humanitarian Use Device)**
- **Hematology-Oncology Clinical Research Unit Study**
- **UCLA reliance on an external IRB review**

○ Yes ◉ **No**

Note: *If you have selected yes, then continue with question 3.0 below.*

3.0 **Please upload a copy of your study protocol below:**

Document Name	Document Version #
There are no items to display	

The following item pertains to investigational drugs and devices only.

4.0 **If the study participant or a third party payor (i.e., medical insurance/Medicare/Medicaid) may be billed for investigational products (i.e., investigational drugs and/or devices), attach relevant documentation to support charges including but not limited to FDA and/or CMS approval letter(s).**

Document Name	Document Version #
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ID: IRB#12-001714 View: NEW 6.1 - Funding and Other Study Characteristics

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Funding and Other Study Characteristics

1.0 ***Indicate the funding status for this study**.

- ◉ **Funded**
- ○ Application for funding is pending
- ○ Departmental funding / Self funding / No funding

2.0 ***Check all that apply**:

- ☑ **The research will be conducted through the UCLA Clinical and Translational Research Center (CTRC)**
- ☐ The study will be supported by or conducted in collaboration with the U.S. Department of Defense (DOD)
- ☐ The study will be supported by or conducted in collaboration with the U.S. Department of Energy (DOE)
- ☐ The study will be supported by or conducted in collaboration with the U.S. Department of Justice (DOJ)
- ☐ The study will be supported by or conducted in collaboration with the U.S. Department of Education (ED)
- ☐ The study will be supported by or conducted in collaboration with the U.S. Department of Protection Agency (EPA)
- ☐ **None of the above**

2.1 **If you selected DOD, DOE, DOJ, ED, and/or EPA support/collaboration, please provide your assurances that you will review the additional requirements for research supported by the relevant federal agency.**

Agree ☐

Note: Please refer to the Federally-Supported Research section of the OHRPP guidance document: Funding Considerations for Federally-Funded and Industry-Sponsored Human Research.

ID: IRB#12-001714 View: NEW 6.2 - Funding - Description

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Funding - Description

Based on the response to section 6.1/item1, this study is or will be funded. Please provide the following information.

The Office of Contract and Grant Administration (OCGA) provides the list of funding sources used by webIRB in this section. Please check your OCGA paperwork to find the correct name of the funding source(s) for this study. Identifying the right funding source is important because:

▪ webIRB will auto-populate the designated funding source name on the approval letter for the study. Many funding sources require an accurate identification of their name on the IRB approval letter before they will release funding;
▪ The Office of Research Administration uses data from webIRB to generate funding reports.

Click here for tips on how to find the funding source name in webIRB.

1.0 Identify the funding source(s).
If a specific funding source has ended, do not delete it, instead please click Update next to the funding entry and **revise item 1.9.**

	Funding Source	Funding Source Information

View NIH - MISCELLANEOUS AGENCIES AND DEPARTMENTS

Name of the Funding Source	NIH - MISCELLANEOUS AGENCIES AND DEPARTMENTS
If other, specify	*No Value Entered*
UCLA PI named on the grant, contract, subcontract or gift:	HELEN LAVRETSKY
Indicate the type of award:	Grant
If other award, specify	*No Value Entered*
Indicate the Grant Title:	Brain aging and treatment response in geriatric depression
Indicate the Award Number assigned by the funding source:	R-01 MH097892
Indicate the description that applies to the source of funding named in the above item. If this is a subcontract, indicate the original source of funding:	Federal
If Other, specify	*No Value Entered*
Attach a copy of the funding proposal, subcontract, or scope of work.	**Document Name**: grantpdf 062512.pdf **Document Version #**: 0.01
Does the content of this IRB application differ from the activities described in the attached funding proposal, subcontract, or scope of work?	Yes
If yes, describe:	The funding is used to hire additional staff to perform analyses for the fMRI portion of the study.
Check this box to indicate that this specific funding has ended	*No Value Entered*

Funding Source	Funding Source Information
View NAT'L ALLIANCE FOR RESEARCH ON SCHIZOPHRENIA AND DEPRESSION	

Name of the Funding Source	NAT'L ALLIANCE FOR RESEARCH ON SCHIZOPHRENIA AND DEPRESSION
If other, specify	*No Value Entered*
UCLA PI named on the grant, contract, subcontract or gift:	HONGYU YANG
Indicate the type of award:	Grant
If other award, specify	*No Value Entered*
Indicate the Grant Title:	Magnetic Resonance Spectroscopy evaluating Memantine Augmentation of Escitalopram in Late Life Depression
Indicate the Award Number assigned by the funding source:	22325
Indicate the description that applies to the source of funding named in the above item. If this is a subcontract, indicate the original source of funding:	Private/Not-for-Profit
If Other, specify	*No Value Entered*
Attach a copy of the funding proposal, subcontract, or scope of work.	**Document Name**: Hongyu_NARSAD_APP.pdf **Document Version #**: 0.01
Does the content of this IRB application differ from the activities described in the attached funding proposal, subcontract, or scope of work?	No
If yes, describe:	*No Value Entered*
Check this box to indicate that this specific funding has ended	*No Value Entered*

This view has been locked by amendment(s)

Warning: Save your work at least every 15 minutes by clicking "Save" or "Continue."

Study Design

1.0 ***Check all that apply to the study design.**

- ☑ **Direct subject contact ONLY – The research activities involve direct contact with study participants (e.g., collection of data or specimens in person or via internet, phone, mail, etc.)**
- ☐ **No direct subject contact** – None of the research activities involve direct contact with study participants and include only analyses of data, records and/or human biological specimens (e.g., medical record or other record review, study of specimens left over from clinical procedures).
- ☐ **BOTH Direct subject contact AND No direct subject contact** – Some of the research activities involve direct contact with study participants and some of the research activities involve analyses of data, records and/or human specimens obtained without contact with participants.

Warning: Save your work at least every 15 minutes by clicking "Save" or "Continue."

Clinical Trial of a Behavioral Intervention, Drug, Biologic or Device

You indicated that this study includes a clinical trial (section 2.3/item 1.0). Please provide the following information

1.0 ***Indicate the type of clinical trial.**

Check all that apply:

- [x] **Randomized**
- [ ] Non-randomized
- [ ] Single Blinded
- [x] **Double Blinded**
- [x] **Placebo**
- [ ] Sham Control
- [ ] Active/Treatment Control
- [ ] Open Label
- [ ] Crossover
- [ ] Washout Period
- [ ] Dose Escalation
- [ ] Other

1.1 **If you indicated "other", specify.**

2.0 ***Indicate the type of clinical trial:**

- ( ) Pilot/Feasibility
- ( ) Phase I
- ( ) Phase I/II
- ( ) Phase II
- ( ) Phase II/III
- (•) **Phase III**
- ( ) Phase III/IV
- ( ) Phase IV
- ( ) Open Label Extension/Rollover
- ( ) Expanded Access
- ( ) Behavioral

3.0 ***Indicate the status of registration of registering this trial with ClinicalTrials.gov**

- (•) **Registered**
- ( ) Registration Pending
- ( ) Not Registered

4.0

If the trial is registered, provide the Trial Registration Number:
NCT01902004

ID: IRB#12-001714 View: NEW 8.6 - Drugs/Biologics/Dietary Supplements

This view has been locked by amendment(s)

Warning: Save your work at least every 15 minutes by clicking "Save" or "Continue."

Drugs/Biologics/Dietary Supplements

You indicated that this study includes drugs/biologics/dietary supplements (section 2.3/item 1.0). Please provide the following information.

1.0 Approved Drugs or Biologics: List any drugs or biologics that will be used in this study in accordance with their approved labeling.

The UCLA Pharmacy will not dispense drugs that have been procured from an external pharmacy or compounding pharmacy. Contact the UCLA Pharmacy - Investigational Section at (310) 267-8522 if you require a compounded drug for the study.

2.0 Enter any drugs/biologics that will be used as part of this study that do not fit in response to item 1.0 above.

	Generic name of the drug/biologic	Investigational Drug/Biologics Information
View	[18F] FDDNP	

The trade name of the Drug/Biologic:	[18F] FDDNP
Indicate the manufacturer:	UCLA Nuclear Medicine
Indicate the source of the study drug/biologic:	Other
If you indicated "Other" and/or that the study drug/biologic is being provided by a pharmaceutical company other than the sponsor, identify the source:	UCLA Nuclear Medicine
Attach the Investigator's Brochure (IB) or package insert	**Document Name**: FDDNP IND master-final_sent.pdf **Document Version #**: 0.01
Indicate the regulatory status of the drug or biologic:	**Investigational radioactive drugs or radiopharmaceuticals.**
Investigational Use of a Marketed Drug or Biologic:	**Describe the approved indications for the use of the drug/biologic and how the drug/biologic will be used in the study:** The PET acquires 109 transaxial images simultaneously, covering an axial field of view (FOV) of 22 cm and a transaxial FOV of 70 cm diameter. A bolus of [F-18] FDDNP (320-550 MBq) experimental tracer is injected via an indwelling venous catheter, and consecutive dynamic PET scans are performed for 45 min. Scans are decay corrected and reconstructed using filtered back-projection (Hann filter, 5.5 mm full-width at half-maximum) with scatter and measured attenuation correction. The [F-18] FDDNP

Generic name of the drug/biologic	**Investigational Drug/Biologics Information**

	binding data are quantified using Logan graphical analysis with the cerebellum as the reference region.
The new use is not intended to be reported to the FDA:	Yes
The new use is not intended to support a significant change in advertising for the drug/biologic:	Yes
The new use does not involve a change in the route of administration, dosage level, subject population or other factor that significantly increase the risks:	No
The new use does not intend to invoke a wavier of informed consent for emergency research:	Yes
If you answered "false" to any of the items above and believe that an IND is not needed, provide a justification:	N/A

Use of an Unapproved Drug or Biologic, or if use of this drug or biologic requires an IND:

Indicate the Investigational New Drug Status:	IND - This product is being studied under an IND
2.6.2.2a. IND number	#74,944-0012
2.6.2.2b. IND Holder	David Geffen School of Medicine at UCLA
2.6.2.2c. Documentation of the IND number unless already attached elsewhere in the application:	**Document Name**: IND 74-944-0012 FDDNP.pdf **Document Version #**: 0.01
2.6.2.2d. If the PI holds the IND, attach a copy of the IND application and any correspondence with the FDA:	
2.6.2.2e. Indicate the date when the	*No Value Entered*

Generic name of the drug/biologic	Investigational Drug/Biologics Information	
	Investigational New Drug (IND) was submitted to the FDA	
	2.6.2.2f. Indicate the date when the Investigational New Drug (IND) was approved by the FDA	*No Value Entered*
	2.6.2.2g. If the PI is the holder on the IND, please provide your assurance that you have read and understand the responsibilities of IND sponsors accoring to 21 SFR 312: Agree?	No
	Identify all persons who will prescribe the drug or biologic:	Dr. Gary Small
	The route of administration:	Injection
	"Other" route, specify:	*No Value Entered*
	The location(s) where the drug/biologic will be administered:	200 UCLA Medical Plaza
	If you indicated that administration will take place in an inpatient unit, or at a non-UCLA site, specify the location and where in the location the medication will be administered:	*No Value Entered*

View Escitalopram

	The trade name of the Drug/Biologic:	Lexapro
	Indicate the manufacturer:	UCLA Pharmacy
	Indicate the source of the study drug/biologic:	UCLA Pharmacy
	If you indicated "Other" and/or that the study drug/biologic is being provided by a pharmaceutical company other than the sponsor, identify the source:	*No Value Entered*
	Attach the Investigator's Brochure (IB) or package insert	**Document Name**: lexapro_pi.pdf **Document Version #**: 0.01
	Indicate the regulatory status of the drug or biologic:	**Investigational Use of a Marketed Drug or Biologic:** The drug/biologic will be used off-label for an indication *not* in the approved labeling.
	Investigational Use of a Marketed Drug or Biologic:	**Describe the approved indications for** Approved indications and usage for Lexapro: Major Depressive

Generic name of the drug/biologic	**Investigational Drug/Biologics Information**				
		the use of the drug/biologic and how the drug/biologic will be used in the study:	Disorder. Lexapro (escitalopram) is indicated for the acute and maintenance treatment of major depressive disorder in adults and in adolescents 12 to 17 years of age. A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least five of the following nine symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicidal ideation. Generalized Anxiety Disorder. Lexapro is indicated for the acute treatment of Generalized Anxiety Disorder (GAD) in adults. Generalized Anxiety Disorder (DSM-IV) is characterized by excessive anxiety and worry (apprehensive expectation) that is persistent for at least 6 months and which the person finds difficult to control. It must be associated with at least 3 of the following symptoms: restlessness or feeling keyed up or on edge, being easily fatigued, difficulty concentrating or mind going blank, irritability, muscle tension, and sleep disturbance. All subjects will receive 10-20 mg of escitalopram throughout the trial. Matching capsules containing memantine (MEM) or placebo will be given and titrated from 5 mg/day to 10 mg/twice a day (or 20 mg a day) over the course of the first four weeks. The subject will be instructed to take one tablet of escitalopram a day in the evening or in the morning; as preferred, and 1 pill of MEM (in 5 mg increments) or placebo at 8 am for the first week, and at 8 am and 3 pm in the second week and thereafter. The dose of MEM will be increased every 7 days: second week 5 mg (1 pill) twice a day; third week 5 mg (1 pill) at 8 am in the morning and 10 mg (2 pills) at 3 pm in the afternoon; fourth week 10 mg (2 pills) at 8 am in the morning and 3 pm in the afternoon. At the end of week 4, the study doctor may increase the dose of Lexapro to 2 tablets, or 20 mg per day. If you experience any side-effects from the study		

Generic name of the drug/biologic	**Investigational Drug/Biologics Information**		
			medication use, the allowed dose adjustment for MEM will be decreasing MEM by 1– 3 pills, to a minimum of 5 mg (or 1 cap per day), and decreasing escitalopram dose to 10 mg, so that the allowed dose range of escitalopram will be 10-20 mg/day. The maximum dose of MEM will be up to 20 mg/day and escitalopram of up to 20 mg/day.
		The new use <u>is not</u> intended to be reported to the FDA:	Yes
		The new use <u>is not</u> intended to support a significant change in advertising for the drug/biologic:	Yes
		The new use <u>does not</u> involve a change in the route of administration, dosage level, subject population or other factor that significantly increase the risks:	Yes
		The new use <u>does not</u> intend to invoke a wavier of informed consent for emergency research:	Yes
		If you answered "false" to any of the items above and believe that an IND is not needed, provide a justification:	*No Value Entered*
	Use of an Unapproved Drug or Biologic, or if use of this drug or biologic requires an IND:		
	Identify all persons who will prescribe the drug or biologic:	The study doctor and PI, Helen Lavretsky, M.D. will prescribe the drug.	
	The route of administration:	Oral	
	"Other" route, specify:	*No Value Entered*	
	The location(s) where the drug/biologic will be administered:	200 UCLA Medical Plaza Study Participant's Residence	
	If you indicated that administration will take place in an inpatient unit, or at a non-	*No Value Entered*	

	Generic name of the drug/biologic	Investigational Drug/Biologics Information
		UCLA site, specify the location and where in the location the medication will be administered:

View Memantine

The trade name of the Drug/Biologic:	Namenda
Indicate the manufacturer:	UCLA pharmacy
Indicate the source of the study drug/biologic:	UCLA Pharmacy
If you indicated "Other" and/or that the study drug/biologic is being provided by a pharmaceutical company other than the sponsor, identify the source:	*No Value Entered*
Attach the Investigator's Brochure (IB) or package insert	**Document Name**: namenda_pi.pdf **Document Version #**: 0.01
Indicate the regulatory status of the drug or biologic:	**Investigational Use of a Marketed Drug or Biologic:** The drug/biologic will be used off-label for an indication *not* in the approved labeling.
Investigational Use of a Marketed Drug or Biologic:	**Describe the approved indications for the use of the drug/biologic and how the drug/biologic will be used in the study:** Approved indications and usage: Namenda (memantine hydrochloride) is indicated for the treatment of moderate to severe dementia of the Alzheimer's type. Patients who meet all eligibility criteria at baseline will be given a 14-day supply of the study medications prepared and dispensed by the UCLA Pharmacy in the matching capsules. All subjects will receive 10-20mg of escitalopram open-label throughout the trial. Matching capsules containing memantine (MEM) or placebo will be given and titrated from 5 mg/day to 10mg/twice a day (or 20mg a day) over the course of the first four weeks. Subjects will be instructed to take one tablet of escitalopram a day in the evening or in the morning, as preferred; and 1 pill of MEM (in 5 mg increments) or placebo at 8 am for the first week, and at 8 am and 3 pm in the second week and thereafter. The dose of MEM will be increased every 7 days: second week 5 mg (1 pill) twice a day; third week 5 mg (1 pill) at eight o'clock in the morning and 10 mg (2 pills) at three o'clock in the afternoon; fourth week 10 mg (2 pills) at eight o'clock in the morning and three o'clock in the afternoon. At the end of week 4, patients with a CGI improvement rating of 3 or greater will be titrated upward on the

Generic name of the drug/biologic	**Investigational Drug/Biologics Information**		
			escitalopram dose and instructed to take two tablets, or 20 mg /day. Patients with a CGI improvement rating of 1 or 2 will continue taking the same dose they have been taking at the end of week 3. If patients experience any side-effects attributed to their study medication use, the allowed dose adjustment for MEM will be decreasing MEM by 1– 3 pills, to a minimum of 5mg (or 1 cap a day), and decreasing escitalopram dose to 10 mg, so that the allowed dose range of escitalopram will be 10-20mg/day. Re-challenge with a higher dose of MEM up to 20mg/ day, or escitalopram of up to 20mg/day may take place at the following visit in case of an incomplete response. All dose adjustments will be documented and considered in the analyses. The expected effective dose range of MEM will be 20mg daily, which has been successfully used and well-tolerated in our pilot study. At the end of 24 weeks, memantine and placebo will be tapered off gradually in the same decrement of 5mg (or 1 pill) per week over the course of 2-4 weeks to reduce the risk of withdrawal symptoms. At 6 months, subjects who decide to discontinue escitalopram will be tapered off gradually over the course of 2-4 weeks with 5mg dose decrements/ week in cooperation with their psychiatrist.
		The new use <u>is not</u> intended to be reported to the FDA:	Yes
		The new use <u>is not</u> intended to support a significant change in advertising for the drug/biologic:	Yes
		The new use <u>does not</u> involve a change in the route of administration, dosage level, subject population or other factor that significantly increase the risks:	Yes
		The new use <u>does not</u> intend to invoke a wavier of informed consent	Yes

Generic name of the drug/biologic	Investigational Drug/Biologics Information	
	for emergency research:	
	If you answered "false" to any of the items above and believe that an IND is not needed, provide a justification:	*No Value Entered*
Use of an Unapproved Drug or Biologic, or if use of this drug or biologic requires an IND:		
Identify all persons who will prescribe the drug or biologic:	The study doctor and PI, Helen Lavretsky, M.D. will prescribe the drug.	
The route of administration:	Oral	
"Other" route, specify:	*No Value Entered*	
The location(s) where the drug/biologic will be administered:	200 UCLA Medical Plaza Study Participant's Residence	
If you indicated that administration will take place in an inpatient unit, or at a non-UCLA site, specify the location and where in the location the medication will be administered:	*No Value Entered*	

3.0 **All drugs and biologics for research at UCLA are to be managed through the UCLA Pharmacy. Provide your assurance that you have or will submit an Investigational Drug Study application to the Pharmacy.**

Agree ☑

Warning: Save your work at least every 15 minutes by clicking "Save" or "Continue."

Genetic Analyses/Genotyping

You indicated that this study includes genetic analyses/genotyping (section 2.3/item 1.0). Please provide the following information.

