Date Generated: Monday, November 30, 2015 9:36:27 AM
Current Date: 2/2/2016, 3:52:21 PM

Date: Monday, November 30, 2015 9:36:28 AM

Print Close

ID: IRB#14-001827 View: NEW 1.1 - Study Title and Key Personnel

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

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:**
Double-blind placebo-controlled trial of levomilnacipran in geriatric depression

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

2.0 ***Working or Lay Title:**
Levomilnacipran in geriatric 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 at item 3.6.1 above.

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.**
NATALIE ST. CYR

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

Note: All personnel listed below are required to complete CITI training courses. HIPAA training is also required if personnel will

be accessing protected health information.
Please make sure to have all key personnel update their webIRB profile, contact information.
Instructions on how to update the webIRB profile: Click here.

	Name	Department	Role	Other Role (if applicable)	Will Obtain Consent?	Manage device accountability?	Access to personally identifiable info?	Access to code key?
View	DAVID MERRILL, MD, PhD	PSYCHIATRY/BIOBEHAVIORAL SCI	Co-Investigator		yes	Yes	Yes	Yes
View	LINDA ERCOLI	PSYCHIATRY/BIOBEHAVIORAL SCI	Co-Investigator		no	Yes	No	No
View	PRABHA SIDDARTH	SEMEL INSTITUTE	Co-Investigator		no	No	No	No
View	KATHERINE NARR, PhD	NEUROLOGY-LONI	Co-Investigator		no	Yes	No	No
View	NATALIE ST. CYR, BA	SEMEL INSTITUTE	Study Coordinator		no	Yes	Yes	Yes

ID: IRB#14-001827 View: NEW 1.1a - Other Personnel

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

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.

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.
There are no items to display

- **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:**
  - ☐ CITI Training
  - ☐ 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#14-001827 View: NEW 1.1b - Type of Study Review

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

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.
		SGIRB reviews social-behavioral research from the Schools

South General Institutional Review Board

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#14-001827 View: NEW 1.2 - Conflict of Interest Information

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

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 #
There are no items to display	

ID: IRB#14-001827 View: NEW 1.3 - Study Locations

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

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.**

ID: IRB#14-001827 View: NEW 1.4 - UCLA Sites or UCLA Health System Sites

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:

- [ ] 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
- [ ] 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.**

ID: IRB#14-001827 View: NEW 2.1 - Project Identification Information

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

Project Identification Information

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

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

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

2.0 **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 and/or involves gene therapy?

( ) 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 6.2 of the webIRB application.

6.0 ***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**

- 6.1
- **If yes, indicate the source of scientific or scholarly review for the study.**
-
- **Check all that apply.**
  - [ ] 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

- 6.1.1
- **If you checked "other", describe.**

- 6.2
- **Attach a copy of the scientific or scholarly review, if applicable.**

Document Name	Document Version #
There are no items to display	

ID: IRB#14-001827 View: NEW 2.2 **-** Lay Summary and Keywords

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

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).**
Summary: We are proposing a 12-week pilot double-blind comparison of levomilnacipran (FETZIMA) to placebo for the treatment of geriatric depression. We are interested in assessing the efficacy of levomilnacipran (LMIL) to placebo (PBO), and exploring the effects of antidepressant response on brain connectivity and neuroplasticity. This pilot study is designed to determine any differences in the efficacy, safety and tolerability of levomilnacipran compared to placebo, and to perform dose finding (20-120 mg per day) in 60 older depressed adults. We anticipate that the LMIL will be superior to PBO in improving levels of depressive symptoms and rates of remission, as well as improving cognition, apathy, and quality of life. This proposal expands the PI♦s focus on the biomarkers of neuroplasticity that have been used in several prior studies and demonstrated responsivity to antidepressant treatment. We are seeking to examine this directly in 60 older adults with major depression. This proposed trial will also serve as a pilot study to estimate the efficacy and tolerability of the drug in older depressed adults, and the dose-finding in this population. The drug placebo differences in geriatric depression are minimal within 5% of each otehr averaging about 30-40% each. We are addressing neural mechanisms of antidepressant response, and the placebo controlled study will help evaluate this better than another active comparator. We will be actively monitoring side-effects of drugs, including emerging and worsening symptoms of depression and suicidality.

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 antidepressant

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**

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
- [ ] Food Additives
- [ ] Color Additives
- [ ] Other

- 4.1.1
- **If Other, describe:**

ID: IRB#14-001827 View: NEW 2.3 - Methods/Procedures - Descriptors

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

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
- [ ] Behavioral Observations (only applicable if you selected Exempt Category 2 in section 5.3)
- [ ] Certificate of Confidentiality
- [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)
- [ ] 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.

Radiation (Standard of Care or Investigational use of radioactive materials 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), professional medical services, clinical treatment, diagnostics, labs, medical supplies, etc.)?**

Please direct any questions about this to the Clinical Trials Administration Office at clinicaltrials@mednet.ucla.edu.

Yes No

ID: IRB#14-001827 View: NEW 2.4 - Coverage Analysis

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

Coverage Analysis

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

Yes - we will **not** 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 does not require additional visits, labs, items or services performed solely due to study participation

Note:

*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?**

- **Investigator-initiated study**
- **Expanded Access (aka Compassionate Use or Treatment Use)**
- **Humanitarian use device study**
- **Chemo/radiation therapy study**
- **UCLA IRB to rely on another IRB for this study**

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 #
LevomiInacipran proposal 042014.docx	0.01

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) will be billed for investigational products (i.e.,

investigational drugs and/or devices), attach any documentation to support these charges including any FDA letter(s) if available.

Document Name	Document Version #
There are no items to display	

ID: IRB#14-001827 View: NEW 6.1 - Funding and Other Study Characteristics

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

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)
- [x] **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#14-001827 View: NEW 6.2 - Funding - Description

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

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).

	Funding Source	Funding Source Information
View	FOREST LABS (INCLUDING FNDN FOR FELLOWS IN ASTHMA RESEARCH)	

Name of the Funding Source	FOREST LABS (INCLUDING FNDN FOR FELLOWS IN ASTHMA RESEARCH)
If other, specify	*No Value Entered*
UCLA PI named on the grant, contract, subcontract or gift:	HELEN LAVRETSKY
Indicate the type of award:	Grant
Indicate the Grant Title:	Double-blind placebo-controlled trial of levomilnacipran in geriatric depression.
Indicate the Award Number assigned by the funding source:	IIT-USA-000620
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**: Levomilnacipran proposal 042014.docx **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*

ID: IRB#14-001827 View: NEW 8.1 - Study Design

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.

- [x] **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.