1.0 ***Are you performing whole genome sequencing?**

○ Yes ○ No

2.0 ***Are you planning to provide study participants with the results of the genetic analyses/genotyping?**

○ Yes ◉ **No**

If you answered "yes", answer the next set of items below. If you answered "no", continue to the next screen.

3.0 **List the types of tests:**

4.0 **Is the genotyping being performed by a Clinical Laboratory Improvement Amendments (CLIA) approved lab?**

○ Yes ○ No

5.0 **Describe the rationale for providing study participants with the results of the genetic tests/genotyping; explain what, how, and by whom the participants and/or their healthcare provider will be told about the meaning, reliability and applicability of the results and how the information will be provided (e.g., in person, by letter).**

6.0 **Indicate the qualifications of the person who will relay the information.**

- ☐ A licensed study physician
- ☐ A licensed genetic counselor
- ☐ Other

6.1 **If "other", specify.**

ID: IRB#12-001714 View: NEW 8.11 - Radiation

This view has been locked by amendment(s)

Warning: Save your work at least every 15 minutes by clicking "Save" or "Continue."

Radiation (read-only historical information)

NOTE: *This section includes read-only* ***historical information*** *for studies that included radiation procedures prior to the September 2018 transition from webIRB to SafetyNet for describing radiological procedures. The contents of this section are superseded by any related SafetyNet application and should* ***not*** *be considered part of the approved application.*

1.0 **Are the radiological procedures standard of care?**

Note: *Please review the guidance to the right before completing this question.*

No

1.1 **If Yes, please provide the following information for EACH procedure:**

a. Type of standard of care radiological procedure.
b. Maximum number of times a subject will undergo this procedure in one year.
c. Building and room number where this procedure will be performed.

The MRSC review process cannot begin until all of the above-referenced information has been provided in the field below.

NOTE: If procedures include a radiopharmaceutical then an Investigational New Drug (IND) or Abbreviated New Drug Application (ANDA) must be described in Section 8.6.

2.0 **Will this study involve radiological procedures beyond the standard of care?**

Note: *If you have questions about what "beyond standard of care" means or questions about the forms to use in 2.1 below, or need help or additional information, please click* ***here****.*

Yes

Important Note: If your study involves beyond standard of care radiological procedures that have not changed since previous approval through the MRSC/RDRC CARE system, upload the previously completed eight-page CARE Application in 2.2 instead of Forms A, B and/or C.

2.1 **If Yes and this is an *initial submission* or *an amendment involving changes to radiological procedures*, check all applicable administrations of radiation.**

Radiation Producing Machines - *Form A required. Click **HERE** to download form.*

2.2 **Upload Forms A, B AND/OR C and other supporting documents.**

Document Name	Document Version #
Form A Rad Pro Mach - WebIRB.pdf	0.01
Lavretsky - IRB#12-001714-AM-00005_MRSC 9-19-14.pdf	0.01
revisions_MRSC_Nameda_Aging_Brain_12-13-12.pdf	0.01

Warning: Save your work at least every 15 minutes by clicking "Save" or "Continue."

Information about Study Data

This information is needed to determine how you will best protect the confidentiality of data.

1.0 ***Indicate all that apply to the study data.**

Check all that apply:

- [x] **Obtained from a medical or clinical record**
- [ ] Created or collected as part of health or mental health care
- [ ] Used to make healthcare or mental healthcare decisions and/or provided to other healthcare professionals
- [ ] Research data will be entered into the participants' medical or clinical record
- [ ] **None of the above**

2.0 ***Is it reasonably foreseeable that the study will collect information that State or Federal law requires to be reported to other officials (e.g., child or elder abuse), ethically requires action (e.g., suicidal ideation), or is a reportable disease?**

(●) **Yes** ( ) No

2.1 **If yes, explain below and include a discussion of the reporting requirements in the consent document:**
Monitoring suicidal ideations: We will identify and monitor suicidal ideations using the SCID at baseline and the 3rd item of the Hamilton Depression Scale during each visit. Monitoring for SI will be done at each visit independent of the outcome assessment. Subjects with the score > 3 on admission signifying active suicidal ideations with or without a plan will be excluded from participation. We will call subjects between visits to monitor suicidal ideations. In case, of the persistent suicidal ideations, subjects will be discontinued from the study and referred to their primary physicians or psychiatrists, or to the clinical services at UCLA, or to the community psychiatrists for treatment and observation.

Elder abuse may be observed in the subject population of this study and will be appropriately reported. If any member of the research team has been informed of elder abuse, he or she is required to report it to the authorities. The obligation to report includes alleged or reasonably suspected abuse as well as known abuse.

3.0 ***Indicate if any of the following are being obtained and used without any direct contact with study participants.**

- [ ] Records (Not medical)

- [ ] Human biological specimens
- [x] **None of the Above**

4.0 *Indicate all identifiers that may be **accessed or included in the research records** for the study**:**

- [x] **Names**
- [x] **Dates**
- [x] **Age (if over 89 years)**
- [ ] Postal Address
- [ ] Phone Numbers
- [x] **Fax Numbers**
- [x] **E-Mail Address**
- [x] **Social Security Number**
- [x] **Medical Record Number**
- [ ] Health Plan Numbers
- [ ] Account Numbers
- [ ] License/Certificate Numbers
- [ ] Vehicle ID Numbers
- [ ] Device Identifiers/Serial Numbers
- [ ] Web URLS
- [ ] IP Address Numbers
- [ ] Biometric Identifiers (including finger and voice prints)
- [ ] Facial Photos/Images
- [ ] Any Other Unique Identifier (this does not include the code assigned by the investigator to identify the data)
- [ ] **None of the above**

4.1 **If social security numbers will be collected explain why they are necessary, how they will be used, how they will be protected and how long they will be retained.**
Social security numbers may be collected in order to issue a check request to pay the participants from UCLA Accounts Payable. The social security numbers will be written on a check request form and will not identify the subject as a participant for the study. The forms will be stored in a locked file cabinet and will be shredded and destroyed as soon as payment has been received (at the end of the duration of the study).

5.0 ***Select all that apply:**

- [ ] The data and/or specimens will be directly labeled with personal identifying information when acquired by the investigator for this research
- [x] **The data and/or specimens will be labeled with a code that the research team can link to personal identifying information when acquired by the investigator for this research**
- [ ] The data and/or specimens will not be labeled with any personal identifying information, nor with a code that the research team can link to personal identifying information when acquired by the investigator for this research
- [ ] The data are restricted use data (A term used in Social-Behavioral research. See guidance on the right.)

5.1 **Indicate how the data will be used when this study is completed.**

Check all that apply:

- [ ] Use for this study
- [x] **Use for possible future research**
- [ ] Use to create a bank or repository at UCLA

☐ Add to existing repository

☐ Other

5.1.1 If Other, specify:

ID: IRB#12-001714 View: NEW 9.2a - Privacy and Confidentiality

Warning: Save your work at least every 15 minutes by clicking "Save" or "Continue."

Privacy and Confidentiality

Important Notes:

- **Privacy is about people.** Privacy refers to a person's wish to control the access of others to themselves.
- **Confidentiality is about data.** Confidentiality refers to the researcher's plan to handle, manage, and disseminate the participant's identifiable private information.

See OHRPP Quick Guide: Protecting Privacy and Maintaining Confidentiality

1.0 *Privacy: How will the investigator maintain privacy in the research setting(s)? (e.g., interviewing participant in a room or area where conversations cannot be overheard by others, or conducting medical procedures in an examination room, or behind a curtain in an emergency room).

We will maintain the subjects' privacy in our data collection methods. The interviews will be conducted in a private interview room where conversations cannot be overheard by others. All medical procedures, including PET and MRI scans, blood draws, and ECGs will be conducted in a private examination room at the UCLA 200 medical plaza and at the 300 medical plaza.

2.0 *Confidentiality: If the protocol will collect and maintain identifiable data, explain how the planned safeguards to maintain confidentiality of identifiable data and data security are appropriate to the degree of risk from disclosure.

Note: Other sections of the application (e.g., Sections 9.3, 9.3a, 9.4, 9.5, and 15.3) will request specifications such as identification of persons who will have access to code keys or measures to comply with HIPAA requirements.

The risk of breach of confidentiality is reduced by: a) storing records in a locked file, with access available only to the PI and designated project staff; b) removing identifying information from all data during the data analysis phase of the project; and c) removing identifying information from all data presented publicly in lectures, seminars, or publications. All files will be kept in locked cabinets, as will copies of the signed informed consent forms, to maintain the anonymity of participants and to bar any unauthorized access. The computerized database will be protected through the use of entry codes available only to authorized personnel.

ID: IRB#12-001714 View: NEW 9.3 - Data Security

Warning: Save your work at least every 15 minutes by clicking "Save" or "Continue."

Data Security

You indicated that the study team will have access to personally identifiable or coded information (Section 9.2/item 5). Please complete the following items.

1.0 *Do you agree to follow the OHRPP Data Security in Research guidance and procedures?

◉ **Yes**

◯ I have an alternate equally effective plan (*Note: The plan must be attached to item #2.1*)

2.0 ***Do you have a data security plan for this study?** *(Note: a plan is not required for all studies; it may be recommended in some instance).*

○ Yes ◉ **No**

2.1 **If yes, attach it here:**

Document Name	Document Version #
There are no items to display	

3.0 ***Indicate all that apply to personally identifiable information or codes <u>during conduct of the study</u>:**

- ☑ **The data and/or specimens will be coded**
- ☐ The personal identifying information will be removed and destroyed
- ☐ Personally identifying information will be maintained with the data and/or specimens

3.1 **If you indicated that the personal identifying information will be removed or destroyed or that the data/specimens will be coded, provide the following information:**

- **The process for removing and destroying the personal identifying information or for coding the information, and**
- **Indicate who will perform the task**

All information will be entered and kept on an encrypted, safe, and secure location. Authorized representatives of the UCLA Office for Protection of Research Subjects including the Food and Drug Administration (FDA) may need to review records of individual subjects. As a result, they may see names; but they are bound by rules of confidentiality not to reveal your identity to others.

All information provided will be kept confidential to the full extent permitted by law. In addition, any names or any other personal identifying information will not be used in any presentations, reports, or publications arising from this study.

After the participant signs the consent form and provides identifying information, the research coordinator will assign a number code to track the participant's questionnaires and interview materials. The informed consent form will be stored in a separate, secure, and locked filing cabinet. At the end of the study, the identifying information will be destroyed.

4.0 ***Will coded or personally identifiable data be collected, transmitted or stored via the internet?**

◉ **Yes** ○ No

4.1 **If yes, indicate all that apply:**

- ☑ **A mechanism such as Survey Monkey, Zoomerang, or an e-mail anonymizing service will be used to strip off the IP addresses for data submitted via e-mail.**
- ☑ **The data will be encrypted.**
- ☑ **A firewall will be used to protect the research computer from unauthorized access.**
- ☑ **Controlled access privileges will be used on the hardware storing the data.**
- ☐ Other.

4.1.1 **If you indicated "Other", describe:**

5.0 ***Provide your assurances that if there is a data security breach for this study, the PI will notify the IRB and your department's IT Compliance Coordinator.**

Agree ☑

ID: IRB#12-001714 View: NEW 9.4 - Data Security Plan - During the Study

This view has been locked by amendment(s)

Warning: Save your work at least every 15 minutes by clicking "Save" or "Continue."

Data Security Plan - During the Study

You indicated that data and/or specimens for this study will be coded (Section 9.3/item 3). Please complete the following information.

1.0 During the study indicate **how data will be stored and secured** including paper records, electronic files, audio/video tapes, specimens. Specify how the **code key** will be securely maintained, as applicable.

Check all that apply:

1.1 ***Electronic Data**

- ☑ **Encryption or password protection software will be used**
- ☑ **Secure network server will be used to store data**
- ☑ **Stand alone desktop computer will be used to store data (not connected to server/internet)**
- ☐ A contracted outside vendor will store the code key. The vendor will have a business associate agreement with UCLA.
- ☐ Other
- ☐ **Not Applicable**

1.2 ***Hardcopy Data, Recordings and Specimens**

- ☑ **Locked file cabinet or locked room with limited access by authorized personnel**
- ☑ **Locked lab/refrigerator/freezer with limited access by authorized personnel**
- ☑ **The code key will be kept in a locked file in a locked room**
- ☑ **The coded data and/or specimens will be maintained in a different room**
- ☐ Other
- ☐ **Not Applicable**

1.3 **If you indicated "Other" in item 1.1 or 1.2 above, describe here.**

2.0 ***By checking this box, I provide my assurance that all the person(s) who will have access to the code key have been identified in section 1.1 or section 1.1a.**

Agree ☑

ID: IRB#12-001714 View: NEW 9.5 - Data Security Plan

Warning: Save your work at least every 15 minutes by clicking "Save" or "Continue."

Data Security Plan

You indicated that the study will have access to personally identifiable or coded information (Section 9.2/item 5). Please complete the following items:

1.0 ***After the study is completed**, indicate how the data codes and/or personal identifying information will be handled.

Check all that apply:

- ☑ **All data files will be stripped of personal identifiers and/or the key to the code destroyed.**
- ☑ **All specimens will be stripped of personal identifiers and/or the key to the code destroyed.**
- ☐ Personal identifiers and/or codes linking the data and/or specimens to personal identifiers will be maintained for future research.
- ☐ Audio or Video recordings will be transcribed and then destroyed or modified to eliminate the possibility that study participants could be identified.
- ☐ Photos or Images will be modified to eliminate the possibility that study participants could be identified.
- ☐ Restricted use data will be destroyed or returned to the source.

1.1 **If you indicated that personal identifiers will be maintained for future research, provide the following information:**
a) How the information will be securely handled and stored
b) assure confidentiality, and
c) who will have access to the identifiers and/or codes.

2.0 **Describe any additional steps, if any, to be taken to assure that the subjects' identities and any personal identifying information are kept confidential.**

ID: IRB#12-001714 View: NEW 9.8 - Data and/or Specimens for Possible Future Use

Warning: Save your work at least every 15 minutes by clicking "Save" or "Continue."

Data and/or Specimens for Possible Future Use

You indicated that prospectively collected data and/or specimens would be stored for future use (Section 9.2/item 5.1). Please provide the following information.

1.0 ***Specify what information directly or indirectly linked to the subject will be provided with data and/or specimens to other investigators.**

Check all that apply:

- ☐ No subject identifiers (The data/specimens are anonymous; no one including the investigator could identify the person from whom the materials were gathered.)
- ☐ The data will be coded (A code links the data/specimens to the study participants. A key to the code exists.)
- ☐ Personal Identifying Information
- ☑ **Not applicable, the data will not be shared outside the study team.**

2.0 **Distribution Rules: Describe the criteria used to determine the adequacy of requests to obtain data and/or specimens (e.g., the type of researchers that will be eligible to receive data):**
All files will be kept in locked cabinets, as will copies of the signed informed consent forms to maintain the anonymity of participants and to bar any unauthorized access. The computerized database will be protected through the use of entry codes available only to authorized personnel (the PI and the study staff). All genetic samples will be de-identified and used anonymously. At this time, we do not plan to share any genetic samples with other investigators.

ID: IRB#12-001714 View: NEW 10.1 - Study Summary - Research Study

This view has been locked by amendment(s)

Warning: Save your work at least every 15 minutes by clicking "Save" or "Continue."

Study Summary - Research Study

1.0 Study Materials: As applicable to this study, attach the following:

- **Protocol, Dissertation Proposal or Study Plan**
- **Preliminary Data**
- **Surveys, Questionnaires or other instruments to be used with study participants**
- **References**

Document Name	Document Version #
Agingbrain R01 resubmission 061512.docx	0.01
fMRI Figures 6-7.docx	0.01
Hongyu_NARSAD_APP.pdf	0.01
IRB 12-001714 Assessment Schedule.docx	0.01
Namenda Brain Again References.pdf	0.01

2.0 *Specific Aims: Indicate the purpose of the research, specifying the problems and/or hypotheses to be addressed.

The specific aims and hypotheses are:
Specific Aim 1. To compare the quality of treatment response in older depressed subjects to escitalopram+placebo (esCIT+PBO) vs. escitalopram+memantine (esCIT+MEM) in a 6 month acute treatment trial with 12 month follow up.

Hypothesis 1. Improved levels of depression and cognition will be observed in depressed subjects treated with combined escitalopram+memantine compared to those treated with escitalopram+placebo.

Specific Aim 2. To determine the role of a) brain pathology (MRI and FDDNP-PET measures) and b) MCI diagnosis in predicting and moderating antidepressant response to study drugs in depressed subjects.
Hypothesis 2a. Measures of brain pathology (volume and localization of white matter hyperintensities, regional gray and white matter volumes, hippocampal atrophy, functional brain connectivity using cognitive task activation , FDDNP-PET binding levels) will predict and moderate antidepressant response to escitalopram and memantine or escitalopram and placebo in: 1) rate of remission; 2) rate of depression relapse; and 3) improvement in cognitive performance.

Hypothesis 2b. MCI diagnosis will predict and moderate preferential antidepressant response to escitalopram and memantine.

Aim 3: To test whether the two treatment conditions can improve neurocognitive performance and working memory function surveyed with task-related fMRI at 12 weeks and/or during the 6 months follow-up. Hypothesis 3a: Compared to escitalopram+PBO, escitalopram+MEM will improve cognitive performance on tests of a) memory after 12week treatment and at 6 months follow-up. Hypothesis3b: Likewise, escitalopram+MEM will increase working memory-related activation of dorso-lateral prefrontal cortex (DLPFC)

Aim 4. To determine whether both structural and functional brain imaging markers will predict and/or moderate antidepressant response in both treatment conditions.

Hypothesis 4: Imaging biomarkers will moderate and predict 1) rate of remission; 2) rate of depression relapse and recurrence; and 3) improvement in cognitive performance.

Exploratory hypothesis 1: We will explore the relationship of apolipoprotein E-4 allele (APOE-4) to [18F]FDDNP PET binding in subjects with DEP+MCI. We expect that APOE-4 allele carriers will have higher FDDNP binding in the medial temporal lobe compared to non-carriers, and will experience greater cognitive decline on neuropsychological tests and fMRI memory tests.

Exploratory hypothesis 2: We will explore changes in 1) telomerase level and 2) NFKappaB expression with treatment and their relationship to clinical and cognitive outcomes, 3) the role of 2 candidate gene APOE-4 and 5-HTTLPR in treatment response and cognitive outcomes.

3.0 *Background and Significance: Provide a summary of the background for this study and explain how it will contribute to existing knowledge.

For greater than minimal risk biomedical studies, include preliminary data. If necessary, attach in Item 1.0 graphs or tables used to convey information. If there no preliminary data are available, briefly indicate why this proposed study is a reasonable starting point.

Significance. Scientific and clinical impact: Among depressed elderly, treatment with antidepressant medication, such as selective serotonin reuptake inhibitors (SSRIs), results in remission rates of only 30%. Hence, there is an urgent need to develop strategies that add to the efficacy of SSRI treatments. The likely contribution of brain aging to poor treatment response has not been addressed. Our preliminary data suggest that memantine, one of the very few currently available neuroprotective agents, administered along with escitalopram, adds to the benefit of escitalopram by further reducing depressive symptoms, apathy, and improving cognitive performance, compared to escitalopram alone. Our group has accumulated sufficient evidence of structural brain changes associated with LLD 51-56. Most recently, we have demonstrated that geriatric depression with and without MCI have different patterns of amyloid and tau brain distribution using [F-18]FDDNP PET in the critical brain regions in patients diagnosed with LLD38,47 that might represent different endophenotypes in the aging brain. Higher [18F]FDDNP at baseline predicted future cognitive decline 57. However, none of these biomarkers have been studied in treatment trials.

The proposed project will address priority areas of NIMH research. The recently published Report of the National Advisory Mental Health Council Work Group called for developing “new treatment strategies to the patient’s genetic, physiological, or behavioral characteristics and affording personalized care; and new and better interventions that incorporate the diverse needs and circumstances of people with mental illness,” and to “define predictors and understand the mechanism of treatment response” and to “create and refine biomarkers, behavioral assessments, and phenotypic characterizations of disease.” Notably, prognostic biomarkers are expected to play a crucial role in the future of personalized medicine. The addition of memantine may serve as a viable approach to improving clinical outcomes of late-life depression because of neuroprotective effect on brain aging. Imaging measures are expected to correlate with specific cognitive features of LLD, particularly in the domains of executive and memory function. The proposed study will go beyond the pilot project in the double-blind placebo-controlled design with expanded assessments at 6-12 months, and cognitive and multimodal neuroimaging biomarkers likely related to treatment outcomes.

B. Innovation. Our approach is innovative in promoting understanding of the role of brain aging in the clinical features of geriatric depression and treatment response. Advanced computational image analysis approaches incorporating cross-modal image analyses for the study of geriatric depression are noticeably absent, especially when considering treatment response. By taking advantage of tools available through the brain imaging community at UCLA and infrastructure available through the UCLA Laboratory of Neuroimaging, the Department of Molecular & Medical Pharmacology and Nuclear Medicine Division, we will apply cutting-edge image analytics methods to characterize brain-aging biomarkers in subjects with LLD with/without a-MCI. We will employ a targeted multimodal imaging battery to identify markers linked with disease and treatment response and relapse in LLD. Image data obtained at 3T field strength will include sequences designed for optimal trade-offs between acquisition time and spatial, temporal and/or angular resolution. All acquisition protocols reflect the most up-to-date capabilities of scanner hardware and software. Each imaging modality is designed to provide unique and complementary information for better evaluation of the neurobiology of geriatric depression and includes novel, noninvasive imaging techniques, such as [F-18]FDDNP PET and structural and functional (s and f)MRI, which have not been widely applied in combination for the study of LLD. Finally, to advance scientific understanding of the complex mechanisms underlying LLD and its treatment outcome, we will employ innovative analytic strategies that integrate data across imaging modalities.

In addition, this is the first trial combining memantine and escitalopram for the treatment of late-life depression (with/without a-MCI) that integrates brain aging biomarkers of cerebrovascular and neurodegenerative changes that focuses on predictors and moderators of treatment response. Stratification by higher risk group for brain aging (i.e., a-MCI; late-onset) has important implications for identifying high-risk subgroups of elderly depressed subjects with preferential response to the combination of an antidepressant and cognitive enhancer that creates a potent “mood+cognitive enhancer,” which acts via glutamatergic and serotonergic neurotransmission. This combination should theoretically have greater efficacy and a more rapid response compared to an SSRI, especially in those with a-MCI and brain aging. Finally, in addition to assessing primary outcomes, we will explore the benefits of each treatment option on resilience, health-related quality of life, and life satisfaction during 12-month follow up. If our hypotheses are correct, this approach will inform clinical practice to use memantine to enhance antidepressant response and maintain such improvements in older adults with major depression and MCI, especially in those with additional biomarkers of brain aging (cortical atrophy, WMH, [F-18] FDDNP binding), thus developing personalized approaches to the treatment of geriatric depression. Future directions of this work will include developing specific interventions targeting biomarkers of brain aging in geriatric depression and the development of preventive interventions for depression relapse and recurrence in older adults, as well as prevention or delay of conversion to dementia in high risk groups.

C. Background and Rationale. 1. Overview. Despite progress in antidepressant therapies, a considerable number of depressed elderly patients develop either a chronic condition or relapse frequently after periods of improvement 58-61. Elderly patients appear to have a particularly brittle response with a higher rate of recurrence and a shorter interval before recurrence.62,63 Cognitive impairment has been implicated in inadequate treatment response 412. Clinical features of geriatric depression. Geriatric depression is associated with greater medical and cognitive comorbidity, structural brain changes, and higher rates of apathy, anxiety, and suicide, as well as poorer treatment response compared to younger adults 41,64-70.

3. The definitions and epidemiology of MCI. MCI originally was defined by significant declines in delayed recall, otherwise intact general cognition, and no functional impairment. 44 Recent studies indicate an overall prevalence of MCI of 15 – 22% 71 with higher prevalence rates in older age groups or among those with depression 72. People with MCI show annual

conversion rates to dementia or AD ranging from 6% to 25% and from 50 – 100% over 5 years 73. Currently, MCI subtypes characterize memory or non-memory impairment, and whether single or multiple domains are impaired 74-76 MCI with memory impairment (a-MCI) is the most studied subtype. In a recent study of outcome in MCI subtypes, 76% of persons who progressed to AD had prior a-MCI 77. We will stratify groups by a-MCI status. By recruiting subjects with depression and memory complaints, it is feasible to increase the proportion of a-MCI subjects to 50% (46% in our pilot samples). MCI in LLD. Cognitive impairment is a hallmark of geriatric depression and may persist despite successful treatment of depression 42,78. Up to 50% of LLD subjects may have MCI diagnosis. 78,79 Lee (2007) reported that 54% of a remitter LLD sample met criteria for MCI 43. Two epidemiological studies found that 13-20% of subjects with depressive symptoms subsequently develop MCI over an average of 3-6 years 80,81. Lyketsos et al reported that 20% of subjects with MCI had concurrent depressive symptoms 82. Comorbid depression accelerates conversion from MCI to dementia 83. Among those with MCI, 63% had amnestic type and 37% had non-amnestic MCI 42. Depression and dementia share common risk factors: geriatric depression could be a prodrome of dementia 78 or lead to damage to the hippocampus through glucocorticoid cascade leading to dementia 84,78,85. The existing studies suggesting irreversibility of cognitive impairment used either SSRI's or TCAs. Drug combination that produce antidepressant and cognitive enhancement is likely to improve treatment response, but the evidence is lacking. Our treatment strategy of combining an SSRI with memantine may lead to improvement in memory, attention, and executive control, particularly in LLD subjects with MCI.

4. Neuroimaging biomarkers of brain aging in geriatric depression. MRI: Findings from clinical and preclinical studies suggest a role for neurodegeneration and vascular mechanisms in the pathophysiology of late-life depression.86-89MRI neuroimaging determinations have identified smaller volumes in critical cortical and subcortical regions of the brain in patients diagnosed with late-life MDD when compared with controls 90,91. Smaller brain volumes on MRI are presumed to reflect neurodegeneration.92 Microvascular cerebrovascular disease with white and gray matter hyperintensities and lacunes is the most commonly reported non-specific finding with higher rates in geriatric depression 93-97. MRI markers of cerebrovascular disease are more typically associated with executive dysfunction; 98,99 memory and language;100, and greater mortality in depression.101 Our research group has contributed to the literature documenting the effects cerebrovascular disease and regional brain atrophy associated with clinical features of late-life depression and cognitive impairment, 51,52,55,91,102-109 and smaller hippocampal volumes,90 in the CA1 and subiculum subfields in LLD subjects related to poor cognitive performance. Steffens et al reported smaller hippocampal volumes associated with APOE4 allele and later age of onset 110,111. Other authors reported the relationship between lifetime duration of depression and hippocampal atrophy,4,112 attributing this to glucocorticoid neurotoxicity; and decreases in brain derived growth factor and plasticity 113. Mixed findings on brain structural changes are likely due to heterogeneity of LLD with respect to neurodegenerative and vascular changes. PET: Preliminary evidence emerging from plasma data indicating that the ratio of Abeta-42:Abeta-40 may be a biomarker of early Alzheimer's disease (AD) in LLD patients 114-118. Depression in the elderly has been identified as both a risk factor and a prodrome for AD 119,120. Butters and authors (2008) used positron emission tomography (PET) with [11C] 6-OH-BTA-1 [Pittsburgh Compound-B (PiB)] in nine LLD subjects 39. The PiB retention was related to cognitive performance. Our group demonstrated different patterns of amyloid and tau PET imaging in subjects with LLD with and without MCI using [18F]FDDNP ((2-(1-{6-[(2-[18F]fluoroethyl)(methyl)-amino]-2-naphthyl}ethylidene) malononitrile) positron emission tomography (PET). Kumar reported that [18F]FDDNP binding was significantly higher globally and in the posterior cingulate and lateral temporal regions in the MDD group compared with controls. Lavretsky et al (2009) reported differences in the regions of greater uptake related to the MCI status (preliminary data)47. In the current proposal, we will address heterogeneity in brain aging using in-vivo neuroimaging techniques in relation to clinical outcomes, thus leading to the individually tailored treatment.

5. Memantine: unique mechanisms of action relevant to efficacy in geriatric depression as an enhancer of cognition and antidepressant response. Drugs that target glutamate neuronal transmission offer novel approaches to treat depression, especially in older patients with cognitive impairment. Memantine was first synthesized in the 1960s, and in 1989, it was found to inhibit NMDARs 121,122 with an IC50 of approximately 1 μM; 123,124 which corresponds well with its therapeutic concentration range. In the treatment of AD, memantine is typically administered at 20 mg/d. 125The clinical utility of memantine probably results from a combination of the ability to bind only (or preferentially) to open channels; an ability to inhibit at two different sites; and NMDAR subtype specificity, or lack thereof. 126-130At high concentrations (10–500 μM), memantine affects many CNS targets, including serotonin and dopamine uptake, nicotinic acetylcholine receptors (nAChRs), serotonin receptors, sigma-1 receptors, and Na+ channels.131 Memantine would be an important target of investigation in older adults with LLD and MCI, as it may act as a stimulant and cognitive enhancer.

6. A clinical and psychopharmacological rationale for the use of escitalopram in geriatric depression. Escitalopram has been effective in the treatment of depression and in relapse prevention. Approximately 6% of the 1144 patients receiving escitalopram in controlled trials of escitalopram in major depressive disorder and GAD were 60 years of age or older. Elderly patients in these trials received daily doses of 10-20 mg. We chose escitalopram because of its superior selectively in inhibiting serotonin reuptake, good tolerability and safety in the elderly, low potential for drug-drug interaction, and simple dosing. Cochrane Database supports escitalopram's superior efficacy compared to other newer antidepressants such as SSRIs and duloxetine and venlafaxine.132 Escitalopram is more effective than citalopram in terms of remission (OR 0.53, 95% CI 0.30 to 0.93), and a faster onset of antidepressant action compared to citalopram in the mixed age samples. 133-136The average SSRI adherence is close to 90% 137, and reached 95% in our pilots.7. Memantine combined with Selective Serotonin Reuptake Inhibitors (SSRIs). A few papers reported synergistic interactions between antidepressants with memantine in animal models of depression in the forced swim test 138. In humans, combined use of an SSRI and memantine is only recommended for dementia patients by the expert consensus panel.50,139-143 The potential risk of metabolic drug-drug interaction is relatively low in both memantine and escitalopram.140 Sixteen to 24 week trials are more

traditional in older subjects 144,145. Besides a recently negative donepezil trial for LLD,146 no other studies addressed cognitive outcomes or investigate underlying mechanisms of action 8. Predictors and moderators of antidepressant response in LLD. Most recently, evidence is emerging that supports predictive or moderating properties of such factors as apathy executive dysfunction, 147-148 but not for the vascular or medical burden. Based on our literature review and pilot data, we intend to use cognitive domains, the MCI diagnosis, neuroimaging biomarkers in the analyses of predictors/moderators of treatment response. Alternative considerations to the study design: a). We decided not to include a group taking memantine alone given the existing negative trial by Zarate et al. (2008) and the fact that non-research based clinicians are not likely to use memantine alone for treatment of depression. b). We have considered using other cognitive enhancers like cholinesterase inhibitors (CHEI), but decided against it due to recently published negative report 146 that did not find benefit for depression or cognitive outcomes with donepezil augmentation in a 2 year follow up of LLD. c). After carefully considering repeating neuroimaging at follow up, we decided against it due to the insufficient evidence of significant MRI or PET changes over 12 months period.
C. Preliminary Studies (Appendix 1). We present our preliminary data in three areas germane to the proposed project: 1) in vivo amyloid and tau protein imaging using [F-18]FDDNP PET studies in patients with depression and MCI suggesting an independent high-risk endophenotype of geriatric depression+amyloid/tau burden that differs in depression+MCI/-MCI subjects; 2) The studies documenting the role of MRI biomarkers of brain aging in late-life depression; 3) The results of our pilot study that used memantine with escitalopram to improve clinical and cognitive outcomes of geriatric depression.

1. a-b). Depression+MCI- is it a separate endophenotype of brain aging that carries high risk for developing Alzheimer's disease?: An FDDNP-PET study validation of the concept.47 Our group recently conducted a number of investigations to document different patterns in the [F-18] FDDNP PET-amyloid/tau marker binding between subjects with major depression and normal controls, and between subjects with depressive symptoms with and without MCI.47 a). Lavretsky et al (2009, Figure 2) included the comparison of subjects with and without a-MCI in 43 non-demented middle-aged and elderly volunteers (23 with a-MCI and 20 -cognitively normal).47 Correlations between standardized measures of depressive and anxiety symptoms and regional FDDNP binding values were calculated. In the MCI group, depression scores correlated with lateral temporal FDDNP binding and trait anxiety scores correlated with posterior cingulate FDDNP binding. In the comparison group, depression scores correlated with medial temporal, and trait anxiety scores correlated with medial temporal and frontal FDDNP binding. The results suggest a relationship between depressive symptoms and biomarkers of cerebral amyloid and tau deposition and vary according to the presence/absence of MCI.
b). Kumar et al found that subjects with MDD (N=20) had higher FDDNP binding in the posterior and anterior cingulate, and lateral and mesial temporal regions in the MDD group compared to normal controls (N=19).38 These findings suggest greater neuronal injury secondary to higher protein load in key brain regions that might provide an important mechanism in the pathophysiology of MDD linking it to cognitive impairment and AD; however, this study did not include subjects with MCI, which may account for the differences in regional findings in subjects with
depression compared to the first report (Figure 3)38. The presence of MCI may signify different pathophysiological mechanisms underlying mood symptoms that we will examine in the proposed study. c). High Resolution Cortical Thickness HC Mapping in Cognitive Risk Groups. We developed a novel method for directly measuring cortical thickness in hippocampal (HC) subregions using HC flattening and unfolding high resolution MRI images at 3 Tesla (.39 x .39 mm; 150. This method obtains flat maps boundary demarcations for HC subregions and neighboring cortex, including entorhinal cortex (ERC), perirhinal (PRC), parahippocampalgyrus (PHG) and fusiform gyrus (FG).151In older control subjects genotyped for APOE4 (16 carriers, 14 non-carriers), we found that carriers had significantly thinner cortex in the ERC and subiculum, while HC volume measures from the same data could not differentiate groups.151 Cortical thickness in the HC was related to delayed memory performance on paired associates learning (R2=.49), delayed story recall (R2=.29), and the Selective Reminding Task (R2=.26). It is currently unknown whether the local presence of tau and amyloid pathology in the brain affects local neural function and subsequently cognition. We measured [F-18]FDDNP binding in 23 older adults (7 mild ADs, 6 MCIs, 10 controls;152 and correlated the 3D [F-18]FDDNP distribution with cognitive performance using voxel-based mapping. Cortical [F-18]FDDNP binding was significantly correlated with cognitive performance, even in healthy controls, and binding increases followed the Braak and Braak trajectory. [F-18]FDDNP predicted cognitive performance even in control subjects, and elevated [F-18]FDDNP signal preceded cortical thinning in the same pattern that thinning is known to occur, suggesting that [F-18]FDDNP provides a sensitive measure of brain changes precede AD.153 e). Hippocampal Sub-Regional Thickness and [F-18]FDDNP Signal. To integrate [F-18]FDDNP findings with high resolution structural imaging of the HC, we examined the relationship between global amyloid and tau burden from [F-18]FDDNP and cortical thickness in HC subregions and surrounding structures; 20 subjects (10 AD, 10 control) were matched for age; MRI T2 FSE images were unfolded using the procedure described in Zeineh and authors (2003) and in the Methods section below.154 We found that HC cortical thickness in the MTL was significantly correlated with [F-18]FDDNP binding across brain regions; including posterior cingulate, frontal lobe, parietal lobe, thalamus, and striatum. Better memory was related to increased cortical thickness in the MTL, and with decreased [F-18]FDDNP binding. The tight links between cortical thickness in MTL and [F-18] FDDNP binding throughout the brain suggests that amyloid and/or tau deposition is linked with neural loss.

2. MRI neuroimaging biomarkers of neurodegenerative and cerebrovascular changes. a. Lavretsky et al 2008. The role of cortical and hippocampal atrophy and subcortical cerebrovascular white matter disease in late life depression.56 We examined MRI correlates of depressed mood, apathy, anhedonia, and anergia in 270 community-dwelling older adults in a longitudinal observational study of subcortical ischemic vascular disease (SIVD). 41% were classified as having subcortical lacunes. Subjects with depression and apathy were more likely to be cognitively impaired and had larger lacunar volume in white matter, thus supporting the role of subcortical ischemic vascular disease in the pathogenesis of late-life neuropsychiatric disorders. b. Mueler et al 2010 155 MRI correlates of depression and cognitive impairment. In a structural MRI study of older adults, frontal, temporal and hippocampal GM were associated with cognitive performance and frontal

WML load with depressed mood indicating that mood and cognitive impairment have different MRI correlates. In summary, Our pilot data indicate that LLD is frequently accompanied by cognitive impairment related to cerebrovascular disease and neurodegenerative changes according to in-vivo neuroimaging biomarkers (i.e., MRI and F-18-FDDNP PET). Stratifying subject groups according to aMCI may, therefore, be an informative strategy to enrich sample for biomarkers of brain aging 47,156-159. Given the demonstrated differences in the pathophysiology of depression and depressive symptoms depending on cognitive and biomarker status, it is likely that we will be able to demonstrate predictive and moderating effects of biomarkers on treatment response. This design is feasible given the 50% prevalence of aMCI in our population.

3. A pilot study of combined treatment with memantine and escitalopram compared to escitalopram alone in subjects with major depression and a-MCI. This study was an open-label comparison of the case-series of 28 older depressed subjects with MCI. In addition, a-MCI was diagnosed if patients performed between -1.5 and -2 SD below age and education norms on the Buschke selective reminding test. We compared the results of treatment of 28 depressed subjects. 14 subjects received 10-20 mg of escitalopram for 12 weeks, and 14 subjects received a combination of escitalopram (10-20 mg /day) and memantine (5-20 mg/day) for 12 weeks. Remission was defined as a Hamilton Rating Scale for Depression (HAM-D) score of<6. Twelve subjects completed the combination treatment and 13 completed treatment with escitalopram. Ten of the 12 completers in the combination group (83.3%), and four of 13 completers in the escitalopram group (30.7%) achieved remission (Chi square=7.0; p=0.008). An effect-size estimate based on the change from baseline to 12 weeks in HAM-D is roughly 0.76 standard deviations, reflecting a large effect size. The effect size from the analyses of continuous HAMD change is 1.2. The graphs of change in HAMD- scores are presented below. (Figures 6 a,b) In the repeated measures ANOVA, the MEM+ESCIT group showed a trend for group difference in improvement over 12 weeks of treatment compared to those on ESCIT (F=2.6; df=1,21; p=0.1; FIGURE 5b). The daily dose was determined according to the efficacy and tolerability of the drugs. The subjects in the MEM+ESCIT group demonstrated greater improvement in apathy, resilience, energy, social functioning and wellbeing.