ID: IRB#14-001827 View: NEW 8.3 - Clinical Trial of a Behavioral Intervention, Drug, Biologic or Device

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:

ID: IRB#14-001827 View: NEW 8.6 - Drugs/Biologics/Dietary Supplements

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 used for research (or clinical investigation) that will be used in accordance with their approved labeling.

levomilnacipran (FETZIMA)

2.0 Fill in an entry for all *investigational* drugs/biologics that will be used as part of this study.

Important Notes
Complete only if one or both of the following apply:

- **The research involves *investigational use of an unapproved drug or biologic.* The drug or biologic is not approved by the FDA for marketing.**
- **The research involves *investigational use of a marketed drug or biologic.* The drug or biologic will use off label for an indication not in the approved labeling.**

Do not complete if the following apply:

- **The only drug(s) in the research is/are used in accordance with their approved labeling, as indicated above in item 1.0, and**
- **The drug(s) used in the research are not investigational.**

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.

Generic name of the drug/biologic	Investigational Drug/Biologics Information
There are no items to display	

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

ID: IRB#14-001827 View: NEW 9.2 - Information about Study Data

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:

- 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:**
  We will monitor suicidal ideations using the third item of the Hamilton Depression Scale during each visit to the site. Monitoring for SI will be done at each visit independent of the outcome assessment. The blind rater will be instructed to inform the PI of scores = 3. Subjects with active suicidal ideations with or without a plan, HAMD-24 score = 3, will be excluded from participation. We will call subjects between visits to monitor suicidal ideations. We will encourage participation of their family members in the study who will be encouraged to call the patient and the study staff in case suicidal ideations emerge during the study. In the presence of persistent suicidal ideations, subjects will be discontinued from the study and referred to clinical services or to the community for treatment.

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)
- [x] Postal Address
- [x] Phone Numbers
- [ ] 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:

  - [x] Use for this study
  - [ ] 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#14-001827 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 in the Semel Institute building. All medical procedures, including fMRI will be conducted in a private examination room at the UCLA 200 medical plaza or the Brain Mapping Center.

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#14-001827 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 during conduct of the study:**

- [x] 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#14-001827 View: NEW 9.4 - Data Security Plan - During the Study

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#14-001827 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#14-001827 View: NEW 10.1 - Study Summary - Research Study

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 #
LMIL Tables and Figures.docx	0.01
LMIL Bibliography and References cited.docx	0.01
Levomilnacipran proposal 042014.docx	0.01

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

Specific Aims and Hypotheses:
Primary Aim: To compare the efficacy and generate estimates of the effect sizes on primary and secondary outcomes between the treatment groups in a 12 week double-blind placebo controlled treatment trial with levomilnacipran compared to placebo.
Hypothesis 1: We will observe detectable differences in primary (mood) and secondary outcomes (cognition, apathy and quality of life) between the two treatment groups favoring LMIL.

Aim 2: To test whether the two treatment conditions will show no difference in tolerability and safety. We will particularly focus on cardiovascular status (blood pressure, heart rate, ECG changes)
Hypothesis 2: There will not be a difference in the rate of adverse events between the two groups.

Exploratory Aim 3: To compare the patterns of functional and structural connectivity in the two intervention groups. Hypothesis 3: LMIL will lead to improved functional connectivity in brain network activity as measured with resting state (rs-) fMRI, and plasticity in brain macro- and micro-structure as measured with structural MRI and DTI compared to the PBO.

Exploratory Aim 4. To determine whether both structural and functional brain imaging markers can predict or moderate mood and functional improvement in both conditions at 12 weeks. Exploratory Hypothesis 4: Imaging biomarkers of connectivity will moderate and predict 1) rate of improvement in symptoms and function; and 2) improvement in cognitive performance.

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.

a. Background and Significance
Depression in the elderly is a major public health concern: Late-life depression (LLD) has a high prevalence (5-10%), and is commonly under-diagnosed and undertreated.1-4 Elderly patients also have lower treatment response rates posing challenges for long-term clinical care.5-8 Older patients are reported to have more physical illness, chronic pain, frailty, psychomotor retardation or agitation, anxiety, cognitive impairment, and anorexia/weight loss than younger adults.9,10,11-18,19 Suicide is more common in aging.20 The proposed will test novel interventions that are expected to enhance antidepressant response, cognition, apathy and quality of life, and biomarkers of fMRI in the depressed elderly.

Critical need for new treatment approaches in late-life depression: Limitations of pharmacotherapy. Despite advances in the diagnosis and treatment of LLD, there is a problem of inadequate treatment response with poor treatment outcomes.21-25 In LLD, remission rates for first-line antidepressants remain at ~30%. Furthermore, there is an urgent need to develop strategies to enhance the efficacy of standard drug treatments to speed recovery and reduce suffering the depressed elderly.

Levomilnacipran use in geriatric depression: Levomilnacipran is a novel serotonin and norepinephrine reuptake inhibitor (SNRI) for the treatment of major depressive disorder. The drug differs from previously available SNRIs in having twice the potency for norepinephrine versus serotonin reuptake inhibition. In four of the six short-term clinical trials, levomilnacipran was statistically significantly more efficacious than placebo. The only available relapse prevention study did not show reduction in time to relapse, perhaps because relapse rates were low. The commonest adverse events occurring twice as often as on placebo were nausea, hyperhidrosis, constipation, tachycardia, vomiting, erectile dysfunction, palpitations, and ejaculation disorder. In a few patients, hypertension or orthostatic hypotension may occur, which is of importance in older adults- we will follow these parameters in the study. Levomilnacipran, given its action profile with dual action on serotonin and norepinephrine reuptake inhibition, may also be helpful for such prominent features of geriatric depression, as apathy, and therefore, improve the overall quality of life.

Pilot data. In our pilot study of 49 family dementia caregivers (mean age 60.3 years, SD=10.2), 39 were randomized and completed either Kundalini yoga (KK) meditation or listening to relaxation music for 12 minutes per day for 8 weeks. Severity of insomnia, depressive and anxiety symptoms, and coping were assessed at baseline and over the course of the study. fMRI showed different patterns of activation distinguishing meditators from controls, meditators showed higher activity in a functional network including the anterior cingulate, fronto-orbital cortex and insula (Fig. 1) - consistent with prior findings and relevant to mood and cognitive regulation. These findings suggest that our fMRI methods are feasible to examine such effects.
In our pilot studies, we have we have also demonstrated significant plasticity of white matter structure in association with antidepressant response to pharmacological treatment in the elderly depressed in the forceps minor; cingulum (cingulate gyrus), superior longitudinal fasciculus, inferior fronto-occipital fasciculus, anterior thalamic radiation and uncinate (Fig. 2).
Evidence for CVRF Effects on outcomes and MRI biomarkers. Several of our studies show relationships among cerebrovascular risk factors, apathy, executive dysfunction, and depression. In our longitudinal follow-up study of elderly depressed subjects,26-28 we found that chronic depression is associated with presence and severity of apathy and cerebrovascular risk factors. Others have reported that severity of vascular burden is associated with depression severity and impaired performance on measures of cognitive control (i.e., inhibition/mental flexibility) and attention.28 In our initial study, we found that even within the normal range, there was a relationship between CVRF and brain function.29 In another study30 of subjects with greater CVRF, there was a pattern of increased fMRI activation on the paired associates learning task, nearly identical to that we reported with APOE-4 risk.29 Thus, even clinically benign increases in CVRF may have important consequences for cognitive and brain function.

b. Approach.
This research proposal incorporates a multidisciplinary investigative team based at the Semel Institute (Dr. Lavretsky, PI; Siddarth and Ercoli) and the Brain Mapping (Dr. Narr).