4. Other relevant studies We have conducted 2 open-label and 2 double-blind placebo-controlled trials of methylphenidate (MPH) (MH001948; MH077650; MH0864481) used as an adjunct to citalopram. All of these studies indicate that adding an augmenting agent with different mechanisms of action improves the speed of response and the overall efficacy of antidepressant treatment with added improvement of cognition and quality of life 56,158,160,161. The dropout rate across all samples was 25%. Summary: The results from the pilot project provided us with a strong basis to propose the current R-01 project. The infrastructure at UCLA is outstanding and sufficient for supporting the proposed study. All members of the research team have collaborated or many years.

Telomerase and NF- kB Activity
Telomerase is a ribonucleoprotein enzyme responsible for maintaining telomere length through reverse transcription. Telomeres, non-coding nucleotide sequences that cap and protect the chromosome, become successively shorter during DNA replication. Without protection from telomeres the end of the chromosome will fuse and rearrange, obstructing replication and eventually leading to cellular senescence. Not only is telomere length related to cellular aging, shorter telomeres are also linked to increased risk for age-related illnesses, and may predict early mortality. By maintaining telomere length, telomerase prevents DNA degradation, and thus extends the life of the cell. Epel et al. (2010) found that leukocyte telomerase activity increases in response to an acute stressor, although chronic stress may act to suppress telomerase activity, eventually shortening the length of the telomeres. Stress acts to increase levels of cortisol, catecholamines, and oxidative stress, which may interact to reduce telomerase activity (Gidron et al., 2006). Research has shown that chronic life stress in caregivers is associated with shorter telomere length, thereby accelerating cellular aging. In our study, we intend to analyze leukocyte telomerase activity in LLD+MCI subjects before and after intervention. This will allow us to determine how telomerase responds to interventions designed to reduce stress.

Chronic resistant stress and depression impair hippocampal-dependent cognitive function and enhances amygdala-dependent fear conditioning, which are consistent with the opposite effects of stress on hippocampal and amygdala structure. Psychosocial stress suppresses neurogenesis and causes dendritic shrinkage, which serves as a mechanism in the pathogenesis of human depressive illness. Indeed, in major depression and a number of other mood and anxiety disorders, there are reports of hippocampal volume loss and enlargement of the amygdala. Treatment with antidepressant and neuroprotective drugs can prevent hippocampal structural volume loss.
NF kappa B is the biomarker of inflammatory pathways that is affected by stress, depression, and may change in response to treatment as we found in our studies of meditation in depressed careigvers.

4.0 ***Research Design and Methods: Describe in detail the design and methodology of the study.**

Research Procedures:
1) Telephone screening (15 minutes): All potential participants will be initially screened using a standardized telephone screen script that received an approval of the UCLA IRB review committee. Only those who meet initial entry criteria will be invited for the in-person screening evaluation.

2) In-person screening interview (2 1/2 hrs): An experienced clinical coordinator will assist in subject recruitment, scheduling, SCID diagnostic interview, clinical and laboratory assessment. Prior to their enrollment in the study all subjects will sign a consent form approved by the UCLA-IRB and all participating institutions. Dr. Lavretsky will will perform most examinations at screen and baseline. Eligibility will be assessed at screening and baseline. No subject will be asked to discontinue

effective antidepressant medications. Only subjects currently not taking psychotropic medications prior to the initiation of the study will be admitted into the study. Subjects will be off all psychotropic medication for at least two weeks prior to entering the study (four weeks in case of fluoxetine, see exclusion criteria). We will apply the Beers (1997) criteria at screening to determine inappropriate medications for older adults that may result in cognitive impairment (e.g. anticholinergic, benzodiazepine, etc) and will control for in the analyses.

Screening for dementia and MCI. Those subjects meeting the DSM-IVr criteria for dementia will be excluded. We will screen subjects for possible incipient dementia, and then verify their condition by comparing baseline assessments to the one at 6 and 12 months. This will include reviewing an extensive history and mental status exam together with corroborating information from a knowledgeable family member and assessment of functional skills. Cases that are clinically ambiguous will be discussed at the consensus meetings among all raters. A Mini-Mental State Examination score of < 24 or an established dementia diagnosis will serve as an automatic exclusion criterion. The evaluation for dementia includes: 1) An interview by a psychiatric nurse to identify physical and cognitive limitations; 2) a standard battery of hematologic studies, blood chemistries, liver and thyroid function tests, B12 and folate levels, and RPR test; 3) neurological examination (UPDRS); 6) neuropsychological examination (detailed below); and 7) psychiatric evaluation (SCID-DSM-IV), as detailed above. Adjudication of dementia is based on DSM-IV criteria, as recommended by Knopman et al (2001) and Lyketsos et al. (2002) At the consensus conference, additional information will be reviewed (e.g., family history, drug use). If there are clinical features suggestive of dementia, the patients will be referred to the UCLA Memory Program (Dir. Gary Small), the UCLA ADRC, or other qualified community providers for management. This approach is consistent with clinical realities and with one used by other research groups.

Diagnosis of MCI. We will conduct consensus meetings to assign patients to diagnostic groups, according to MCI criteria that we have used in prior studies and clinical judgment. MCI criteria are: 1) The patient is neither cognitively normal nor demented; 2) a decline in cognition as reported by the subject or a collateral; 3) cognitive testing shows impairment and corroborates subjective report of decline; and 4) functional activities are not significantly impaired. Subjects will be classified as amnestic type MCI (a-MCI) if they show mild impairment in memory with or without other domains impaired. We will use performances between -1.5 and -2 (SD) below age and education norms on one of two screening memory tests; WMS-IV Logical Memory and WMS-IV Visual Reproduction 164 to denote mild impairment 45,75,165. We chose a -1.5 SD index, as this is most widely used 74 and will be most relevant for comparisons with other studies in the literature. We will stratify the groups by the presence of amnestic MCI (either single or multiple domains).
Age at onset of depression: we will explore the role of age at onset in heterogeneity of MCI and treatment response by stratifying groups by onset before or after age 60, as commonly defined.

Medical evaluation. All subjects will receive an initial medical assessment including a complete physical examination with neurological and neuropsychiatric examinations, electrocardiogram (ECG), and laboratory testing at baseline. These tests are used to rule out new-onset medical illnesses that could account for behavioral and cognitive symptoms. All abnormal physical or laboratory findings will be reported to subjects' primary physicians with the subject's consent. If abnormal physical or laboratory results are considered responsible for depression, the subject will be excluded from participation.

3) Baseline assessment.
Depression evaluation: All subjects will undergo a Structured Clinical Interview for DSM-IV (SCID) for the purposes of establishing a diagnosis of Major Depression (MDD). A history of depressive illness includes the length of the current episode of MDD, age of onset of the illness, prior duration of the illness, and number of episodes. Assessment of depressive symptoms will be based upon administration of the Hamilton Rating Scale for Depression (HAM-D-24-item). Other domains of baseline assessment will address issues thought to be important in understanding risk factors for LLD will be tabulated. High levels of inter-rater reliability will be maintained. For example, inter-rater reliability for the total HAM-D-24 score or the SCID diagnosis of depression has been excellent, as demonstrated by ICCs of 0.78 to 0.95. The age at depression onset will be determined using subjects' report, and medical records. We will stratify both groups by the age at onset with cut off at age 60 to examine the role of late vs. early onset in treatment response.

Comorbid anxiety and insomnia. Comorbid anxiety disorders and insomnia can be present and assessed at baseline and follow up.

Assessment instruments. All instruments have been selected because of their validation with geriatric patients in clinical trials, as well as their direct relevance to the posed hypotheses. They provide a comprehensive assessment of the severity of depression, medical comorbidity, cognitive and functional impairment, life satisfaction, and quality of life. The use of these instruments will enable the PI to compare results of the study to other investigations. Most instruments, except the cognitive tests and self-administered ones, will be administered by the PI or the co-investigator (Tables 2;4).

Measures of cognition (administered at baseline; repeated at 6 and 12 months, or upon early termination).
Neuropsychological assessment: Our neurocognitive battery was developed by Linda Ercoli, PhD, an Associate Professor of Psychiatry and Chief Psychologist for the Geriatric Psychiatry Division at UCLA. Dr. Ercoli's expertise spans the study of depression, dementia and mild cognitive impairment. She applies neurocognitive assessment in randomized clinical trials, and evaluates neurocognitive consequences of treatment using cognitive enhancers. Domains of cognition will be assessed that are likely to show impairment in geriatric depression: (1) selected language functions-phonemic and semantic fluency, confrontation naming; (2) executive functioning (we will include measures of cognitive set-switching and inhibitory control); (3) episodic memory. The primary analyses will focus on immediate and delayed recall indices; (4) information processing

speed and attention, including an indices of complex and sustained attention); (5) visuospatial ability. Most of the measures have 2- 4 alternate forms that will be used to reduce learning bias. In addition to the cognitive outcomes, we will include a brief word reading test, the WAIS-IV Test of Premorbid Functioning (TOPF), a revision of the Wechsler Test of Adult Reading, to estimate an individual's premorbid cognitive functioning. We will conduct a confirmatory factor analysis to assess the goodness of fit of our a priori domain assignments, and use data reduction methods. Each a priori composite domain assignment will focus on memory, executive dysfunction, and processing speed as major components of geriatric depression.

Randomizaton and stratification procedures: After all screening and baseline test results are reviewed and eligibility criteria are confirmed, medications will be dispensed if patients continue to meet eligibility criteria and have signed the informed consent form. All eligible subjects will be randomized to the EsCIT+MEM or EsCIT+PBO control group using a computer-generated random assignment scheme, which assigned subjects in a 1:1 ratio to each group. The groups will be stratified by the a-MCI status, and by late/early onset.

Study medications and treatment procedures. Patients who meet all eligibility criteria at baseline will be given a 14-day supply of the study medications prepared and dispensed by the UCLA Pharmacy in the matching capsules. All subjects will receive 10-20 mg of escitalopram open-label throughout the trial. Matching capsules containing memantine (MEM) or placebo will be given and titrated from 5 mg/day to 10 mg/twice a day (or 20 mg a day) over the course of the first four weeks. Subjects will be instructed to take one tablet of escitalopram a day in the evening or in the morning, as preferred; and 1 pill of MEM (in 5 mg increments) or placebo at 8 am for the first week, and at 8 am and 3 pm in the second week and thereafter. The dose of MEM will be increased every 7 days: second week 5 mg (1 pill) twice a day; third week 5 mg (1 pill) at eight o'clock in the morning and 10 mg (2 pills) at three o'clock in the afternoon; fourth week 10 mg (2 pills) at eight o'clock in the morning and three o'clock in the afternoon.

4) Magnetic Resonance Imaging (MRI) Structural Scan and Functional Scan or one Computerized Tomography (CT) Structural Scan. MRI Scanning Methods and Procedures at baseline. All subjects will receive either two magnetic resonance imaging (MRI) scans (at baseline and then 12 weeks) or only one CT structural scan (baseline only) and one positron emission tomography (PET) scan (baseline only). Subjects will undergo a metal screen and will be asked to remove all metal from their body before the scan and lie still for about 60 minutes while the scan is taking place. Subjects will only receive a CT structural scan if found ineligible for MRI due to having metal implants. The CT structural scan is provided as a co-registration for the PET scan. Subjects will be asked to have one MRI scan of their brain in the beginning of the treatment course. The scan will occur at the UCLA Brain Mapping Center.
Subjects who cannot undergo MRI scanning will undergo one Diagnostic Brain Computed Tomography scan in the UCLA Department of Nuclear Medicine or the Department Radiology.

Imaging Biomarkers: Imaging data will be acquired from each subject at baseline and at 12-wks post-randomization on a Siemens 3T Trio system using a 32-channel head coil. Each scanning session will last 60 minutes and include 1) a T1-weighted multi-echo MPRAGE (MEMPR) sequence for the examination of brain structure; 2) a bandwidth matched T2-space sequence for detection and quantification of WMHs and CSF; and 3) three separate BOLD EPI sequences for the acquisition of rs- and task-related fMRI data used for the examination of emotional and working memory processing and functional connectivity (Table 2). In addition, a 3-plane localizer and a non-BOLD EPI sequence co-planar to the fMRI data for cross-modal image registration will be acquired. The morphometry sequences are optimized for determining brain tissue contrast with reduced distortion.145

Functional Imaging: To address our hypotheses that Esit_ MEM versus ESCIT_ PBO will result in greater activation in right VLPFC and the amygdala during emotional processing and greater working memory-related activation in the DLPFC and other network regions we will employ two widely-validated brain activation tasks that probe emotional processing and working memory function. Similarly, analysis of rs-fMRI data will determine whether ESIT+ MEM associates with plasticity in brain network activity. Faces Affective Reactivity Task. We will use a previously detailed Faces/Shapes brain activation task shown to produce robust and reliable activations in amygdala and PFC regions during emotion processing, making this paradigm particularly appropriate for longitudinal investigation.146,147,148,171In brief, during this task participants are required to match emotions (activating the amygdala and VLPFC), label emotions (activating the VLPFC) or match forms (a control condition) while presented with faces showing different emotional expressions or geometric shapes[Fig. 6]. Since subjects are not asked to attend or regulate their affect, brain activation is more closely linked with affective reactivity, rather than with affect perception.148 The task includes 5 blocks of the control shape-matching task interleaved with 4 blocks of the experimental faces condition. Button press responses monitor accuracy and reaction time. Though some mixed findings exist, previous studies, and our pilot data suggest that implicated VLPFC hypoactivity, as well as task-related activation of the amygdala may vary with response to treatment and clinical state.149

Working Memory Task. We will use a well-established 2-back version of the n-back task detailed in Townsend et al.,115 to elicit neural activation linked with working memory. This task consists of two blocked conditions with a 20 s resting condition interleaved between conditions. In the experimental 2-back condition subjects track letter sequences and press a button when they detect a letter that appeared 2 positions back. In the control 0-back condition, subjects will press a button every time the letter "X" appears on-screen. Button presses record accuracy and response time. This version of the n-back has been employed in our laboratory to show significant reductions in activation of the DLPFC and posterior parietal cortex across mood state in bipolar subjects compared to controls115 as well increased activation in association with clinical response in LLD.

Resting State-fMRI: During acquisition of BOLD rs-fMRI data, subjects will be asked to remain awake with their eyes closed. Though resting state connectivity is highly reproducible over time in healthy subjects150, experience-based neural plasticity in resting state connectivity has been shown to occur over periods as short as 2-9 days.151 Recent research points to significant changes in DLPFC and cingulate connectivity in association with ECT.75,76

Imaging data will be collected for each subject at baseline and 12-weeks after pharmacotherapy on a Siemens 3T Trio system using a 32-channel head coil. Each scan session will include T1 sequences of brain structure that will be used to correct for tissue content for MRS post-processing. Single voxel MEGAPRESS
1HMRS Siemens works-in-progress sequences (TR = 2500 ms, TE = 1/2J= 68 ms, 128 averages, automatic shimming) allowing dissociation of GABA as well as Glu and NAA (from the unedited spectrum) will be used to examine 3 regions of interest (ROIs) as based on MRS publications on depression treatment (Bustillo,
2013). One voxel each (30x20x20mm) will be positioned in the left and right hippocampus, with the long axis parallel to hippocampus length. The other ROI (40x30x20mm) will be placed in dorsal anterior cingulate cortex (ACC).

Preprocessing and Analysis: Preprocessing of all fMRI data will follow similar workflows executed in the LONI pipeline environment, where standard and state-of-the-art image analysis programs interact seamlessly in a parallelized supercomputing environment. Specifically, preprocessing steps incorporating FSL (www.fmrib.ox.ac.uk/fsl) and custom processing modules, will include: a) removal of non-brain tissue; b) rigid-body head motion correction; c) spatial smoothing (5-6 mm FWHM); d) denoising and high pass filtering using FSL's MELODIC; and d) co-registration of the BOLD and T1 images using the matched bandwidth EPI images for intermediate registration. First-level analysis will include the modeling of activation between task conditions (e.g. match emotion vs. shapes; or0-back vs. 2-back). Temporal derivatives and the 6 motion parameters will be included as covariates of no interest to improve statistical sensitivity. Second-level (fixed effects) and third-level (mixed effects) analyses will average runs within subjects and across groups respectively for subsequent comparisons between the SE-WE and TCC-WE treatment groups. Longitudinal analysis: In addition to subtracting changes in activation between baseline and follow-up scans within individuals for subsequent group comparisons, we will represent fMRI maps as statistical change maps in time, with each voxel representing a smooth change in magnitude (positive or negative) from the baseline dataset. These maps will be presented against the structural template, to determine the effects of structural change, functional change, and their interaction. One sample t-tests will determine if activation for each individual changes significantly over time. Task-related connectivity analysis: To investigate effective "functional" connectivity, we will perform a psychophysiological interaction (PPI) analysis,152 which determines differences in task-dependent functional connectivity between regions-of-interest (ROIs). We will investigate the effect of the emotion-labeling task relative to the shape control, using voxels in the amygdala as "seeds" and voxels in the PFC as the "target." Group-level FSL FEAT analyses will produce statistical maps indicating voxels throughout the brain showing significantly correlated task-dependent activity with the ROI. Regressors include the physiological variable (e.g., amygdala activity), the psychological variable (emotion vs. shape), and their interaction. Higher-level analyses will determine the degree of functional coupling among treatment groups.
Resting state analysis: After applying preprocessing steps similar to those described above, widely documented independent components analysis (ICA),73,153 using FSL's MELODIC, will estimate the optimal number of components for each subject and will remove components representing artifacts. After low pass filtering (0.1-0.01 Hz) and transformation into atlas space, the best-fit DMN component for a subject will be selected for higher-level group analysis. We will explore components of other networks. We will also examine voxel correlation within particular networks in follow-up analyses of ROIs71,73,154 Changes in functional connectivity will be quantified by comparing Fisher z-transformed correlation coefficients between ROIs.

Structural Imaging. Structural image analysis will incorporate methods refined and validated by project co-investigators and include: 1) volumetric analysis using automated and manual segmentation, 2) refined shape/surface structure analyses and 3) tensor based morphometry (TBM) analysis using Jacobian determinates to quantitatively map voxel-level morphometric change throughout the brain. In brief, widely used freesurfer http://surfer.nmr.mgh.harvard.edu/) processing streams that include a) correction for magnetic field inhomogeneities; b) removal of non-brain tissue; c) tissue segmentation; d) separation of the hemispheres and subcortical structures; e) extraction of the white/gray and pial cortical surface and f) initial segmentation of cortical and subcortical ROIs (with manual correction of errors) will be used to estimate regional tissue volumes for comparison across treatment groups and time. These analyses will be followed by more refined morphometric analysis to reveal local changes in the shape/surface structure of the amydgala and other ROIs as informed by the volumetric and TBM results (see below). Procedures include manual segmentation and the use of surface-based mesh modeling and skeletonization methods that have been used to assess extremely local changes in the morphology of the amydgala, striatum and hippocampus in several clinical groups including LLD and across time in our prior studies. Finally, we will employ TBM methods that are shown as highly sensitive for detecting subtle changes in brain morphometry associated with maturation/aging or disease,149,157-162 to examine both global and local changes in brain tissue structure across treatments and time. In brief, TBM matches structures with similar intensity patterns, after which the gradients of the non-linear deformation fields required to inversely warp baseline to follow-up scans within subjects, and individual images to an anatomical minimal deformation target (MDT) across subjects are used to determine longitudinal effects and cross-sectional group effects respectively at the voxel-level.Using general linear models (GLMs), discrete local volumetric changes in brain tissue structure may thus be determined across groups, in association with clinical and cognitive measures, where rate of change in local tissue structure (% change at follow-ups) may be quantified.
For example, application of TBM in preliminary data to the T1 images acquired from 8 subjects with major depression scanned at baseline and after receiving six ECT treatments showed significant treatment effects in the right anterior

temporal lobe, ACC white matter and the nucleus accumbens. These structural changes demonstrate treatment-associated plasticity and confirm detection of treatment change over a relatively short period of time, (2-3 weeks) ($r=.62$; $p<0.01$).
Fig.7. ECT-related brain changes, FDR-corrected p-values are overlaid on the group-derived MDT in color.
WM Hyperintensities (WMH). The 3D T2-space images will be used to visualize WMHs by employing a semi-automated WMH identifier.165 Briefly, WMH burden will be assessed based on the signal intensities of co-registered 3D MEMPR and T2-SPACE images, and population statistics on the spatial distribution and neighborhood structure of WM lesions. With every unit increase in WM burden, we will estimate % reduction in local brain tissue volume. GLM and multiple regression analyses will determine links between WM burden, clinical measures and vascular risk factors in each treatment group that may need to be controlled for.

Integration with Mood and Neurocognitive Measures. To test hypotheses about the relationships between imaging metrics and change in mood and cognition, we will derive domain summary scores for the 3 domains of interest, mood, memory, and executive function. Percent change in the mean Z scores will be calculated for each domain score and entered into analysis. We will first test the specific hypotheses described in the aims using separate GLMs for each MRI method. Integration of Predictive Variables. After analysis is complete on the predictive validity of each MRI measure, those that significantly predict remission/relapse or cognitive decline at follow-up will be combined for regression analysis. We will use the best single predictor in each modality. The final analysis will include a step-wise multiple regression analysis of clinical outcomes.

5) Positron Emission Tomography (PET) Scan. Subjects will have one PET scan performed for this study in the beginning of the treatment course. The PET examination will require approximately 2 hours for completion, during which time they will be asked to lie quietly on a comfortable bed in a relaxed position while pictures are made of the radioactivity of their brain by a special radioisotope scanner. We have inserted at the end of the informed consent form a checkbox to indicate if the subject is agreeing to participate in the PET scan procedure. We will be injecting intravenously an experimental radioactive substance, [18F]FDDNP. In order to accurately determine the amount of [18F]FDDNP in different areas of the brain, the level of tracer in the blood must be determined. A needle will be placed in a vein of the subjects' arm/hand in order to draw venous blood samples after resting their hand/arm in a warm water bath. There may be some slight discomfort when the needle is inserted into the arm vein. However, this is no more than the discomfort encountered when blood samples are taken during a periodic medical examination or when blood is donated at a blood bank. The total amount of blood removed will be 11 teaspoons (55 ml) of venous blood.

6)Genetic testing.
Participation in the genetic portion of the study is voluntary. If subjects are deemed ineligible, they will not undergo genetic testing.

5-HTTLPR: Genomic DNA will be extracted from whole blood and isolated using a Wizard Genomics DNA Purification Kit (Promega Corporation, Madison, WI, USA), and determined with 0.7 % agarose gel (Beutler et al., 1990) according to the standard protocol.

Telomerase and NFkappa B collection: Standard Operating Procedures (SOP): The procedures that will be taken to protect the confidentiality of the subjects who donate samples. Telomerase and NFkB samples will be obtained once at baseline and once at week 12 to evaluate telomerase activity in response to the antidepressant intervention. Telomerase and NFkB samples will be collected concurrently with the other investigational labs, so no additional needlestick is necessary for this test. Subjects will not be asked to fast before the draw and will not receive any additional monetary compensation for this portion of the research. 10ml of blood will be drawn into one green Heparin tube yielding 50 - 150 micrograms of the specimen. After collection, telomerase samples will be labeled with the study code, date and time of collection, and an identification number assigned to each subject by the PI or the study coordinator. This identification number will be the only link between the samples and the subjects and will only be accessible to the PI and to certified members of the research team. This information will be stored in an electronic log that is password protected. No other personal identifiers will be listed on the specimen. The collection will be performed at the UCLA Clinical and Translational Research Center (CTRC).

The de-identified samples will be prepared and stored at the UCLA Clinical and Translational Research Center in a locked refrigerated container that can only be accessed by certified laboratory staff. At the completion of data collection, telomerase and NFkB samples will be stored at the Clinical and Translational Research Center. Telomerase activity will be assayed under the guidelines of the Telomerase Repeat Amplification Protocol (TRAP) using a commercial kit (TRAPeze, Telomerase Detection Kit, Upstate/CHEMICON, Temecula, CA). Following analysis, all samples will be destroyed. They will not be retained for future analysis by the PI or any other investigative team. Individual results of telomerase activity will not be released to the study participants due to the investigational nature of the analysis.

The de-identified samples for the analyses of telomerase and NFKabba B will be stored in the Clinical and Translational Research Center under the supervision of Dr. Michael Irwin. Although the plasma samples will be coded and no subject identifiers will be attached to the samples, the codes will be maintained by the PI or the study coordinator in the records (in locked file cabinets and in password-protected computers) along with the date of collection on the tube containing genetic and plasma material and in the specimen log book. This will protect the identity of the donor from anyone who has access to the storage, but is not working on the study. The samples will be coded but not anonymous. Therefore the policy will read: “The procedures by which samples will be stored including the information that will be attached to samples: The donor’s identity will be protected (process of coding and de-identifying samples) including the location where the information that links a sample to the identity of the donor is kept and who has access to this information.”

Policy: Samples will be coded to protect the identity of the Donor from anyone who is not a part of the research team. The link will be maintained between subject identifiers and stored samples in the PI's records. Samples will be stored in a manner that optimizes the viability of the specimen and the utility of the cells for research. All equipment used in preparation or storage of human specimens shall be subject to routine maintenance to ensure optimal preservation of specimens.
Process: On receipt of a sample, the PI or study coordinator will assign a code to the sample and record the code and the date of collection on the tube containing genetic material and in the specimen log book. This will be the only link between the samples and the subjects and will be only accessible to the PI and members of the research team. The sample will then be processed in accordance with the research needs of the project.

DNA samples and genotyping. Genotyping will be performed by the Core Laboratories of UCLA Department of Human Genetics (Director - Dr. Nelson B. Freimer). DNA samples will be collected from all participants who provide informed consent. The Oragene DNA Self-Collection kit (DNAgenotek) will be used to collect and extract DNA from saliva. A sample of 2ml of saliva will be collected. It will be processed from the UCLA Department of Human Genetics (Director - Dr. Nelson B. Freimer). An additional sample of 20 ml of whole blood will be collected in citrate-treated vacuum tubes, and lymphocytes will be extracted and cryopreserved using standard methods. DNA and RNA will be extracted from isolated lymphocytes using GenePure chemistry (Qiagen) and preserved by standard methods and stored at the UCLA Department of Human Genetics for future analyses.

Phenotypes. All phenotypes will be related to clinical outcomes (e.g. responder/non-responder, remitter/nonremitter), and cognitive outcomes (improvement/no improvement).

Candidate gene selection. We have changed the genomic hypothesis to reflect its exploratory nature to test multiple candidate genes related to the memory and mood regulation pathways that are likely to be involved in the regulation of treatment response.

"Hello, my name is _____ and I'm a researcher from the UCLA Department of Psychiatry. I would like to talk to you about donating your blood to be used in the research. This study looks at the drug levels and treatment response and genetic markers of drug response. If you agree to participate, you will receive a complete medical and psychiatric evaluation to determine if you are suitable for the study. The rest of the protocol will follow schedule described in our 'Intervention study for geriatric depression.' This form is called the Informed Consent Form. It contains all the details about our research program. Let's go through it together; I'll give you a copy of the form when we're finished. It contains phone numbers for you to call if you have any more questions."
Transporting the samples to the laboratory.

Policy: Shipping of samples shall be performed in a manner that protects any person handling the material from exposure to the tissue and which preserves the sterility and viability of the samples.
Process: Once collected the samples will be stored in the GCRC laboratory freezer at –20C. The GCRC will have a research associate transport the de-indentified DNA samples to the UCLA Department of Human Genetics, Tissue Core where they will be stored at –80C.

Procedure: Place de-identified samples in cooler with ice and seal the lid. Transport directly to the UCLA Department of Human Genetics, Tissue Core and place into the designated refrigerator. The procedures that will be used to document the IRB status of future studies for which samples are used. The names of the investigators who may access the samples for future use. A description of how the bank will be maintained if you or any of the investigators leave UCLA.

We are not planning to use the DNA samples for future studies, which will be the extension of the proposed protocol addressing new genetic markers of treatment response, as new information becomes available. The PI will be working in this research area, at least, for the next several years. We will continue to renew our protocol with the UCLA IRB as long as we are investigating genetic markers of treatment response to assure the current approved status. No other investigators will be permitted access to the genetic information. Consequently, all samples will be destroyed with the completion of the projects. If the PI leaves UCLA for another academic institution and has on-going studies of the similar nature transferred to another academic institution, we will make arrangements transferring the DNA samples to that institution. If such arrangement cannot be made, all samples will be destroyed. The samples will not be shared with any investigators who are not a part of the research team.

7) Follow up assessment: The follow up will take place weekly for the first 4 weeks of treatment and every 2 weeks for the remaining 5 months of the 6 months trial, followed by naturalistic follow up monthly up to 12 months. Each follow up assessment will include measures of efficacy and safety. The need for repeated assessments stems from our hypothesis of difference in time-to-remission occurring during the extension treatment. The weekly frequency of contact with all subjects will serve as an additional safeguard to monitor worsening of depression, as well as the emergence of side-effects or suicidal ideations. All assessment procedures described below are identical for the two groups. Most of the instruments have been administered in our ongoing studies, and our subjects age 60 and older tolerate their administration quite well (Table 2).

Primary outcomes will be measured and defined as follows: 1) Remission will be defined as HAM-D scores of 6 or less for 3 consecutive weeks, week 12 and at 6 months visit; 2) Depressive relapse is defined as an episode of major depressive disorder that occurs within 6 months after remission, while 3) recurrence is defined as another depressive episode that

occurs after 6 months have elapsed.

Assessment and monitoring of suicidal risk will occur at each visit and by phone between visits. We have applied the standard procedures that are required and approved by the UCLA Institutional Review Board. We have employed the same procedures in our ongoing studies of late-life depression since 1995, and have had no suicide attempts among our subjects. We will monitor suicidal ideations using the 3rd item of the Hamilton Depression Scale during each visit to the site and the Beck Scale of Suicidal Ideations (SSI). Monitoring for SI will be done at each visit independent of the outcome assessment.

Monitoring of expectations for symptomatic improvement: Since subjects will enter the treatment process for symptomatic improvement, we will account for a differences in expectations between the two groups. Thus, subjects' expectations for improvement will be assessed during the baseline visit, at week 12, at the end of the acute treatment trial (Week 24), and during follow up. We will control for any differences in the analyses.

At the end of week 4, patients with a CGI improvement rating of 3 or greater will be titrated upward on the escitalopram dose and instructed to take two tablets, or 20 mg /day. Patients with a CGI improvement rating of 1 or 2 will continue taking the same dose they have been taking at the end of week 3. If patients experience any side-effects attributed to their study medication use, the allowed dose adjustment for MEM will be decreasing MEM by 1– 3 pills, to a minimum of 5 mg (or 1 cap a day), and decreasing escitalopram dose to 10 mg, so that the allowed dose range of escitalopram will be 10-20 mg/day. Re-challenge with a higher dose of MEM up to 20 mg/ day, or escitalopram of up to 20 mg/day may take place at the following visit in case of an incomplete response. All dose adjustments will be documented and considered in the analyses. The expected effective dose range of MEM will be 20 mg daily, which has been successfully used and well-tolerated in our pilot study. At the end of 24 weeks, memantine and placebo will be tapered off gradually in the same decrement of 5 mg (or 1 pill) per week over the course of 2-4 weeks to reduce the risk of withdrawal symptoms. At 6 months, subjects who decide to discontinue escitalopram will be tapered off gradually over the course of 2-4 weeks with 5mg dose decrements/ week in cooperation with their psychiatrist.

Concomitant medication: No additional psychotropic medications will be allowed in the trial. At the end of the trial, the PI in consultation with the patient's physician will decide whether to continue or switch the prescribed medications based on treatment response and tolerability. The PI will offer monitoring for any emerging symptoms for an additional month after study completion.

8) Remission and naturalistic 6 month follow up: Subjects who achieve remission (HAMD<6) will be offered up to additional six months of continuation treatment with escitalopram to determine stability of remission, while memantine and placebo will tapered off. The goal of continuation treatment is to ensure stability of remission, and to optimize coping, cognition, physical functioning, and life satisfaction. Although subjects achieved remission, we will continue monitoring their safety every month during in-person visits monthly up to 12 months. The frequency of these visits is consistent with the clinical practice, where stable subjects are generally seen every 1-6 months. They will be also encouraged to contact the investigators if they experience worsening of depression or suicidal ideations. Subjects who do not remit during the acute treatment phase or relapse during the continuation phase will be offered treatment outside the protocol in the Geriatric Mood Disorders Clinic or other community clinics. They will be invited to come for the 6 and 12 month follow up to assess their progress and the patterns of response to treatment while tracking and controlling any changes in treatment.

Safety evaluations. Vital signs and body weight will be obtained at each visit, in addition to a 12-lead ECG at baseline, and if any cardiac complaints are present. The UKU Side Effect Rating Scale, a comprehensive rating scale for monitoring adverse events of psychotropic drugs will be collected at all visits. Laboratory assessment. A comprehensive baseline laboratory study is required to arrive at accurate differential diagnoses in "organic" and potentially treatable causes of depression or cognitive impairment. All laboratory tests and ECG assessments will be done at the UCLA CTSA center. Treatment compliance will be assessed by employing indirect measures of adherence, i.e., direct questioning of the patients and their available relatives, and returned pill count.

Decoding procedures. In case of emergency or adverse event, the blind will be broken for clinical management of the patient after the decision has been made to discontinue the patient from the study and final ratings have been obtained. The pharmacist will provide a patient randomization number and corresponding treatment assignment to the PI.

In the end of the trial after unblinding procedures, the PI, in consultation with the patient's primary physician, will decide whether to continue the prescribed medications or switch to another antidepressant based on treatment response and tolerability. If a decision is made to discontinue both medications, they will be stopped and further observation for any withdrawal symptoms will be provided either by the patient's primary physician or the PI for two weeks following the discontinuation.

4.1 * **Will you be providing results of any experimental tests that are performed for the study?**

- ◯ Yes - Complete Items 4.1.1 and 4.1.2
- ◉ **No**
- ◯ Not Applicable

4.1.1 **You indicated in Item 4.1 that the research involves experimental tests. Please describe the tests, provide a rationale for providing participants with the experimental test results and explain what, how and by whom participants and their health care provider will be told about the meaning, reliability, and applicability of the test results for health care decisions.**

4.1.2 **Will tests be performed by a Clinical Laboratory Improvement Amendments (CLIA) approved lab?**

◯ Yes ◯ No

5.0 ***Indicate how much time will be required of the subjects, per visit or contact, and in total for the study.**

This study will require that the subjects complete up to 20 (twenty) visits in 12 (twelve) months to the study site during their participation. The time required for each visit are as follows:
1) Screening Procedures and Initial Visit (Screening / Visit 1): The initial visit will last approximately 2 ½ to 3 hours.
2)Baseline Diagnostic / Neuropsychological Evaluation Visit (Visit 2) will last approximately 2 hours.
3) Magnetic Resonance Imaging (MRI) Scans (2) : Subjects will be asked to lie still for about 60 minutes while the scan is taking place at baseline and at 12 weeks.
4) Positron Emission Tomography (PET) Scan: This examination will require approximately 2 hours for completion.
5) Follow-Up Visits (Visits 7-13, 15-20): Follow-up visits will occur weekly for the 4 weeks (6 visits), bi-weekly (every 2 weeks) for visits 7-14 (up to 6 month visits), and every month until the end of the study. Each visit will last approximately 30 minutes.
6) Final visit (Visit 14):The last visit will be approximately 2 hours.

6.0 ***Statistics and Data Analysis: Describe the proposed statistical procedures or descriptive analyses for the study. If applicable, indicate how the sample size was determined.**

Data Analysis. Primary analyses will be carried out on an intent-to-treat basis; additional analyses considering dropout or other observable post-randomization outcomes will make use of an instrumental-variable analysis framework. 17 Data will be examined initially to identify issues such as departures from normality, which would suggest the need for transformations (e.g., logarithmic) and influential observations (outliers). Descriptive statistics will be computed and reported overall and by group. Demographic variables and variables characterizing the course of depression (e.g., age of onset, chronicity, number of episodes) will be screened to determine which have relationships with the outcome variables that would suggest their value as covariates. Variables that demonstrate meaningful associations with outcomes controlling for treatment group and are substantially different across groups are candidates for covariates. Demographic variables, baseline depression, and other potential covariates will be compared between the two groups to help determine if the randomization was successful in making the two groups comparable. Specific analysis plan follows below.
Hypothesis 1. The primary outcome, namely responder/remitter status, will be compared between the esCIT+MEM and esCIT+PBO groups using chi-square statistics. Days to remission will be analyzed using the Kaplan-Meier survival method with treatment group as a stratification variable using the day on which response was observed as the event indicator. The survival function estimates the proportions achieving the response criterion, while the overall survival curve reflects speed of response. The independent variable is treatment group with two levels. A log-rank test will be used to assess the significance of any difference between treatment arms, and Cox regression to reflect the role of baseline covariates. We will also report the total time spent below the response threshold, compare summary statistics, and patterns of response within the patient over time. Analysis of change over time will be performed using linear mixed model analysis of covariance (SAS PROC MIXED). The linear mixed model permits flexible specification of the covariance structure of the repeated measures within patient), and allows analysis of incomplete cases using maximum likelihood. The outcome measures will be the HAM-D scores as well as cognitive domain scores (i.e. memory, processing speed, executive function) with the baseline rating/score on each domain as a covariate.
Hypothesis 2a. The role of brain neuroimaging biomarkers in variability of treatment response is examined in this Hypothesis. Predictor variables: We predict that baseline measures of neuroimaging biomarkers (white matter hyperintensity, regional gray or white matter volumes, hippocampal thickness and regional FDDNP binding levels) will be related to treatment outcomes. These predictions will be evaluated in the context of the models described above (i.e., general linear mixed model) by adding the posited prognostic variable as an additional predictor. Moderator variables: A limited number of exploratory analyses will be performed to evaluate possible moderators of each treatment strategy. Statistical evaluation of moderators will be done by including the posited moderator variable as an independent variable and evaluating the moderator x treatment group interaction term. Mediator Variables: We will evaluate the variable as a potential

mediator using a principal stratification framework.17,20
Hypothesis 2b. We will also perform categorical data modeling in a 2 (MCI present/absent) x 2 (treatment group) x 2 (response: remitter/non-remitter) table. Randomized stratification by MCI will ensure balanced ratio of subjects with MCI across treatment groups. We will use the Grizzle, Starmer, Koch (1969) approach to linear modeling as implemented in SAS PROC CATMOD. The hypothesis that there is a MCI effect only in the esCIT+MEM condition is tested by the cognition x drug interaction term. Subsequent linear contrasts will compare cognitive groups within treatment groups. The test of MCI on cognitive domain scores will use an analysis paralleling the analysis of treatment effects noted above (mixed effects model with cognitive domain serving as a repeated measure), but with MCI and treatment defining groups. We anticipate that there will be a main effect of MCI associated with poorer baseline performance, but also a main effect of MCI on change (as indicated by a treatment x MCI) interaction effect. Similar analyses, replacing MCI present/absent by early/late onset, will be performed with age of onset. Significance of the treatment x onset interaction effect will allow us to determine if early or late onset is associated with improved performance.