The rationale for the duration of the interventions, follow up, and blinding procedures: The proposed study is of standard duration for the geriatric population requiring 12 weeks or longer trials to document antidepressant efficacy.

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

Subjects: We anticipate screening about 100 subjects to recruit 60 older depressed adults (>60 y.o.) who will be randomized to receive 20-120 mg of levomilnacipran blindly with increment dose titration 20 mg per day -3 days; 40 mg per day-3 days. Based on efficacy and tolerability, we will increase by 40 mg per day each following week 2nd-4th week the maximum recommended doses is 120 mg per day. The comparison group will receive similar blinded titration with matching placebo. Doses of the drugs will be adjusted according to individual tolerability and safety. We expect an attrition rate of about 10% based on our prior experience thus 54 subjects will complete the study. Patients will be assessed pre-treatment; and then weekly during the first four weeks and bi-weekly thereafter. At all visits, clinical ratings of mood, vital signs, and safety will be obtained.
Inclusion criteria: 1) The presence of a major depressive disorder diagnosed according to the DSM-IV criteria. 2) A 24-item Hamilton Rating Scale for Depression (HAMD) score of 17 or higher at baseline. 3) Mini-Mental State Exam (MMSE) score > 24.

Exclusion criteria: subjects will be excluded if they had 1) any current and/or lifetime history of other psychiatric disorders (except unipolar depression with or without comorbid generalized anxiety disorder), or 2) recent unstable medical or neurological disorders; 3) any disabilities preventing their participation in the study or in the MRI; 4) diagnosis of dementia; 5) acute suicidality; 6) those with known allergic reactions to milnacipran, uncontrolled narrow angle glaucoma, seizures, poorly-controlled hypertension or ischemic changes on ECG, serotonin syndrome, or the recently used MAOIs within last 4 weeks; 7) ineligible for MRI (e.g., metal in the body or claustrophobia)
Primary outcome will be measured and defined as follows: 1) Remission will be defined as HAMD scores of 6 or less for three consecutive weeks and at week 12; 2) Improvement in depression severity using HAMD scores.
Measures and Outcomes: Assessment instruments. All instruments 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. Inter-rater reliability sessions on all assessment instruments will be established at the beginning of the trial on the first 5 volunteers. Master level research associates supervised by the PI will be trained to be reliable in administering the diagnostic interview (SCID) as well as other behavioral assessments.

Diagnosis. Structured Clinical Interview DSM-IV (SCID)31 will be used to make a diagnosis of major depression or rule out other diagnosis (e.g., psychosis and dementia) according to the DSM-IV criteria at screening. A trained interviewer, using the SCID-IV will complete a comprehensive structured clinical interview. The final diagnosis will be determined by consensus during weekly investigator meetings. The inter-rater correlation coefficient (ICC) for the SCID ratings among SCID interviewers is = 0.9.
Primary outcomes: Efficacy evaluations (administered at all visits or upon early termination): Hamilton Rating Scale for

Depression (HAMD)32 24-item, will be used to quantify mood symptoms.

Secondary measures (administered at all visits or upon early termination): Clinical Global Impression - Severity and Improvement scale (CGI).33 A measure of the overall the severity and clinical improvement over time (2 min) Geriatric Depression Scale (GDS),34 a self-assessment scale often used in geriatric depression trials (10 min).
Measures of comorbid neuropsychiatric symptoms (administered at baseline and at week 12 or upon early termination): Hamilton Anxiety Scale,35 a widely used measure of anxiety symptoms on a 0-5 scale (10 min). Apathy Evaluation Scale (AES),36 a measure of the severity of apathy (15 min). Unified Parkinson's Disease Rating Scale (UPDRS)37 used for the assessment of psychomotor slowing and extrapyramidal symptoms (10 min).
Measures of medical comorbidity (administered at baseline and at week 12 or upon early termination): Stroke Risk Factor Prediction Chart (SRF)38,39 of the American Heart Association for rating cerebrovascular risk factors (5 min). Cumulative Illness Rating Scale-Geriatric (CIRS-G),40 used for rating the severity of chronic medical illness in 14 organ-systems (15 min).
Health-Related Quality of Life and Physical functioning ((administered at baseline and at week 12 or upon early termination): Medical Outcomes Study Short Form 36-Item Health Survey (SF-36)41, an instrument that measures health-related quality-of-life, mental, physical, and social functioning (15 min). The Connor-Davidson Resilience scale (CD-RISC), as a measure of stress coping ability42 (5 min); the Quality of Life Enjoyment Scale (Q-LESS-Q),43 a brief assessment instrument of life satisfaction, which has been commonly used in the clinical trials in psychiatric populations including the elderly (5 min). We have included a self-reported physical activity record for monitoring physical activity in both groups (3 min).44

Neuropsychological assessment (at baseline, at 12 weeks): Our approach to cognitive assessment and analyses is based on our prior work and benefits from input from Dr. Linda Ercoli. We will use a focused test battery developed by Dr. Ercoli, assessing domains which have shown impairment in geriatric depression, according to prior research by our group45 and others: 9,46-48 (1) cognitive control, which relates to mental flexibility and inhibition and adjustment of behavior; (2) verbal fluency, which requires strategic searching/organization of verbal knowledge; (3) episodic memory: including explicit memory for verbal and nonverbal information; and (4) information processing speed and attention, including an indices of complex and sustained attention. Most of the measures have 2 or 4 alternate forms that will be important in repeating them during follow up. In addition to the cognitive outcome measures, 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 (WTAR),49 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. Finally, we will assess the validity of assignment to composite domains using confirmatory factor analysis. The tests variables derived from each and a priori composite domain assignment: Verbal Fluency (Category and Letter Fluency tests): Cognitive Control (Trailmaking test part B and Stroop Color-Word Interference test); Attention and Processing Speed (Trailmaking test part A; Stroop rapid color and word reading scores (averaged); Digit vigilance d-prime); and Episodic Memory (Rey Auditory Verbal Learning; Brief Visual Spatial Memory tests).