Power analysis. The power analysis is focused on the primary aim of the study to assess whether the group receiving combined MEM and escitalopram demonstrate remission (HAM-D<6) compared to the other group. In the PI's pilot data, we observed remission in 83.3% of patients receiving the combination esCIT+MEM, compared to 30.7% in those receiving esCIT+PBO. In line with the message of Kraemer, et al. (2006) emphasizing that it is not safe to ignore uncertainty in pilot-study estimates of effect size, which risks underpowering the subsequent study, we derive a sample size appropriate to an effect considerably smaller than the observed difference. Specifically, we work with an assumption that the remission rate in the esCIT+MEM arm would be 70% (smaller than the observed rate of 83.3%) and that the remission rate in the esCIT+PBO arm would be 40% (larger than the observed rate of 30.7%). More involved analyses would be possible that average over a range of scenarios; the approach used here captures the essential feature that it is important to allow for possible regression to group means that are less different than those observed in the pilot study. We will draw on frameworks from the Institute of Medicine report on avoiding missing data,22 but if we recruit a total of 134 patients (67 per group) with a projected 25% dropout rate, we will be able to compare 50 completers in the esCIT+MEM group with 50 subjects in the esCIT+PBO group. Assuming that 70% of the group receiving esCIT+MEM respond versus 40% of the control subjects, the power for this chi-square test, at the 0.05 level of significance with 1 degree of freedom, exceeds 80%. To assess the impact of the proposed sample size on other analyses, we also investigated a repeated-measures analysis of our pilot data with continuous HAM-D scores as an outcome, comparing the treatment groups at 24 weeks, using the baseline measure as a covariate. We found that the effects observed in the pilot data (but reassessing with the proposed sample size) yielded a power over 0.9. In addition, we will compare the groups on the number of days until response using survival analysis. If we combine the groups and assume 40% dropout, the power of the two-sided log rank test at the 0.05 level of significance will be 0.869 with the proposed sample size.
Data management. Data management and analysis support will be provided by the UCLA Semel Institute Statistical Core (SI-Stat) (Dr. Siddarth).The SI-Stat will provide needed software and technical support with a data manager operating under the supervision of Dr. Siddarth. The SI-Stat has a Dell PC computer network with automated CD R/W backup and is set up for medium to large-scale data processing and analysis using available commercial database and statistical software. Upon receipt of the data, each form will be visually scanned for obvious errors and logged in. The data clerk will perform the data entry and generate a daily and monthly report, and a quarterly patient accrual report. Data entry will be facilitated by 1) having visual screen formats similar to the actual forms; 2) having range boundaries on each field, where appropriate, to be checked automatically as data is entered; 3) having default values incorporated into the data entry system to minimize typing. All data including patient information will be carefully handled and securely stored. Patient study forms will be stored in locked file cabinets and will be accessible only to authorized personnel. A shredder will be used to discard all unwanted study documents. A single computer will be dedicated to this study. Access to the system will be password protected with only authorized persons having knowledge of the password.

Warning: Save your work at least every 15 minutes by clicking "Save" or "Continue."

Characteristics of the Study Population

1.0 ***Is this an observational or ethnographic study for which the number of participants observed or interviewed cannot be determined in advance.**

○ Yes ◉ **No**

2.0 **If you answered "no" to item 1.0, indicate the maximum number of study participants you hope to enroll:**

134

3.0 How many participants do you expect you will need to recruit, consent and/or screen to meet the target number above?
400

4.0 *Indicate the specific inclusion criteria for enrollment of each of the groups of research participants in this study. If there are any inclusion criteria based on *gender, pregnancy/childbearing potential, race, ethnicity or language spoken*, explain the nature of and scientific rationale for the inclusions.
Inclusion criteria:1)The presence of a major depressive disorder diagnosed according to the DSM-IVr criteria; 2) A 24-item Hamilton Rating Scale for Depression (HAM-D) score of 20 or higher at baseline; and 3) Mini-Mental State Exam (MMSE) score > 24; 4) Age > 60 years old; 4) Include participants after discontinuing anti-depressants during a washout period. The washout period will be performed at least 14 days before starting the study and between the administration of escitalopram and MAOI and other antidepressants; except fluoxetine (there will be a 4 week washout period).

5.0 *Indicate the specific exclusion criteria for each of the groups of research participants in this study. If there are any exclusion criteria based on *gender, pregnancy/childbearing potential, race, ethnicity or language spoken*, explain the nature of and scientific rationale for the exclusions.
Exclusion criteria: subjects will be excluded if they had any current and/or lifetime history of other Axis I psychiatric disorders (except unipolar MDD; and stable comorbid anxiety disorders and insomnia), or recent unstable medical or neurological disorders; diagnosis of dementia; those with known allergic reactions to escitalopram or memantine. We will also exclude participants from taking all anti-depressant psychotropic medication and MAOIs for at least two weeks prior to entering the study (four weeks for fluoxetine). Escitalopram has low potential for interacting with most other drugs, including beta blockers, neuroleptics, lithium, and alcohol. The serotonergic syndrome has been reported in combined use of reversible MAOI, meclobomide, and linezolid, an antibiotic, which is a reversible non-selective MAOI. The washout period will be performed at least 14 days should be allowed between the administration of escitalopram and MAOI and other antidepressants; except fluoxetine there will be a 4 week washout period. We will not discontinue effective antidepressants. The taper will be instructed by the primary care physician or the psychiatrist.

6.0 *How (chart review, additional tests/exams for study purposes, etc.), when and by whom will eligibility be determined?
Research Procedures: Telephone screening (15 minutes): All potential participants will be initially screened using a standardized telephone screen script will be used that received an approval of the UCLA IRB review committee. Only those who meet initial entry criteria will be invited for the in-person screening evaluation. In-person screening interview (21/2 hrs): An experienced clinical coordinator, with HIPPA certification, CITI IRB training, CareConnect training, and under supervision of the prinicipal investigator will assist in subject recruitment and scheduling. The principal investigator will be responsible for the SCID diagnostic interview, clinical and laboratory assessment. Prior to their enrollment in the study all subjects will sign a consent form approved by the UCLA-IRB and all participating institutions. Dr. Lavretsky will obtain the informed consent, and will perform most examinations at baseline. Eligibility will be assessed at screening and baseline. No subject will be asked to discontinue effective antidepressant medications. Subjects on ineffective antidepressant medications will have to consult with their treating primary care physician or psychiatrist who will determine the need for participation in the trial. In addition, the principal investigator will review the HAM-D scores to determine eligibility if HAM-D scores are less than 10 and subjects will be eligible to participate if they have less than 30% improvement. Only subjects currently not taking psychotropic medications prior to the initiation of the study will be admitted into the study. Subjects will be off all psychotropic medication for at least two weeks prior to entering the study (four weeks in case of fluoxetine, see exclusion criteria). We will apply the Beers (1997) criteria at screening to determine inappropriate medications for older adults that may result in cognitive impairment (e.g. anticholinergic, benzodiazepine, etc) and will control for in the analyses.162

Baseline assessment: Depression evaluation: All subjects will undergo a Structured Clinical Interview for DSM-IV (SCID) for the purposes of establishing a diagnosis of Major Depression (MDD). A history of depressive illness includes the length of the current episode of MDD, age of onset of the illness, prior duration of the illness, and number of episodes. Assessment of depressive symptoms will be based upon administration of the Hamilton Rating Scale for Depression (HAM-D-24-item). Other domains of baseline assessment will address issues thought to be important in understanding risk factors for LLD will be tabulated. High levels of inter-rater reliability will be maintained. For example, inter-rater reliability for the total HAM-D-24 score or the SCID diagnosis of depression has been excellent, as demonstrated by ICCs of 0.78 to 0.95.
The age at depression onset will be determined using subjects' report, and medical records. We will stratify both groups by the age at onset with cut off at age 60 to examine the role of late vs. early onset in treatment response.

Comorbid anxiety and insomnia. Comorbid anxiety disorders and insomnia can be present and assessed at baseline and follow up.
Medical evaluation. All subjects will receive an initial medical assessment including a complete physical examination with neurological and neuropsychiatric examinations, electrocardiogram (ECG), and laboratory testing at baseline. These tests are used to rule out new-onset medical illnesses that could account for behavioral and cognitive symptoms. All abnormal physical or laboratory findings will be reported to subjects' primary physicians with the subject's consent. If abnormal physical or laboratory results are considered responsible for depression, the subject will be excluded from participation.

Screening for dementia and MCI. Those subjects meeting the DSM-IVr criteria for dementia will be excluded. We will screen subjects for possible incipient dementia, and then verify their condition by comparing baseline assessments to the one at 6 and 12 months. This will include reviewing an extensive history and mental status exam together with corroborating

information from a knowledgeable family member and assessment of functional skills. Cases that are clinically ambiguous will be discussed at the consensus meetings among all raters. A Mini-Mental State Examination score of < 24 or an established dementia diagnosis will serve as an automatic exclusion criterion. The evaluation for dementia includes: 1) An interview by a psychiatric nurse to identify physical and cognitive limitations; 2) a standard battery of hematologic studies, blood chemistries, liver and thyroid function tests, B12 and folate levels, and RPR test; 3) neurological examination (UPDRS); 6) neuropsychological examination (detailed below); and 7) psychiatric evaluation (SCID-DSM-IV), as detailed above. Adjudication of dementia is based on DSM-IV criteria, as recommended by Knopman et al (2001) and Lyketsos et al. (2002) 82,163. At the consensus conference, additional information will be reviewed (e.g., family history, drug use). If there are clinical features suggestive of dementia, the patients will be referred to the UCLA Memory Program (Dir. Gary Small), the UCLA ADRC, or other qualified community providers for management. This approach is consistent with clinical realities and with one used by other research groups.

Diagnosis of MCI. We will conduct consensus meetings to assign patients to diagnostic groups, according to MCI criteria that we have used in prior studies and clinical judgment. 74,75 MCI criteria are: 1) The patient is neither cognitively normal nor demented; 2) a decline in cognition as reported by the subject or a collateral; 3) cognitive testing shows impairment and corroborates subjective report of decline; and 4) functional activities are not significantly impaired. Subjects will be classified as amnestic type MCI (a-MCI) if they show mild impairment in memory with or without other domains impaired. We will use performances between -1.5 and -2 (SD) below age and education norms on one of two screening memory tests; WMS-IV Logical Memory and WMS-IV Visual Reproduction 164 to denote mild impairment 45,75,165. We chose a -1.5 SD index, as this is most widely used 74 and will be most relevant for comparisons with other studies in the literature. We will stratify the groups by the presence of amnestic MCI (either single or multiple domains).
Age at onset of depression: we will explore the role of age at onset in heterogeneity of MCI and treatment response by stratifying groups by onset before or after age 60, as commonly defined.1

Randomizaton and stratification procedures: After all screening and baseline test results are reviewed and eligibility criteria are confirmed, medications will be dispensed if patients continue to meet eligibility criteria and have signed the informed consent form. All eligible subjects will be randomized to the EsCIT+MEM or EsCIT+PBO control group using a computer-generated random assignment scheme, which assigned subjects in a 1:1 ratio to each group. The groups will be stratified by the a-MCI status, and by late/early onset.

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Characteristics of Study Population

1.0 ***Indicate the age range of the study participants.**

Check all that apply:

- ☐ 0 to 6 years
- ☐ 7 to 11 years
- ☐ 12 to 17 years
- ☐ 17 or younger **in California** who can consent for themselves - see note below
- ☐ 17 or younger **outside California** who can consent for themselves - see note below
- ☑ **18 years or older**

NOTE:

- For additional information on minors **in California** who are permitted to consent for themselves please refer to the section "Legal Exceptions Permitting Certain Minors to Consent" in the OHRPP Guidance document, Child Assent and Permission by Parents or Guardians
- For additional information on minors **outside of California** who are permitted to consent for themselves please refer to the section "Exceptions Outside of California" in the OHRPP Guidance document, Child Assent and Permission by Parents or Guardians

2.0 ***Indicate if any of the following populations/specimens will be specifically recruited/obtained for the study.**

- ☑ **Adults who are competent to give informed consent**
- ☐ Adults unable to give informed consent
- ☐ Adults with diminished capacity to consent
- ☐ Fetal Tissue

Neonates

- [ ]
- [ ] Participants Unable to Read, Speak, or understand English
- [ ] Pregnant Women/Fetuses
- [ ] Prisoners
- [ ] UCLA Faculty/Staff
- [ ] UCLA Students
- [ ] Wards
- [ ] **Unknown/Not Applicable**

3.0 * **Is it possible that there may be non-English speakers enrolled in this study or children whose parents are non-English speaking?**

○ Yes ◉ **No**

ID: IRB#12-001714 View: NEW 14.1 - Risks & Benefits

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Risks & Benefits

Benefits

1.0 ***Are there any potential direct benefits (physical, psychological, social or other) to study participants?**

◉ **Yes** ○ No

1.1 **If yes, describe.**
The possible benefits the study participants may experience from being in this study may include an evaluation and some alleviation of symptoms, general health discussions with the study doctor and help in referrals for additional treatment if needed. The participant may possibly experience some relief of the symptoms of depression.

2.0 ***Describe the potential benefits to society including the importance of the knowledge to be gained.**

Potential Benefits: There are potential benefits for both the subjects and broader segments of society. For individuals, the complete diagnostic assessment may identify underlying medical disorders so that appropriate referrals for treatment can be made. Both volunteers and patients often express great satisfaction from knowing they have been able to make a personal contribution to the advancement of human understanding and to the search for solutions to health problems -- either their own or others'. For society, the increased understanding gained through this study may provide further information about AD, and may benefit many elderly persons.

Risks

3.0 ***Indicate the potential risks/discomforts, if any, associated with each intervention or research procedure.**

Additionally discuss any measures that will be taken to minimize risks. If data are available, estimate (a) the probability that a given harm may occur, (b) its severity, and (c) its potential reversibility. The information provided should be reflected in risks section of the informed consent documents.

If this is an exempt study and there are no risks, indicate N/A. Otherwise, please see the help text.

Potential problems and solutions.

Adverse events. Adverse events produced by either memantine or escitalopram, or a combination may occur. A number of potential side effects are described below. All adverse events will be carefully monitored during each visit by using the UKU Side Effect Rating Scale. If any serious medical complication occurs, the patient will be referred to their primary care physician. Although minimal complications have been reported in patients with cardiovascular disease, careful monitoring will take place during patient visits. If consistent elevation of a patient's blood pressure or arrhythmia occurs, it will be reported to the patient's primary physician. An adjustment of the dose of their standing medications may be attempted once seen by their primary care physician. If no improvement occurs or if a prescription of a new medication is required, the study medications will be discontinued.

Potential Risk and Discomforts:
Blood Draw for Routine Analysis. The risks include problems associated with blood drawing. This is a routine procedure performed under standard and sterile medical conditions. The potential side effects of removing blood may include: momentary discomfort during the puncture, lightheadedness, faintness, soreness and discoloration of the area for several days. In very rare instances, either bleeding or infection can develop at the venipuncture site. There is no more discomfort encountered than when blood samples are taken during periodic medical examinations, or when blood is donated at a blood bank.

Neuropsychological Evaluation. Subjects may experience boredom or fatigue while completing the neuropsychological evaluation. In rare instances, subjects may experience some anxiety or emotional discomfort. If subjects do have the above reaction to the evaluation, it should go away at the completion of the test.

Venous Blood Sample for PET scan. Venous blood samples may be obtained. This blood is sampled to compare the time and rate of radioactive sugar arriving in the brain. A needle may be placed in the vein of a hand warmed in a water bath for the removal of several blood samples. There may be some slight discomfort when the needle is inserted into the arm vein. However, this is no more than the discomfort encountered when blood samples are taken during a periodic medical examination or when blood is donated at a blood bank. The potential side effects of removing blood may include: momentary discomfort during the puncture, lightheadedness, fainting, soreness and discoloration for several days. In very rare circumstances, either bleeding or infection can develop at the venipuncture site. However, since the procedure is conducted under sterile and standard medical practices, this is unlikely. The total amount of blood removed will be about 11 teaspoons (55ml).

Radiation Exposure. The Positron Emission Tomography (PET) scan will expose the subject to a small amount of radiation. We are exposed to radiation every day of our lives from both natural (sun, earth, etc.) and man-made sources. The average radiation dose from these sources for residents of the United States (U.S.) is about 300 mrem per year. Individuals who use radiation in their work (for example x-ray technicians, radiologists, etc.) may legally receive up to 5000 mrem of radiation dose per year. By comparison, the amount of radiation dose that the subject will receive in this entire study is about 26% of the annual limit for these radiation workers. The added radiation dose that will be received from this study is well below the levels that are thought to result in a significant risk of harmful effect.

Estimated Radiation Dose for One Helical CT Scan of the Head: If the CT scan is performed, the total estimated radiation dose to the whole body would be 220 millirem, or 4% of the 5,000 millirem annual whole body limit allowed adult radiation workers.

If the subject should participate again in the following 12 months in a research study involving radiation at UCLA, the investigator/or associates will ensure through accurate record keeping, that the total amount of radioactivity administered for research purposes will remain small and again is not expected to cause any adverse effects.
If the subject participates in a research project outside UCLA within a year, the subject will tell the researchers about the study at UCLA. If the subject has participated in research at a different institution over the past year, the subject should tell the researcher at UCLA so that he/she can check on the subject’s previous absorbed dose of radiation.

Risk Classification. The overall risk classification is considered to be more than minimal. The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Potential risks and discomforts will be minimized by:
•Appropriate monitoring of subjects during all phases of the research project.
•Withdrawal of the subject from the research protocol upon evidence of a specific adverse event or clinical sign(s).
All appropriate steps will be taken to protect subjects from harm.

Risks in taking Escitalopram. (See attached Risk chart for study drugs in section 24.0 item 1.0).
Side effects of escitalopram are generally mild and tend to diminish after a few weeks of treatment. The most common side effects are nausea, headache, tremor, dry mouth, and ejaculation failure. Patients should be cautioned about operating machinery, including automobiles. Since there is a possibility that the study drug may cause drowsiness, patients will be advised not to drive or engage in other activities requiring mental alertness until their tolerance to the drug has been determined. Safety in overdose. The suicide rate is higher in the elderly than in any other age group and highest of all in white men 85 years or older. Therefore, low toxicity of antidepressant medications is an important feature. Both citalopram and escitalopram have produced low toxicity in animal experiments. In the few known cases of overdose on citalopram, the

maximum amount taken was 2000 mg with full recovery. Interactions with other drugs: Drug-drug interactions are an important consideration in prescribing antidepressants for the elderly who often take multiple drugs metabolized through the liver and may have reduced hepatic metabolism. Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies with case-control and cohort design that have demonstrated an association between gastrointestinal bleeding and SSRIs. Interaction at the level of liver enzymes becomes likely. In general, escitalopram appears to be less likely to cause important drug interactions than the other SSRIs. Escitalopram is unlikely to interact with lithium, carbamazepine, benzodiazepines, warfarin, or erythromycin. Escitalopram has low potential for interacting with most other drugs, including beta blockers, neuroleptics, lithium, and alcohol. The serotonergic syndrome has been reported in combined use of reversible MAOI, meclobomide, and linezolid, an antibiotic, which is a reversible non-selective MAOI. At least 14 days should be allowed between the administration of escitalopram and MAOI. Central serotonin syndrome could be lethal. Other potential adverse effects include discontinuation syndrome after abrupt discontinuation of escitalopram with symptoms of irritability, agitation, dizziness, sensory disturbances, and paresthesias that are usually self-limiting. Abnormal bleeding, hyponatremia, activation of mania, hypomania, or seizures might occur. Increased agitation and irritability may occur. All adverse events will be carefully monitored during each visit using the UKU Side Effect Rating Scale. If any serious medical complication occurs, the patient will be referred to their primary care physician.

Emergence of anxiety is a reported adverse effect of escitalopram use. This side effect occurred in two of our subjects, and required lowering the drug dose. If this occurs, dose and schedule adjustment of study medication, escitalopram, will be attempted and project staff will contact such subjects twice a week to evaluate their symptoms and monitor for emergent suicidal ideations. Relaxation tapes will be offered for use at night by subjects with insomnia. Sleep hygiene will be encouraged as well, with recommended walks in the evening and warm baths before bedtime. Subjects' relatives will be encouraged to be involved in the study to ensure subjects' safety and compliance.