Safety evaluations. Physical examination and vital signs at baseline: pulse rate, systolic blood pressure, and body weight will be obtained at each visit, in addition to a 12-lead ECG at baseline, if any cardiac complaints are present. Laboratory tests (as listed below) will be performed at baseline. The UKU Side Effect Rating Scale,50 a comprehensive rating scale for monitoring adverse events of psychotropic drugs used in clinical trials, will be completed at all visits except screening.

Procedures: Telephone screening (15 min): All potential participants will be initially screened by telephone when they call for the study in response to an advertisement or by referral from their physician. 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: A research nurse and a research assistant 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. Informed consent (30 minutes); neuropsychiatric and physical examination, and laboratory tests to be performed in the first visit (2 1/2 hours). Dr. Lavretsky will obtain the informed consent prior to all evaluations, and will perform most neuropsychiatric and physical examinations. Eligibility will be assessed at screening and baseline. Participation may be terminated if the subject stops meeting the entry criteria. No subjects in the proposed study will meet the criteria for dementia and; therefore, all should have capacity to give informed consent for participation in the study. No subject will be asked to discontinue effective antidepressant medications. Discontinuation of the current ineffective antidepressants will be carried out by the patient's primary physician. Only subjects currently not taking psychotropic medications prior to the initiation of the study will be admitted into the study.

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. Hamilton depression rating scale (HAM-D) will be used to measure symptom severity. Inter-rater reliability for the total HAMD-24 score or the SCID diagnosis of depression has been excellent, as demonstrated by ICCs of 0.78 to 0.95.

Comorbid anxiety and insomnia will be assessed at baseline visit to decide whether the only allowed concomitant medication allowed in the trial will be lorazepam up to 1 mg/day should be used for treatment of chronic anxiety or insomnia, especially in the "habitual benzodiazepine users." We will control for lorazepam use in the statistical analyses. (In all of our pilot studies, the use of lorazepam did not bias the outcomes).

Medical evaluation. All subjects will receive an initial medical assessment including a complete physical examination with neurological and neuropsychiatric examinations, 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 subject's consent. If abnormal physical or laboratory results are considered responsible for depression, the subject will be excluded from participation. All subjects will be interviewed about their recent history of psychiatric and medical illnesses, recent psychosocial stressors, current medications, and health status. Because of the concerns of cardiovascular toxicity in older adults- we will do

ECG evaluations at baseline and during last visit.

Dementia and Mild Cognitive Impairment screening. We will screen subjects for possible incipient dementia, and then verify their condition by comparing baseline assessments to the one at follow up. This will include reviewing an extensive history and mental status exam together with corroborating information from the assessment of functional skills. 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; 3) neurological examination (UPDRS); 3) neuropsychological examination (detailed below); and 4) psychiatric evaluation (SCID-DSM-IV), as detailed above. Adjudication of dementia is based on DSM-IV criteria.51,52 At the consensus conference, additional information will be reviewed (e.g., family history, drug use). Mild Cognitive Impairment diagnosis. Subjects with mild cognitive impairment will not be excluded. We will use performances between -1.5 and -2 (SD) below age and education norms on one of two memory tests used in our cognitive battery according to a widely accepted practice, and control for it in the analyses.

Randomization and treatment schedule: 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 sign the informed consent form. All eligible subjects will be randomized to levomilnacipran or placebo group using a computer-generated random assignment scheme, which assigned subjects in a 1:1 ratio to each group. Randomization will be done prior to subject's being assigned to the groups.

Follow up assessment: The follow up will take place weekly for the first four weeks of treatment, every two weeks for the remainder of the study. Each follow up assessment will include measures of efficacy and safety. 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.

Study medications and treatment procedures. Subjects will be randomized to: 1) LMIL20-120 mg per day or 2) matching placebo. The allowed range of the drugs according to tolerability and efficacy assessments will be between 20-120 mg per day for LMILN. The dose finding procedures will be only performed in the first four weeks and after that will remain stable until the end of the acute trial, as it worked in our pilot study. We will assess the optimal dose of LMIL based on tolerability and safety in this population. The balance will be maintained between the efficacy and tolerability of medications. If symptoms worsen, the study drug will be tapered and discontinued. Subjects will be referred for clinical care at UCLA or the community. The PI will continue the observation for safety until the appointment is scheduled with the primary psychiatrist. The dose will be titrated according to the titration schedule, including if side-effects are mild or well tolerated and if CGI scores for improvement is 3 or higher. The titration rate is based on the currently recommended titration to achieve the greatest efficacy that may not work for geriatric patients. For that reason, we have safeguards against rapid titration with potential side-effects that will require a slower titration or staying at a lower dose.

Involvement in alternate treatments. All subjects will be medically stable prior to entry into the study protocol. However, if for medical or psychiatric reasons subjects engage in alternate treatments, they will be advised to inform the PI of this action. If the alternate treatment is judged to interfere significantly with the intervention, the subject will be withdrawn from the study. All changes will be assessed at each visit. We will measure the severity of depression, and monitor the symptoms of major depressive episode. Discontinuation of the current ineffective antidepressants will be carried out by the patient's primary physician. The responsibility for medical, psychiatric, nursing, and social care of subjects will remain with the individual's primary physician. Should the participant not have a physician in the area, a referral will be made to one in the patient's geographic area. With the subject's consent from a signed HIPPA form, the conclusions of their study evaluation will be shared with the primary physician.

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.

Anticipated outcomes. We also anticipate that improvement in depressive symptoms will be associated with the improvement in cognition, apathy, and fMRI biomarkers of brain connectivity.

Imaging Biomarkers: Imaging data will be acquired from each subject at baseline and at 12-weeks 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 with real time motion correction53 for the examination of brain structure and for use in network analyses ; 2) a matched bandwidth T2 sequence for the detection and quantification of WMHs and CSF; 3) rs-fMRI to examine treatment related changes in functional activity at rest and intrinsic network connectivity; and 4) high angular resolution diffusion imaging (HARDI) to isolate changes in white matter microstructure and structural connectivity. Both rs-fMRI and diffusion imaging will utilize recently developed accelerated multiband pulse sequences with optimized spatial and temporal resolution (Table 3).54,55 Notably, the same multimodal imaging protocol has been implemented for a NIH study addressing biomarkers of geriatric depression in association with escitalopram both with and without augmentation of memantine treatment. In a separate extramurally funded project, we are also using this protocol to examine treatment effects and brain aging associated with Kundalini yoga. We are thus able to pool data and/or contrast results across studies as might be appropriate.

Resting State fMRI: During acquisition of blood-oxygen-level-dependent (BOLD) rs-fMRI data, subjects will remain awake with their eyes closed. Preprocessing will occur in a parallelized supercomputing environment using FSL56-58 and custom processing modules. Independent components analysis (ICA),59,60 will estimate the optimal number of components for each subject and time point and identify components representing artifacts. After low pass filtering (0.1-0.01 Hz) and transformation into atlas space, the best-fit default mode network (DMN) and executive and memory function network will be selected for each subject/time point for higher-level analysis. In follow-up analyses, seed regions-of-interest (ROIs) will be employed to examine voxel-level correlations between particular network nodes.60-62 In addition to subtracting changes between baseline and follow-

up scans to determine associations with clinical response and neuropsychological function, 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. Notably, resting state activations are highly reproducible over time63 and experience-based neural plasticity in resting state connectivity has been shown over periods as short as 2-9 days.64 Recent research also shows significant changes in fronto-limbic connectivity in association with antidepressant treatment such as ECT65,66 as we have also shown [Fig. 3].

Diffusion Imaging: Diffusion data will be analyzed using FSL tools and include correction for slice prescription and residual eddy current distortions, tensor fitting, and tract based spatial statistics (TBSS)67 Changes in white matter FA, indicating fiber coherence and integrity, and radial, axial and mean diffusivity that point to changes in axonal structure and myelination, will then be examined across time and in relation to clinical outcome and neuropsychological function. Tractography methods will augment whole brain tract analysis and will be used to extract particular fronto-limbic fiber pathways using seed regions from both anatomical and functional imaging data. More sophisticated HARDI reconstruction techniques will be explored to determine more sensitive approaches for identifying changes in structural connectivity across treatment groups. Our previous data has shown increased FA and complementary decreases in mean and radial diffusivity in association with ECT and links with treatment-related clinical response that appear associated with processes of myelination (Lyden et al., 2014) [Fig. 4].

Structural Imaging. Structural image analysis will incorporate: 1) volumetric and 2) tensor based morphometry (TBM) analysis methods. In brief, widely used Freesurfer http://surfer.nmr.mgh.harvard.edu/) processing streams that include segmentation of cortical and subcortical ROIs (with manual correction) will estimate regional tissue volumes for comparison across time and in association with clinical response. ROI segmentations will also be used for the connectivity analyses as described below. For whole brain analysis, TBM methods, shown as highly sensitive for detecting subtle changes in brain morphometry associated with maturation/aging or disease,68-74 will examine both global and local changes in brain tissue structure across treatment 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 and cross-sectional effects respectively at the voxel-level.68,71,75 Using general linear models (GLMs), discrete local volumetric changes in brain tissue structure may thus be determined across treatment groups, in association with clinical and cognitive measures, where rate of change in local tissue structure may be quantified.76 For example, we have applied TBM in 10 subjects with major depression scanned at baseline and after receiving six ECT treatments and 10 matched controls to show significant anterior cingulate volume reductions in patients vs. controls (Fig 5, top) and hippocampal volume expansions between baseline and the 6th ECT in patients (Fig 5, bottom). These structural changes demonstrate treatment-associated plasticity and confirm detection of treatment change over a relatively short period of time, (2-3 weeks).

Network Connectivity: Based on observations that brain regions are interconnected and that these connectivity patterns exhibit certain regularity as well as randomness associated with “small world networks”, we will use graph theory-based methods to determine whether changes in network connectivity reflect plasticity associated with treatment response. Specifically, diffusion and anatomical data will be used to capture features such as local clustering (between cortical ROIs obtained from the structural analyses described above) combined with long-distance connections between clusters (white matter tracts) [Fig. 6].77-82 Connectivity metrics will include overall strength, coherence, and efficiency in local networks and globally across the entire brain.

WM Hyperintensities (WMH). The 3D T2-space images will be used to visualize WMHs by employing a semi-automated WMH identifier.83 Briefly, WMH burden will be assessed based on the signal intensities of co-registered 3D MEMPR and T2 images, and population statistics on the spatial distribution and neighborhood structure of WM lesions. GLM and multiple regression analyses will determine links between WM burden, clinical measures and vascular risk factors in each group, which may be controlled for other analyses.

The drug placebo differences in geriatric depression are minimal within 5% of each other averaging about 30-40% each. Because we are addressing neural mechanisms of antidepressant response, placebo-controlled study will help evaluate this better than another active comparator. We are skilled in monitoring risks and side-effects of drugs, including emerging and worsening symptoms of depression and suicidality.

Depression and Suicidality.
We will include the Columbia Suicide Rating Scale as a supplemental measure of suicidality and worsening of depression. The measure is designed to include all suicide-relevant variables as well as other risk and protective factors to assist the study doctor in weighing these factors for determining overall risk.

- 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 participants make up to 10 visits in 12 weeks (three months) to the study site during their participation. Each participant will be required to commit approximately 10 hours in 3 months: visit 1 (2 hours); visit 2 (2 hours); visit 3-9 (each 30 minutes); visit 10 (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. Data will be analyzed using the SAS (v9.3) statistical package. Data will be examined initially to identify issues such as departures from normality, which might suggest the need for transformation (e.g., logarithmic). Demographic variables (e.g., age, gender, etc.) and variables characterizing the course of depression (e.g., age of onset, chronicity, number of episodes, length of the current episode, etc.) will be compared by treatment group and examined in relation to outcome variables; this would define one possible set of appropriate covariates, if needed. Correlations (a) among outcome measures and (b) among potential covariates in the same domain will be examined to eliminate redundancy via possible data reduction, e.g., formation of composite scores or selection of single measures from sets of highly inter-correlated variables. Corrections for multiple significance testing will be performed within measurement domains when multiple measures are involved using Simes methods. Tests of the primary hypotheses that specify a predefined outcome measure will not be adjusted.

Hypothesis 1: The primary analyses will focus upon HAM-D24 scores and will be analyzed using general linear mixed model analysis (e.g., SAS PROC MIXED). The two treatment groups will be compared for time course of HAM-D-24 with the initial endpoint EOT at 12 weeks. Covariates may be included in the model as noted above. In addition, likelihood ratio ?2 comparison will examine group differences in remission (HAM-D24 =6) and response (HAM-D24 =10) at EOT. Analyses for the cognitive outcome variables will be akin to those described above for the continuous HAM-D scores. As noted in the Neuropsychological Assessment section, there are four cognitive domains that are being assessed. Of these, the two primary cognitive domains of interest for this proposal are Cognitive Control and Episodic Memory. A separate general linear mixed model as above will be estimated using these two domain scores as dependent variables. The remaining domains, namely Verbal Fluency and Information Processing/Attention will be examined as secondary outcome measures. Apathy will be examined using the AES total score and quality of life using SF-36 scores in similar mixed models.

Hypothesis 2: We will examine adverse events in the two treatment groups. A detailed comparison of the number as well as type of side-effects in the two treatment groups will be conducted using chi-square tests.