Risks associated with memantine. The following Adverse Drug Reactions have been accumulated in clinical studies with memantine since its introduction in the market. Body as a whole – general disorders: Common-Headache; Uncommon-Fatigue; Psychiatric disorders: Common- Somnolence; Uncommon- Confusion, Hallucinations; Not known-Psychotic reactions; Gastro-intestinal system disorders: Common-Constipation; Uncommon-Vomiting; Not known Pancreatitis; Central & Peripheral nervous system: Common-Dizziness disorders; Uncommon- Gait abnormal; Very rare-Seizures. Overdose. There have been very few cases of overdose. In the case of an overdose (a suicide attempt), for which the highest memantine dose has been reported, the patient survived an oral intake of up to 400 mg memantine with effects on the central nervous system (that is, restlessness, psychosis, visual hallucinations, proconvulsiveness, somnolence, stupor, and unconsciousness) that resolved without permanent sequelae. Treatment of overdosage should be symptomatic.

Risks associated with combination of memantine and escitalopram. Combination of memantine with escitalopram is commonly used in clinical practice with rare side effects including increased anxiety and sleep disturbances. Dose modification is typically sufficient to lower the rate of side-effects.

Discontinuation from the study will be considered if subjects experience. We will monitor blood pressure and pulse once a week in the first four weeks, and at every visit. If any changes on the baseline ECG signifying ischemia occur, we will obtain additional tests of cardiac enzymes to rule out myocardial infarction (MI) (e.g., CK-MB; troponin). Dr. Hu is a part of the consulting and the DSMB teams and has advised us on the following parameters for discontinuation from the trial if cardiovascular complications arise. These include:
a. Any changes in subject's physical complaints of a potentially vascular nature (e.g., angina or chest pain, fainting, dizziness, arrhythmia); increase in pulse over 10 beats per minute from baseline or tachycardia over 120 beats per min, changes in BP over 20 mm Hg;
b. Changes on ECG or in cardiac enzymes indicating cardiac ischemia or a new onset arrhythmia;
c. The development of any severe side-effects on the UKU Side Effect Rating scale rated as 3 or greater.

All severe adverse events will be reported to the subjects and to their primary physicians and the UCLA IRB/ DSMB committee within 1 week of the PI's awareness, and within 2 weeks to the NIH.
d. If a patient demonstrates worsening of their symptoms or no response by week 8 (i.e., less than 30% improvement in HAM-D scores or CGI score of > 4) of treatment, they will be discontinued from the study and referred for appropriate clinical services.
e. The allowed dose range for MEM will be 5-20 mg/day; escitalopram 10-20 mg/day. If patients are not able to tolerate these medications, they will be discontinued from the trial.
f. Suicidal ideations with the HAM-D item 3 score of 3 and greater, or worsening of the sore on the Beck Suicidal Ideation scale.

All dropouts will be analyzed by the reason for termination and classified as: 1. Reasons: a) Lack of efficacy; b) Side-effects; c) Lost-to-follow up; d) Hospitalization; e) Death; f) Other
2. Relation to the study drug use: a) likely; b) probable; c) unlikely.

Structural and Functional Magnetic Resonance Imaging (s- and f-MRI) Scan. The risks or discomforts associated with MRI scans may include anxiety from being in a tight, enclosed space, or discomfort from staying still for too long. Should you become anxious or agitated during the MRI scan, this research study will be immediately discontinued. The sound of the MRI scanner can be loud. We will provide earplugs to minimize the noise, but some people find the noise annoying. The tests themselves can be boring or difficult, and you may get fatigued during the scan or from the diagnostic tests.

Occasionally subjects report having a headache, feeling stiff, or feeling anxious from claustrophobia after the scan.

The magnetism of the machine attracts certain metals; therefore, people with metals in them (specifically, pacemakers, infusion pumps, aneurysm clips, metal prostheses, joints, rods, or plates) will be excluded from the study. The "metal" in dental fillings is less susceptible to magnetism and is therefore allowed. The participant will be asked about any potential sources of metal, and you pockets will be emptied prior to the study. The participant may wish to stop the study at any stage, including the testing stage. Testing will last less than 15 minutes.
The procedure may involve risks that are currently unforeseeable. The participant will be informed of any changes to our understanding of the risks of this study. The MRI scanner used for this research is an experimental device evaluated by the FDA to be an “insignificant risk device.”

The participant will be asked to have an MRI scan of their brain. The procedure involves making brain images with magnetic fields and does not involve radiation, blood samples or injections. A total of two MRI scans will be conducted: one MRI scan will be obtained in the beginning of the study and another scan will be obtained at the end of the study at 12 weeks.

Genetic Analysis.
The purpose of this optional study is to determine the genetic risk factors associated with response to antidepressants. If the investigators are able to identify a group of patients with similar DNA patterns, then they may be able to learn about the individual differences in the ability to tolerate and respond to medications used to treat depression. As other genetic risk factors are identified, blood samples will be tested to determine whether these other risk factors are also associated with the response of depressed individuals to antidepressants.

Risk/Benefit Analysis

4.0 ***RISKS/BENEFIT ANALYSIS: Indicate how the *risks to the participants are reasonable in relation to anticipated benefits*, if any, to participants and the importance of the knowledge that may reasonably be expected to result from the study:**
Risk/benefit ratio. Benefits from the proposed study outweigh its risks by providing treatment for severe and potentially lethal chronic depression. Patients will be exposed to potential side effects of the medications, which are moderate. Laboratory and neuropsychiatric tests carry minimal risk.
Potentials for drug side-effects and interactions are listed above; they are relatively low for both drugs.
The risk of breach of confidentiality is reduced by: 1) storing records in a locked file, with access available only to the PI and designated project staff; 2) removing identifying information from all data during the data analysis phase of the project; and 3) removing identifying information from all data presented publicly in lectures, seminars, or publications; as well as 4) using de-identified blood samples.

Alternatives

5.0 ***Indicate the alternatives to participating in this study.**

Check all that apply.

- [x] **All types of studies - Choose not to participate in the study**
- [x] **Clinical/Intervention Studies - Receive standard of care instead of participating in the study**
- [x] **Clinical/Intervention Studies - Medication, device, or other treatment is available off study**
- [ ] Item is Not Applicable (e.g., study of existing data)
- [ ] Other

5.1 **If "other" was selected, specify.**

5.2 **If this is a clinical/intervention study:**

Describe the standard of care or activities at UCLA (or study site) that are available to prospective participants who do not enroll in this study. If not applicable to your study, state not applicable (N/A).
None.

Warning: Save your work at least every 15 minutes by clicking "Save" or "Continue."

Data & Safety Monitoring Plan

1.0 ***Is a Data and Safety Monitoring Plan (DSMP) required by the funding agency or other entity?**

(●) **Yes** ( ) No

ID: IRB#12-001714 View: NEW 15.2 - Data & Safety Monitoring Plan (continued)

Warning: Save your work at least every 15 minutes by clicking "Save" or "Continue."

Data & Safety Monitoring Plan (continued)

Important Note:

All interventional studies involving more than minimal risk must include a Data and Safety Monitoring Plan (DSMP). A DSMP is a plan established to assure that each research study has a mechanism for appropriate oversight and monitoring of the conduct of the study to ensure the safety of participants and the validity and integrity of the data. The DSMP should indicate specifically whether or not there will be a formal Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC).

Most, but not all studies (i.e., non-interventional studies) undergoing full board review will require a DSMP. You will need a DSMP if any of the following apply:

1. This is a Phase I, II or III clinical trial
2. This is an investigator initiated trial (Section 2.1/item 3.0)
3. This study involves treatment in an emergency setting (Section 2.3/item 1.0)
4. A Data/Safety Monitoring Plan is required by the funding agency (Section 15.1/item 1.0)
5. This study is greater than minimal risk (Section 1.1b/item 1.0)

1.0 ***Indicate who will be responsible for overseeing the study safety. Check all that apply.**

- [x] **The Principal Investigator**
- [x] **Designee of the Principal Investigator**
- [x] **The DSMP includes at least one person who is not associated with the study**
- [ ] A formally constituted Data and Safety Monitoring Board (DSMB)
- [ ] Medical monitor designated by the sponsor
- [ ] Other

1.1 **If you indicated that a designee would be responsible for overseeing the study safety, or that the DSMP would include at least one person not associated with the study, provide the name(s) of this individual (s). Also, provide a brief explanation of why this person(s) would be appropriate in this role(s).**

In addition, we will arrange for the internal Data Safety Monitoring Board meetings at approximately 6 month intervals. The DSMB will consist of two external members and one internal member: Dr. Randall Espinoza, an expert geriatric psychiatrist, Dr. Hu, an expert geriatrician, and a statistician, Prabha Siddarth. All DSMB members have considerable experience in geriatric clinical and pharmacological issues. The DSMB will meet at least once every six months to review the progress of the study. The Board will also issue a report annually to the PI and the IRB. The board will review summaries of the study progress to ensure that consent documentation is properly obtained and stored. They will also review progress in filling subject recruitment ethnic requirements and will determine whether study coordinators and investigators are collecting and organizing data properly. Key personnel will provide progress reports to facilitate this review. The board will also review any recent research relevant to the study. The summary reports will provide data on enrollment and adverse events. Adverse events will be monitored using the UCLA Adverse Event and/or Incident Reporting forms (Forms HS-5 &

HS-6). Additional support for these activities will be provided by the General Clinical Research Center of the UCLA School of Medicine, which appointed Associate Dean, Stanley Korenman, and a full-time staff member, Laurie Shaker-Irwin, Ph.D., to assist in data safety monitoring in all protocols administered through the GCRC. A committee consisting of at least four medical school faculty members will review the findings of the DSMB and make recommendations for additional action as needed.

1.2 **If you indicated "other," describe or indicate where the information can be found in the attached protocol.**

2.0 ***Provide your assurance that information about serious, unanticipated problems related to the study (e.g., adverse events, incidents and violations) will be reported to the IRB within the time frames specified by the Summary Sheet of Reporting Requirements.**

Agree ☑

Provide the following information as appropriate to the study:

3.0 ***Are there plans to perform an interim safety analysis?**

○ Yes ◉ **No**

3.1 **If yes, describe or indicate where the information can be found in the attached protocol.**

4.0 ***Have stopping rules been established for the study?**

◉ **Yes** ○ No

4.1 **If yes, describe or indicate where the information can be found in the attached protocol.**

If patients experience any side-effects attributed to their study medication use, the allowed dose adjustment for MEM will be decreasing MEM by 1– 3 pills, to a minimum of 5 mg (or 1 cap a day), and decreasing escitalopram dose to 10 mg, so that the allowed dose range of escitalopram will be 10-20 mg/day. Re-challenge with a higher dose of MEM up to 20 mg/ day, or escitalopram of up to 20 mg/day may take place at the following visit in case of an incomplete response. All dose adjustments will be documented and considered in the analyses. The expected effective dose range of MEM will be 20 mg daily, which has been successfully used and well-tolerated in our pilot study. At the end of 24 weeks, memantine and placebo will be tapered off gradually in the same decrement of 5 mg (or 1 pill) per week over the course of 2-4 weeks to reduce the risk of withdrawal symptoms. At 6 months, subjects who decide to discontinue escitalopram will be tapered off gradually over the course of 2-4 weeks with 5mg dose decrements/ week in cooperation with their psychiatrist.

Discontinuation from the study will be considered if subjects experience:
We will monitor blood pressure and pulse once a week in the first four weeks, and at every visit. If any changes on the baseline ECG signifying ischemia occur, we will obtain additional tests of cardiac enzymes to rule out myocardial infarction (MI) (e.g., CK-MB; troponin). Dr. Hu is a part of the consulting and the DSMB teams and has advised us on the following parameters for discontinuation from the trial if cardiovascular complications arise. These include:
a. Any changes in subject's physical complaints of a potentially vascular nature (e.g., angina or chest pain, fainting, dizziness, arrhythmia); increase in pulse over 10 beats per minute from

baseline or tachycardia over 120 beats per min, changes in BP over 20 mm Hg;
b. Changes on ECG or in cardiac enzymes indicating cardiac ischemia or a new onset arrhythmia;
c. The development of any severe side-effects on the UKU Side Effect Rating scale rated as 3 or greater.

5.0 ***Are there defined rules for withdrawing participants from study interventions?**

◉ **Yes** ○ No

5.1 **If yes, describe or indicate where the information can be found in the attached protocol.**

Subjects have the right to refuse to participate or to withdraw from this research at any time without prejudice, but if they do, they will receive payment only for the time of their participation.

All patients will be carefully monitored for emergence of adverse effects. Dose of medications will be reduced, if necessary. If subjects continue to experience side effects despite dose reduction they will be discontinued from the study and alternative treatment will be recommended or appropriate professional referrals will be made. Discontinuation due to adverse events will be reported to the IRB.

All severe adverse events will be reported to the subjects and to their primary physicians and the UCLA IRB/ DSMB committee within 1 week of the PI's awareness, and within 2 weeks to the NIH.
d. If a patient demonstrates worsening of their symptoms or no response by week 8 (i.e., less than 30% improvement in HDRS scores or CGI score of > 4) of treatment, they will be discontinued from the study and referred for appropriate clinical services.
e. The allowed dose range for MEM will be 5-20 mg/day; escitalopram 10-20 mg/day. The only concomitant psychotropic medication allowed in the trial is lorazepam (1 mg or less a day). If patients are not able to tolerate these medications, they will be discontinued from the trial.
f. Suicidal ideations with the HAM-D item 3 score of 3 and greater, or worsening of the sore on the Beck Suicidal Ideation scale.
All dropouts will be analyzed by the reason for termination and classified as:
1. Reasons: a) Lack of efficacy; b) Side-effects; c) Lost-to-follow up; d) Hospitalization; e) Death; f) Other
2. Relation to the study drug use: a) likely; b) probable; c) unlikely.

Warning: Save your work at least every 15 minutes by clicking "Save" or "Continue."

Payment, Costs, and Injury

1.0 ***Indicate what the participants will receive for their participation in the study.**

Check all that apply.

- ☐ No payment will be provided
- ☑ **University check**
- ☐ Course Credit

☑ **Cash**

☐ Gift Cards/Bruincard Deposit

☐ Non-Monetary Gifts or Services

☐ Other (including vouchers for parking)

1.1 **If you selected Non-Monetary Gifts or Services or Other, describe:**

1.2 **If you selected *Cash* and/or *Gift Cards/Bruincard Deposit* please specify the estimated total amount of money you will require to pay all participants during the length of the entire study. This information is required by UCLA Business and Finance Services (BFS), the office that will provide the cash/gift cards for payment.**
$22,880.00

2.0 **If study participants will receive financial or other payment for their participation in the study, please provide the following information:**

- If applicable, the amount each participant will receive and the payment schedule to be followed including whether partial payment will be provided when the participant does not complete the study.
- If there are different plans for different populations or sub-studies, specify the groups and describe the plans.
- If families or children will be involved in the research, clarify how the payments, items or services will be apportioned.

Payment for participation: Because the procedures are time-consuming, subjects will receive a $200.00 honorarium ($10 per visit) for their participation in the trial, which will also help to cover their travel costs. We will offer parking reimbursement of $11.00/day for up to $220.00 for 20 visits. Those participating in the 12 month follow up will receive additional $100.00. Those participating in MRI/PET scans will be reimbursed at 25.00 per hour spent up to a total of one hundred dollars ($100) per year, but not less than fifty dollars ($50.00). Subjects will incur no financial obligations.

3.0 ***Will subjects** incur **any financial obligations from participation in the study?**

○ Yes ◉ **No**

3.1 **If yes, describe:**

4.0 ***Indicate below that you are familiar with UCLA policy related to treatment and compensation for injury and that you will use in the consent form for this study the appropriate UC required statement describing "Treatment and Compensation for Injury." Click here to access the UCLA policy: Treatment and Compensation for Research Related Injury.**

Note: Select **Not Applicable** if study is minimal risk.

◉ **Agree**

○ Not Applicable

Warning: Save your work at least every 15 minutes by clicking "Save" or "Continue."

HIPAA Authorization

According to your responses to section 9.2/item 1.0, this study uses protected health information. Please provide the following information.

1.0 ***Indicate all that apply to use of or disclosure of PHI in this study:**

- [x] **All UC participants will sign a UC HIPAA Research Authorization for Release of Personal Health Information for Research.**
- [ ] **Another Institutions' Healthcare Authorization** for Release of Health Information will be used **or a waiver** for release of health information will be granted **from another Institution**.
- [ ] **A Waiver of HIPAA Research Authorization** is requested for **screening** using UC medical records. I assure that the PHI collected for this study will not be reused or disclosed, except as indicated in this application.
- [ ] **A Total Waiver of HIPAA Research Authorization** is requested for the entire study. I assure that the PHI collected for this study from UC records will not be reused or disclosed, except as indicated in this application.
- [ ] **Limited Data Set with a Data Use Agreement** will be obtained from UC medical records. I assure that I will follow the data security plan outlined in this application to protect the identifiers from improper use or disclosure.
- [ ] **None of the above. This study will be conducted outside the United States**

2.0 ***Indicate to whom or where you will grant access to personal identifying information (including PHI) as part of the study process:**

- [x] **There is no plan to share identifiers outside the study team**
- [ ] The study sponsor; on site only (if there is more than one study sponsor, specify below).
- [ ] A foreign country or countries
- [ ] Other

2.1 **If you checked "other", "a foreign country or countries", or if "there is more than one sponsor", specify.**

3.0 ***The investigator's agreement is needed to the following:**

- The protected health information requested is the minimum necessary to meet the research objectives

- The protected health information that is obtained as part of this study will not be used or disclosed to any other person other than study personnel or to the parties listed in item Section 17.1/item 2, except as required by law.

- Study Sponsors will **not** be provided with personal identifying information (including PHI) to take from the study site at any time, including the end of the study.

- Data and specimens shared with outside entities, such as study sponsors, will be coded or de-identified.

Agree ☑

ID: IRB#12-001714 View: NEW 18.1 - Identification/Recruitment Methods

Warning: Save your work at least every 15 minutes by clicking "Save" or "Continue."

Identification/Recruitment Methods

1.0 ***How will you identify and/or recruit participants for this study.**

Check all that apply:

- [x] **Advertisements/Flyers/Information Sheet/Internet Postings**
- [ ] Direct recruitment of potential study participants (e.g., physicians talking with their own or clinic patients about the study, contact between the study team and potential subjects in person, on the phone or on the internet, etc.)
- [ ] Random or Other Probability Sampling

- [ ] Recruitment Letters/Emails
- [ ] Referrals (e.g., referrals from non-investigator healthcare providers, snowball sampling, participants referring other participants, etc.)
- [ ] Review of medical records to identify potential research participants
- [ ] Review of publicly available records
- [ ] Review of other records
- [ ] Participant pool for which potential research participants have given permission for future contact
- [x] **Potential Study Participants are identified from another IRB approved study or IRB approved screening protocol**
- [ ] Other

Warning: Save your work at least every 15 minutes by clicking "Save" or "Continue."

Recruitment Methods

1.0 Please upload copies of your recruitment materials below. This includes advertisements, flyers, internet postings, recruitment scripts and letters/emails.

Document Name	Document Version #
Namenda Aging Brain Ads 4-22-2013.doc	0.01
Namenda Aging Brain Ads 4-22-2013_marked.doc	0.01
Namenda Aging Brain Flyer 4-22-2013.doc	0.01
Namenda Aging Brain Flyer 4-22-2013_marked.doc	0.01

Ads/Flyers/Info Sheets/Internet Postings

2.0 If you have indicated that study participants will be recruited with advertisements/flyers (Section 18.1/Item 1.0), please indicate the type of media that will be used (e.g., newspaper, radio, internet, etc.) and/or where information will be posted or distributed.
IRB approved flyers will be posted in designated advertising areas around the UCLA medical campus. We will also publish small advertisements in the Los Angeles Times using IRB approved advertising text.