Hypothesis 3: LMIL will lead to improved functional connectivity in brain network activity as measured with resting state (rs-) fMRI, and plasticity in brain macro- and micro-structure as measured with structural MRI and DTI compared to the PBO. To address these hypothesis, summary MRI measures (e.g., substructure volume, diffusion metrics) will be included in the GLMMs as "covariates of interest." For whole brain or structure voxel-level or point based measures (e.g., thickness or activation), the GLMMs will be implemented in R (www. R.org). Time (of scan) will be treated as a continuous variable with random intercepts and slopes to account for within-subject correlations between repeated measurements to assess change and interactions amongst the interventions. Difference scores between baseline and 12-week follow-up may be substituted for some analyses. FDR and/or permutation methods will be used to control for multiple anatomic comparisons in whole-brain contexts.

Hypothesis 4: 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 of emotional responsivity; working memory and connectivity 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.

Power. With a significance level (alpha) of 0.05, 80% power, and N = 30 in each treatment arm, we can detect an effect size (ES, difference between group means as a multiple of the standard deviation) of 0.7. Using appropriate covariates such as age of onset, chronicity, and number of episodes can be expected to reduce variance and increase power for a given difference in mean, hence the two-sample power computations are conservative for this situation. This study will thus yield sufficient pilot data to justify conducting a larger study in the future.

Data management. Data management and analysis support will be provided by the UCLA SI-STAT services and Dr. Siddarth will supervise the data gathering duties of the study coordinator, including reviewing all data entry forms. 1. Randomization. The pre-study forms must be submitted before a patient can be randomized. A separate portion of the database will also be maintained for patients screened but not enrolled or randomized. Randomization schedules will be prepared in a masked manner by the statistician. 2. Data submission and quality control. Data forms will be delivered from the originating location to the central data unit within one week of being generated. When errors, omissions, or unclear information is detected on the paper forms, a copy

will be returned for corrections. The data manager will generate monthly reports summarizing missing and incorrect data will be sent to the PI. 3. Data confidentiality. 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. Access to the data will be password protected with only authorized persons having knowledge of the password.

ID: IRB#14-001827 View: NEW 11.1 - Characteristics of the Study Population

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:**
60

3.0 **How many participants do you expect you will need to recruit, consent and/or screen to meet the target number above?**
100

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-IV criteria. 2) A 24-item Hamilton Rating Scale for Depression (HAMD) score of 17 or higher at baseline. 3) Mini-Mental State Exam (MMSE) score > 24.; 4) Aged 60 years and older; 4) No acute suicidality based on item #3 HAMD score <2 (Subjects with active suicidal ideations with or without a plan, item #3 HAMD-24 score = 3, will be excluded from participation).

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 1) any current and/or lifetime history of other psychiatric disorders (except unipolar depression with or without comorbid generalized anxiety disorder), or 2) recent unstable medical or neurological disorders; 3) any disabilities preventing their participation in the study or in the MRI; 4) diagnosis of dementia; 5) acute suicidality; 6) those with known allergic reactions to milnacipran, uncontrolled narrow angle glaucoma, seizures, poorly-controlled hypertension or ischemic changes on ECG, serotonin syndrome, or the recently used MAOIs within last 4 weeks; 7) ineligible for MRI (e.g., metal in the body or claustrophobia).; 8) under the age of 60 years.

6.0 ***How (chart review, additional tests/exams for study purposes, etc.), when and by whom will eligibility be determined?**
Procedures: Telephone screening (15 min): All potential participants will be initially screened by telephone when they call for the study in response to an advertisement or by referral from their physician. 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: A research coordinator and a research assistant 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. Informed consent (30 minutes); neuropsychiatric and physical examination, and laboratory tests to be performed in the first visit (2 1/2 hours). Dr. Lavretsky will obtain the informed consent prior to all evaluations, and will perform most neuropsychiatric and physical examinations. Eligibility will be assessed at screening and baseline. Participation may be terminated if the subject stops meeting the entry criteria. No subjects in the proposed study will meet the criteria for dementia and; therefore, all should have capacity to give informed consent for participation in the study. No subject will be asked to discontinue effective antidepressant medications. Discontinuation of the current ineffective antidepressants will be carried out by the patient's primary physician. Only subjects currently not taking psychotropic medications prior to the initiation of the study will be admitted into the study.

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. Hamilton depression rating scale (HAM-D) will be used to measure symptom severity. Inter-rater reliability for the total HAMD-24 score or the SCID diagnosis of depression has been excellent, as demonstrated by ICCs of 0.78 to 0.95.
Comorbid anxiety and insomnia will be assessed at baseline visit to decide whether the only allowed concomitant medication allowed in the trial will be lorazepam up to 1 mg/day should be used for treatment of chronic anxiety or insomnia, especially in the "habitual benzodiazepine users." We will control for lorazepam use in the statistical analyses. (In all of our pilot studies, the use of lorazepam did not bias the outcomes).

Medical evaluation. All subjects will receive an initial medical assessment including a complete physical examination with neurological and neuropsychiatric examinations, 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 subject's consent. If abnormal physical or laboratory results are considered responsible for depression, the subject will be excluded from participation. All subjects will be interviewed about their recent history of psychiatric and medical illnesses, recent psychosocial stressors, current medications, and health status. Because of the concerns of cardiovascular toxicity in older adults- we will do ECG evaluations at baseline and during last visit.

Dementia and Mild Cognitive Impairment screening. We will screen subjects for possible incipient dementia, and then verify their condition by comparing baseline assessments to the one at follow up. This will include reviewing an extensive history and mental status exam together with corroborating information from the assessment of functional skills. 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; 3) neurological examination (UPDRS); 3) neuropsychological examination (detailed below); and 4) psychiatric evaluation (SCID-DSM-IV), as detailed above. Adjudication of dementia is based on DSM-IV criteria.51,52 At the consensus conference, additional information will be reviewed (e.g., family history, drug use).

Mild Cognitive Impairment diagnosis. Subjects with mild cognitive impairment will not be excluded. We will use performances between -1.5 and -2 (SD) below age and education norms on one of two memory tests used in our cognitive battery according to a widely accepted practice, and control for it in the analyses.

Randomization and treatment schedule: After all screening and baseline test results are reviewed and eligibility criteria are confirmed by Helen Lavretsky, M.D., medications will be dispensed if patients continue to meet eligibility criteria and sign the informed consent form. All eligible subjects will be randomized to levomilnacipran or placebo group using a computer-generated random assignment scheme, which assigned subjects in a 1:1 ratio to each group. Randomization will be done prior to subject's being assigned to the groups.

Monitoring of Suicidality.
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 third item of the Hamilton Depression Scale during each visit to the site. Monitoring for SI will be done at each visit independent of the outcome assessment. The blind rater will be instructed to inform the PI of scores = 3. Subjects with active suicidal ideations with or without a plan, HAMD-24 score = 3, will be excluded from participation. We will call subjects between visits to monitor suicidal ideations. We will encourage participation of their family members in the study who will be encouraged to call the patient and the study staff in case suicidal ideations emerge during the study. In the presence of persistent suicidal ideations, subjects will be discontinued from the study and referred to clinical services or to the community for treatment.

ID: IRB#14-001827 View: NEW 11.2 - Characteristics of Study Population

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

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
- [x] 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.**

- [x] 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#14-001827 View: NEW 14.1 - Risks & Benefits

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

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 participants may not experience any benefit from participating in this study. The possible benefits from being in this study may include an evaluation of symptoms, general health discussions with the study doctor and help in referrals for additional treatment if needed. Participants may possibly experience the relief of the symptoms of depression.

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

This study will help the researchers learn more about the study medication which may help improve knowledge of a more effective treatment for depression in the elderly. Hopefully this information will help in the treatment of future patients with depression.

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.
The procedures involve more than minimal risk associated with potential side effects of the medications and drug-drug interaction. This research study may involve risks that are currently unforeseeable. Side effects of significant concern include increased irritability, agitation, or restlessness.

Levomilnacipran (FETZIMA) may cause other side effects, including: High blood pressure and/or increased heart rate;

Abnormal bleeding: Levomilnacipran may increase your risk of bleeding or bruising, especially if you take blood thinners (e.g., warfarin, Coumadin, or Jantoven), a non-steroidal anti-inflammatory drug (NSAID), or aspirin; Visual problems: Eye pain; changes in vision; swelling or redness in or around the eye. Only some people are at risk for these problems; Trouble urinating; Hypomania (manic episodes): Greatly increased energy; severe trouble sleeping; racing thoughts; reckless behavior; unusually grand ideas; excessive happiness or irritability, or talking more or faster than usual; Seizures or convulsions; Low salt (sodium) levels in the blood: Symptoms may include headache, difficulty concentrating, memory changes, confusion, weakness, and unsteadiness on your feet. Severe or sudden cases may produce hallucinations (seeing or hearing things that are not real), fainting, seizures, and coma. If not treated, severe low sodium levels could cause death. Elderly people may be at greater risk.

Lorazepam (Ativan) possible side effects (optional supplemental medication): Most adverse reactions to benzodiazepines, including CNS effects and respiratory depression, are dose dependent, with more severe effects occurring with high doses. In a sample of about 3500 patients treated for anxiety, the most frequent adverse reaction to Ativan (lorazepam) was sedation (15.9%), followed by dizziness
(6.9%), weakness (4.2%), and unsteadiness (3.4%). The incidence of sedation and unsteadiness increased with age. Other adverse reactions to benzodiazepines, including lorazepam are fatigue, drowsiness, amnesia, memory impairment, confusion, disorientation, depression, unmasking of depression, disinhibition, euphoria, suicidal ideation/attempt, ataxia, asthenia, extrapyramidal symptoms, convulsions/seizures tremor, vertigo, eye-function/visual disturbance (including diplopia and blurred vision), dysarthria/slurred speech, change in libido, impotence, decreased orgasm; headache, coma; respiratory depression, apnea, worsening of sleep apnea, worsening of obstructive pulmonary disease; gastrointestinal symptoms including nausea, change in appetite, constipation, jaundice, increase in bilirubin, increase in liver transaminases, increase in alkaline phosphatase; hypersensitivity reactions, anaphylactic/oid reactions; dermatological symptoms, allergic skin reactions, alopecia; SIADH, hyponatremia; thrombocytopenia, agranulocytosis, pancytopenia; hypothermia; and autonomic manifestations.

The most common side effects of Levomilnacipran include: Nausea or vomiting, constipation, sweating, increased heart rate, erectile dysfunction, and heart palpitations. The study doctor will be available by pager at (310) 825-0511 for 24 hours a day, 7 days a week. All subjects 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. Subjects will be asked to report any changes in medications, and warned against the use of alcohol. They will be asked to report the emergence of suicidal ideations immediately. Management of the side-effects will be performed as specified.

The risks of the neuropsychiatric assessments are minimal. The possible risks and/or discomforts associated with the procedures are also described in the consent form.

Potential Risks and Discomforts of MRI:
The MRI scanning procedure requires that you be confined in a small partially enclosed space. Some individuals find this to be uncomfortable and may exhibit symptoms of claustrophobia including nervousness, sweating or other minor discomfort. The sound of the MRI scanner can be quite loud; the subject will be given special ear plugs to minimize the noise. In addition, the magnetism of the machine attracts certain metals; therefore, people with these metals within their bodies (such as pacemakers, infusion pumps, aneurysm clips, metal prostheses, joints, rods, or plates) will be excluded from the study. The "metal" in dental fillings is less responsive to magnetism and is therefore allowed. The MRI technician will ask you if you have any metals within your body. The subjects will be expected to notify the investigator conducting the study of any metal implants, other than dental fillings. There are no other known side effects resulting from exposure to the MRI scan.

Depression monitoring.
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.
1. If a patient demonstrates worsening of their symptoms or no response by week 8 or during follow up (i.e., CGI-I score > 3) of treatment, they will be discontinued from the study and referred for appropriate clinical services.
2. Suicidal ideations with the HAMD item 3 score of 3 or greater
3.The participants will take 20-120 mg of LMIL per day with titration in blinded 40 mg pills prepared by the UCLA pharmacy. The only concomitant psychotropic medication allowed in the trial is lorazepam, 1 of mg or less a day. If patients are not able to tolerate these medications, they will be discontinued from the trial.

The PI will withdraw subjects and discontinue the study treatment if the subject demonstrates worsening symptoms. The study drug will be tapered and discontinued and subjects will be referred for clinical care at UCLA or the community. The PI will continue the observation for safety until the appointment is scheduled with the primary psychiatrist.

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:**
Patients will be exposed to potential side effects of the medications both levomilnacipran and lorazepam, which are moderate. Laboratory and neuropsychiatric tests carry minimal risk. We would like to emphasize that none of our subjects exposed to milnacipran in our pilot study have experienced any elevations in pulse or blood pressure to-date, or ECG changes, although the majority of the subjects had a history of cardiovascular disease and /or hypertension. The subjects with hypertension normalized their blood pressure and had no change in pulse rate with treatment. The risks will also be minimized by weekly frequency of contact with all subjects to serve as an additional safeguard to monitor worsening of depression, as well as the emergence of side-

effects or suicidal ideations. If depression symptoms worsen, the subjects will be given an appropriate referral by the study doctor to psychiatric services provided at UCLA or other mental health clinics within the community; as well as the study doctor will be available to communicate to the subjects primary care physician.

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).
The standard of care activities at UCLA include psychotherapy, cognitive behavioral therapy, and other antidepressant medications like Prozac, Zoloft, Pamelor, or electroconvulsive therapy (ECT). The subject may chose to be treated with one or more of these rather than participate in the study. The study doctor is available for questions about alternative therapy for subjects who decide not to enroll in the study. Also, the study drug levomilnacipran is available by prescription without participating in the research.