Direct Recruitment

3.0 If you have indicated that participants will be recruited through direct contact (Section 18.1/Item 1.0), please provide the following information:

- A description of how, when, and where initial contact would be made (e.g. in a public setting, in a waiting room, via a phone call, via a letter, via the internet, etc.)
- If applicable to the study, indicate how the potential research participant's privacy will be maintained.
- Who will make the contact (e.g. the investigator, a patient's physician, etc.)

3.1 If you will be directly recruiting potential participants who are your patients, students, laboratory workers or any others with whom you have a relationship of authority or unequal power, describe what measures you will put in place to avoid those approached from feeling pressured or unduly influenced to participate in the study.

Recruitment Letters/Emails

4.0 **If you have indicated that recruitment letters will be distributed to participants (Section 18.1/item 1.0), please indicate who will send out the recruitment letter (i.e. will it be the investigator or other persons who have authorized access to the information), how inquiries will be handled, and if there will be follow-up contacts.**

Referrals

5.0 **If you have indicated that study participants will be identified from referrals (Section 18.1/item 1.0), please indicate the source of the referral (e.g., friends, other participants, healthcare providers) and how the referral will be elicited.**

Research Participant Pools/Recruitment Databases

6.0 **If you have indicated that subjects will be identified and recruited from a subject pool(s) or recruitment database, (Section 18.1/item 1.0), please indicate the name of the Pool or Recruitment Database and UCLA Department. If the Pool or Recruitment Database is not at UCLA, identify the location.**

ID: IRB#12-001714 View: NEW 18.3 - Identification Methods

Warning: Save your work at least every 15 minutes by clicking "Save" or "Continue."

Identification Methods

Random or Other Probability Sampling

1.0 **If you have indicated that probability sampling will be used to identify potential study participants (Section 18.1/Item 1.0), please indicate the specific technique(s) and how it will be used in this study.**

Review of Publicly Available Records

2.0 **If you have indicated that publicly available records will be used to identify potential participants for the study (Section 18.1/item 1.0), please indicate the type(s) of records to be used.**

Review of Other Records

3.0 **If you have indicated that other records will be used to identify potential study participants (Section 18.1/item 1.0), please indicate the type(s) of records to be used.**

3.1 **If applicable, indicate the permissions that you have received to review the records.**

Another IRB Approved Study or Screening Protocol

4.0 **If you have indicated that potential subjects are identified from another study or from a screening protocol (Section 18.1/item 1.0), please provide the IRB# for the study.**
10-001413

4.1 **If you do not have the IRB#, please provide the title of the study.**
The Use of Methylphenidate to Improve Clinical Outcomes in Geriatric Depression: A Double-Blind Placebo-Controlled Trial of Methylphenidate (Ritalin) Augmentation of Citalopram (Celexa) in Depressed Patients at Least 60 Years of Age

Identification/Recruitment - Other

5.0 **If you have indicated that "other" ways will be used to identify or recruit study participants (Section 18.1/item 1.0), please describe.**

Warning: Save your work at least every 15 minutes by clicking "Save" or "Continue."

Eligibility Screening

1.0 ***Will you be conducting a preliminary assessment with potential research participants to determine study eligibility during the recruitment process?**

(●) **Yes** ( ) No

You indicated that eligibility screening will be conducted during the recruitment process (Section 19.1/item 1.0). Please provide the following information.

2.0 ***Will private identifiable information be collected during the screening?**

(●) **Yes** ( ) No

2.1 **If private identifiable information is collected during screening, are there plans to retain data from participants found to be ineligible for the study?**

( ) Yes (●) **No**

2.2 **If private identifiable data will be collected during the screening, indicate your plans for retaining the data.**

- [x] **The data will be retained with identifiers**
- [ ] The data will be retained without identifiers
- [x] **The data will be destroyed**

2.2.1 **If you chose more than one response above, explain.**
After telephone screening, all documents containing personal identifying information will be stored in a locked file accessible only to designated study staff. It will be destroyed after the study.

3.0 **Describe how screening will be performed.**
The initial telephone screening (15 minutes) will be conducted over the phone by the research coordinators using the screening script (see attached Telephone Screen). Eligibility for the study will be determined by the PI during the first visit. We will de-identify the data of subjects found ineligible during the screening process. Dr. Lavretsky will obtain the informed consent prior to all evaluations. During the first visit and baseline visit, all screening test results and eligibility criteria will be reviewed. Medications will be dispensed only if patients continue to meet eligibility criteria.

4.0 **Attach screening script(s), if applicable.**

Document Name	Document Version #
Namenda Aging Brain Telephone Screen 9-2-2014 clean.doc	0.01
Namenda Aging Brain Telephone Screen 9-2-2014 marked.doc	0.01

Warning: Save your work at least every 15 minutes by clicking "Save" or "Continue."

Informed Consent Process

You indicated that adults (and/or minors who are permitted to consent for themselves) are participating in the study (Section 11.2/item 1.0 or Section 12.2/item 1.0).

For additional information on minors who are permitted to consent for themselves please refer to the section "Legal Exceptions Permitting Certain Minors to Consent" in the OHRPP Guidance document, Child Assent and Permission by Parents or Guardians.

1.0 ***Indicate your plans for obtaining informed consent for this study.**

Check all that apply:

- [x] **Signed consent will be obtained from the research participant or Legally Authorized Representative.**
  - **Signed consent means research participants will be asked to sign and date a written consent form.**
- [ ] **A waiver of signed consent is requested for the entire study.** One of the following procedures will be conducted:
  - **A written information sheet will** be used. Signed consent will not be obtained from research participants.
  - **Oral consent** will be obtained from the research participant or Legally Authorized Representative (LAR)
  - This option should be selected if the study involves consenting participants via the internet.
- [ ] A **waiver of consent** is being requested.
  - Research participants will **not** be asked to sign a consent form or give oral consent
- [ ] Consent will be obtained by a collaborating institution.

1.1 **- If you checked more than one plan above, list the study groups and the plan that you will use for each.**
- If you checked "Consent will be obtained by a collaborating institution", explain the consent process and upload a copy of the most recent approved consent document in item 1.2.

1.2 **If applicable, attach the consent document(s) from collaborating institution(s).**

Document Name	Document Version #
There are no items to display	

ID: IRB#12-001714 View: NEW 20.3 - Description of the Consent Process

This view has been locked by amendment(s)

Warning: Save your work at least every 15 minutes by clicking "Save" or "Continue."

Description of the Consent Process

1.0 ***Indicate the type of setting(s) in which the consent process will be conducted.**

Check all that apply.

- [ ] In a private home
- [x] **In a private room**
- [ ] In a waiting room
- [ ] In a public setting
- [ ] In a group setting
- [ ] On the internet
- [ ] Over the telephone
- [ ] Other

1.1 **If you checked more than one response, or indicated other, describe.**

1.2 **If the setting is not private, describe the measures to protect confidentiality or indicate "not applicable."**

2.0 ***Indicate the measures that will be taken to provide prospective research participants with sufficient opportunity to consider whether or not to participate in the study.**

Check all that apply.

- ☑ **Member(s) of the study staff will meet with the prospective participants/families to review the consent document(s) and/or provide an oral explanation of the study. Individuals will be given a chance to ask questions before making a considered decision about whether or not to participate in the study.**
- ☑ **Prospective participants/families will have the opportunity to take the consent form(s) home and may discuss the documents with others prior to deciding whether or not to participate in the study.**
- ☐ Prospective participants will self-administer the consent and send it back if they decide to participate in the study.
- ☐ Other

2.1 **If you indicated other, describe.**

3.0 ***Indicate the length of time subjects are given to decide whether they wish to participate in the study.**
Subjects will be given as much time as needed to read all consent forms prior to signing. They may take the consent forms home and discuss them with their family members and/or health care practitioners.

4.0 ***How will you assess whether subjects understand the information conveyed during the consent process?**

Check all that apply.

- ☐ Use the Subject Comprehension Tool form for research
- ☑ **Investigator or study team member will evaluate during the consent process**
- ☐ Other
- ☐ Not Applicable

4.1 **If you indicated other, describe.**

5.0 ***Attach copies of the informed consent documents, information sheets, consent scripts as applicable to this study. Include copies of translated forms, if applicable.**

Document Name	Document Version #
Namenda Consent 11-21-2014 marked.docx	0.01
Namenda Consent 11-21-2014.docx	0.01

Warning: Save your work at least every 15 minutes by clicking "Save" or "Continue."

Cultural Considerations

The following items are designed to acquaint the IRB with cultural features of the population that you are studying that may require procedures to ensure truly informed consent.

1.0 ***Check all that apply to the population(s) with which this study will be conducted.**

- ☐ Participants may be illiterate or insufficiently literate to be able to comprehend a conventional written informed consent form.

- ☐ The participants may be reluctant or unwilling to sign a written informed consent form.
- ☐ The husbands make decisions for their wives.
- ☐ Elders make decisions for younger adult family members.
- ☐ Elders make decisions for their community.
- ☐ It is considered impolite to refuse a request.
- ☐ People are fearful of refusing requests that they regard as coming from authorities.
- ☑ **None of the above are applicable to this study.**

1.1 **If any of the above items are applicable to this study, indicate the steps that you will take to ensure voluntary participation after providing the study information, and if applicable, any planned involvement with the community regarding the consent process.**

Warning: Save your work at least every 15 minutes by clicking "Save" or "Continue."

Additional Information and/or Attachments

1.0 **Attach any other documents that have not been specifically requested in previous items, but are needed for IRB Review.**

Document Name	Document Version #
Risk chart for Memantine or Escitalopram.docx	0.01

2.0 **If there is any additional information that you want to communicate about this study, include it in the area provided. Note: this section should not be used instead of the standard application items.**

Instructions for Study Submission

You have completed your application, **but it has *not yet been submitted*.**

FOLLOW THESE STEPS TO SUBMIT THE APPLICATION TO THE IRB FOR REVIEW:

1. Click the **Finish** button to return to exit the SmartForm and return to the study workspace.
2. Use the **View SmartForm Progress** function to make sure that the application is complete.
3. If you are the PI or PI Proxy, click **Submit Study** under **My Activities**. If you are a member of the study team, you can let the PI know that the study is ready to submit by clicking **Send Ready Notification.**
4. Once the study is submitted, the state indicator at the top of the page will no longer display **Pre-Submission.**
5. After submission of the study, the **PI Assurances** activity will immediately become available under **My Activities**. The PI should provide his/her assurances at that time. If the PI is not available, the study can be submitted by a PI Proxy and the assurances provided at a later time. The study will be reviewed by the IRB while the **PI Assurances** are pending; however, it will not be approved until the **PI assurances** are completed.
6. ***If there is a Faculty Sponsor for the study***: The study can not be submitted to the IRB until the Faculty Sponsor provides his/her assurances through **FS Assurances** activity.

Audio, Visual or Digital Recordings

Click "OK" below to return to the SmartForm page where you can select the appropriate response.

ID: IRB#12-001714 View: Display - Method Description

Certificate of Confidentiality for research not supported by NIH

The Certificate of Confidentiality button in this section is only if your study is NOT supported or conducted by NIH but you will obtain a Certificate of Confidentiality (for example, for studies collecting information about illegal drug use).

If you previously checked this box for an NIH-supported study before the policy change, you do not need to change your response here.

Certificates of Confidentiality are issued by the National Institutes of Health (NIH) to protect the privacy of research subjects by protecting investigators and institutions from being compelled to release information that could be used to identify subjects with a research project. Certificates of Confidentiality are issued to institutions or universities where the research is conducted. They allow the investigator and others who have access to research records to refuse to disclose identifying information in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level.

Effective October 1, 2017, NIH has updated its policy for issuing Certificates of Confidentiality for NIH-funded and conducted research. For information about the policy change or about obtaining Certificates for research supported by other agencies, please see https://humansubjects.nih.gov/coc/index.

Click "OK" below to return to the SmartForm page where you can select the appropriate response.

ID: IRB#12-001714 View: Display - Method Description

Clinical Trial of a Drug, Biologic, Device or a Behavioral Intervention

A clinical trial is a research study designed to answer specific questions about medical or behavioral treatments. The trial may be interventional or observational. Interventional studies are those in which the research participants are assigned by the investigator to a treatment or other intervention, and the outcomes measured. Observational studies are those in which individuals are observed and the outcomes are measured by the investigators.

Click "OK" below to return to the SmartForm page where you can select the appropriate response.

ID: IRB#12-001714 View: Display - Method Description

Community Based Research

Click "OK" below to return to the SmartForm page where you can select the appropriate response.

ID: IRB#12-001714 View: Display - Method Description

Controlled Substances (Schedule I or II)

Check here only if you are using a Schedule I or II Controlled substance in this study. Research using Schedule I or Schedule II controlled Substances must be submitted to the Research Advisory Panel of California for review and approval prior to initiation. Research using Schedule III, IV, or V Controlled Substances as a study drug do not require review by the Research Advisory Panel. For further information see: http://ag.ca.gov/research/guide.php o Schedule I Controlled Substances are drugs or substances with a high potential for abuse, that have no currently accepted medical use in treatment in the United States. Examples of Schedule I Controlled Substances are: heroin, lysergic acid diethylamide (LSD), methylenedioxy-methamphetamine (MDMA), marijuana, and psilocybin. o Schedule II Controlled Substances are drugs or substances with a high potential for abuse, that have a currently accepted medical use in treatment in the United States, or a currently accepted medical use with severe restrictions. Examples of Schedule II

Controlled Substances are: fentanyl, methadone, methylphenidate, morphine, and oxycodone. For further information see: http://www.deadiversion.usdoj.gov/schedules/index.html

Click "OK" below to return to the SmartForm page where you can select the appropriate response.

ID: IRB#12-001714 View: Display - Method Description

Deception or Partial Disclosure

Deception includes withholding information about the real purpose of the study or purposely giving subjects false information about some aspect of the research to prevent bias. Some professions, such as the American Psychological Association (APA) have ethical codes regarding the use of deception in research. (See sections 8.07 and 8.08 at http://www.apa.org/ethics/code/index.aspx#807) If deception is included in the study, you must also apply for approval of a waiver of the informed consent process (Section 20.1) in addition to selecting the other consent procedures planned for the study (e.g., written or oral consent).

Click "OK" below to return to the SmartForm page where you can select the appropriate response.

ID: IRB#12-001714 View: Display - Method Description

Devices/Diagnostics (including Humanitarian Devices - HUD)

A medical device is defined, in part, as any health care product that does not achieve its primary intended purposes by chemical action or by being metabolized. Medical devices include, among other things, surgical lasers, wheelchairs, sutures, pacemakers, vascular grafts, intraocular lenses, and orthopedic pins. Medical devices also include diagnostic aids such as reagents and test kits for in vitro diagnosis (IVD) of disease and other medical conditions such as pregnancy. For further information see: http://www.fda.gov/oc/ohrt/irbs/irbreview.pdf

Click "OK" below to return to the SmartForm page where you can select the appropriate response.

ID: IRB#12-001714 View: Display - Method Description

Drugs/Biologics/Dietary Supplements

- Drug: The term "drug" means: articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and articles (other than food) intended to affect the structure or any function of the body of man or other animals.
- Biologics vs. Drugs: Most drugs consist of pure chemical substances and their structures are known. Most biologics, however, are complex mixtures that are not easily identified or characterized. Biological products differ from conventional drugs in that they tend to be heat-sensitive and susceptible to microbial contamination. This requires sterile processes to be applied from initial manufacturing steps. For more information see: http://www.fda.gov/consumer/updates/biologics062608.html#drugs
- Dietary Supplements are products that are intended to supplement the diet and have one of the following ingredients:
  - A vitamin
  - A mineral
  - An herb or other botanical
  - An amino acid
  - A dietary substance for use by man to supplement the diet by increasing the total daily intake
  - A concentrate, metabolite, constituents, or an extract of combinations of these ingredients.

For additional information see: http://www.foodsafety.gov/~dms/supplmnt.html

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Expanded Access to Drug, Device or Biologic for Treatment Purposes (aka Compassionate Use, Treatment Use)

Click "OK" below to return to the SmartForm page where you can select the appropriate response.

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Genetic Analyses/Genotyping

Genetic analyses/genotyping include, but are not limited to, studies of inheritable conditions or traits, gene markers or mutations, and pedigrees.

Click "OK" below to return to the SmartForm page where you can select the appropriate response.

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Human Embryonic Stem Cells and/or Induced Pluripotent Stem Cells

Research with human embryonic stem cells (hESC) and related lines requires IRB review under the following conditions: o Clinical research in which human subjects are given hESCs or related products. o When the UCLA research team will have a research related direct interaction or intervention with the cell donors, including donation of blastocysts or gametes for the purpose of creating hESCs,. o Cells provided to the UCLA research team that have identifiers or codes that can be linked back to the donor. Research involving hESC requires review and approval by the ESCRO Committee. For further information see: http://www.stemcell.ucla.edu/research

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Human Gene Transfer/ Recombinant DNA

Studies involving gene transfer and/or recombinant DNA require approval of the UCLA Institutional Biosafety Committee (IBC) and the NIH Recombinant DNA Advisory Committee (RAC) . Human gene transfer is an investigational method for correcting defective genes responsible for disease development through one of the following techniques: o A normal gene may be inserted into a nonspecific location within the genome to replace a nonfunctional gene. o An abnormal gene could be swapped for a normal gene. o The abnormal gene could be repaired through selective reverse mutation, which returns the gene to its normal function. o The regulation of a particular gene could be altered. Recombinant DNA molecules, according to the NIH Guidelines, are defined as either: (i) molecules that are constructed outside living cells by joining natural or synthetic DNA segments to DNA molecules that can replicate in a living cell, or (ii) molecules that result from the replication of those described in (i) above.

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Infectious Agents

Studies involving the use of Risk Group 2 or 3 infectious agents (such as bacteria, fungi, parasites, prions, rickettsia, viruses, etc.) require approval of the UCLA Institutional Biosafety Committee (IBC).

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Non-FDA approved medical equipment used with UCLA hospital patients or research participants that operate under the UCLA Hospital License.

Clinical Engineering is responsible for completing incoming inspections on investigational devices that are used to diagnose, treat or monitor a patient and that are used in the patient care area on site at UCLA, but *not* in other hospitals such as Cedars Sinai, CHLA, or Drew. If a device is FDA and/or testing - laboratory approved for the purpose it was designed, then evaluation is not required of the device. If you have a copy of an inspection report from Clinical Engineering, please attach here. As appropriate, please contact Clinical Engineering at 310-267-9000 to arrange an inspection.

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Radiation (Standard of Care or Investigational Use of radioactive materials, radiation producing machines or ionizing radiation)

Note: This includes CT-guided biopsy, fluoroscopy use, etc.; MRI is not included. The radiological procedures included in this study must be described in the SafetyNet system. Please create a new SafetyNet application after submitting this webIRB application to the IRB for review.

Click "OK" below to return to the SmartForm page where you can select the appropriate response.

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Substance Abuse Research (with Medication)

Research for the treatment of controlled substance addiction or abuse that uses any drug (scheduled or not) as treatment, requires the review and approval of the Research Advisory Panel of California prior to initiation. For further information see: For further information see: http://ag.ca.gov/research/guide.php

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Treatment in an Emergency Setting (with request to waive consent)

Federal regulations allow certain research activities to be conducted in emergency settings with waiver of informed consent - in the interest of facilitating potentially life-saving and life-enhancing research with protecting the rights and welfare of participants. For further information see: o OHRP Guidance: http://www.hhs.gov/ohrp/humansubjects/guidance/hsdc97-01.htm o FDA Guidance: http://www.fda.gov/oc/ohrt/irbs/except.html

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None of the above

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