ID: IRB#14-001827 View: NEW 15.1 - Data & Safety Monitoring Plan

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#14-001827 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
- [ ] 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).**
- Data safety monitoring committee will be composed of David Merrill (geriatric psychiatrist) who will be available to monitor emerging suicidality and other psychiatric SAE, Prabha Siddarth (statistician) and Peifeng Hu (geriatrician) will oversee data safety on semi-annual basis or as needed in case of SAEs.

- 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 [x]

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.**
- Adverse events produced by levomilnacipran may occur. 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 PI may discontinue the study medication and may proceed with unblinding the treatment assignment or stopping treatment. We may discover undiagnosed mental and medical conditions in the process of the study, and we will ask for permission by means of a signed Permission to Use Personal Health Information form to report the results of the subjects examination to their primary physician or psychiatrist. 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.

  Discontinuation from the study will be considered if subjects experience:
  a. Changes on ECG or in cardiac enzymes indicating cardiac ischemia or a new onset arrhythmia;

b. The development of any severe side-effects on the UKU Side Effect Rating scale rated as 3 or greater.
We will monitor blood pressure and pulse at every visit. We will repeat the ECG once during the trial to ensure safety. If any changes on ECG that signify ischemia occur, we will obtain additional tests of cardiac enzymes to rule out myocardial infarction (MI) (e.g., CK-MB; troponin).
All adverse events will be reported to the subjects and to their primary physicians and the UCLA IRB/ DSMB committee within 10 days of PI's awareness.
1. If a patient demonstrates worsening of their symptoms or no response by week 8 or during follow up (i.e., CGI-I score >3) of treatment, they will be discontinued from the study and referred for appropriate clinical services.
2. Suicidal ideations with the HAMD item 3 score of 3 or greater
3. The participants will take 20-120 mg of LMIL per day with titration in blinded 40 mg pills prepared by the UCLA pharmacy. The only concomitant psychotropic medication allowed in the trial is lorazepam, 1 of mg or less a day. If patients are not able to tolerate it
4. These medications, they will be discontinued from the trial.
All dropouts will be analyzed by the reason for termination and the reasons will be classified as:
1. 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.
All SAE will immediately be reported to the IRB within 3 days or to the Study sponsor Forest Global Drug Safety of all SAE that occurs after informed consent is obtained and if Drug results in:
• Death
• Is an immediate threat to life
• Requires inpatient hospitalization, or prolongation of existing hospitalization
• Results in persistent or significant disability/incapacity
• For all AEs, the PI provide an assessment of causal relationship to the LMIL.

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.**
- In the end of the trial after the final 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.

  Discontinuation from the study will be considered if subjects experience:
  a. Changes on ECG or in cardiac enzymes indicating cardiac ischemia or a new onset arrhythmia;
  b. The development of any severe side-effects on the UKU Side Effect Rating scale rated as 3 or greater.
  We will monitor blood pressure and pulse at every visit. We will repeat the ECG once during the trial to ensure safety. If any changes on ECG that signify ischemia occur, we will obtain additional tests of cardiac enzymes to rule out myocardial infarction (MI) (e.g., CK-MB; troponin).

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 adverse events that meet the definition of an unanticipated problem will be reported as described below:
1. If a patient demonstrates worsening of their symptoms or no response by week 8 or during follow up (i.e., CGI-I score> 3 of treatment, they will be discontinued from the study and referred for appropriate clinical services.
2. Suicidal ideations with the HAMD item 3 score of 3 or greater.
3. The participants will take 20-120 mg of LMIL per day with titration in blinded 40 mg pills prepared by the UCLA pharmacy. The only concomitant psychotropic medication allowed in the trial is lorazepam, 1 of mg or less a day. If patients are not able to tolerate these medications, they will be discontinued from the trial.

The PI will withdraw subjects and discontinue the study treatment if the subject demonstrates worsening symptoms. The study drug will be tapered and discontinued and subjects will be referred for clinical care at UCLA or the community. The PI will continue the observation for safety until the appointment is scheduled with the primary psychiatrist.

All dropouts will be analyzed by the reason for termination and the reasons will be classified as:
1.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.

All SAE will immediately reported to the IRB or to the Study sponsor Forest Global Drug Safety of all SAE that occurs. For all AEs, the PI provide an assessment of causal relationship to the LMIL.

ID: IRB#14-001827 View: NEW 16.1 - Payment, Costs, and Injury

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:**
- We will offer reimbursement for parking of $13.00/day for up to $130.00.

- 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.**
-

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.

The subjects will receive a $100.00 honorarium for their participation in the 12 week trial ($10 per visit), and $50.00 per MRI scan ($100.00) for a total up to $200.

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

ID: IRB#14-001827 View: NEW 17.1 - HIPAA Authorization

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:__

☑ 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:**

☐ 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.**
- Administration of a drug through the UCLA pharmacy requires a medical record number and the pharmacy research data will be entered into the medical record. Researchers will access subjects' medical records.

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#14-001827 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:

☑ 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
- [x]
- [ ] Other
- [ ]

ID: IRB#14-001827 View: NEW 18.2 - Recruitment Methods

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 #
Levomilnacipran_Flyer.pdf	0.03
LMIL Ads.doc	0.02

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 as well as the UCLA-NPH Geriatric Evaluation clinic. We will also publish small advertisements in local newspapers 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#14-001827 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.**
12-001714; 12-000074

- 4.1
- **If you do not have the IRB#, please provide the title of the study.**
-

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.**

ID: IRB#14-001827 View: NEW 19.1 - Eligibility Screening

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

ID: IRB#14-001827 View: NEW 19.2 - Eligibility Screening - Plans

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

Eligibility Screening - Plans

You indicated that eligibility screening will be conducted during the recruitment process (Section 19.1/item 1). Please provide the following information.

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

(•) **Yes** ( ) No

- 1.1
- **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**
- 1.2
- **If private identifiable data will be collected during the screening, indicate your plans for retaining the data.**
-

☐	The data will be retained with identifiers
☐	
☐	The data will be retained without identifiers
☐	
☑	The data will be destroyed
☑	

-
  - 1.2.1
  - **If you chose more than one response above, explain.**
  - Identifiable information of potential subjects who fail the

screening criteria will not be retained. The data will be destroyed.

2.0 ***Indicate your plans for obtaining informed consent and/or parental permission for the screening procedures.**

Check all that apply.

- [x] Oral consent will be obtained for the screening procedures. Participants will not be asked to sign a consent form (Waiver of written consent).
- [ ] A waiver of informed consent is requested for the screening procedures
- [ ] A waiver of Research Authorization for HIPAA is requested for the screening procedures.
- [ ] Signed consent will be obtained prior to performing any of the screening procedures

- 2.1
- **If you checked more than one plan above, list the study groups and the plan that you will use for each.**

3.0 **Describe how screening will be performed.**

- 3.1
- **Attach screening script(s), if applicable.**

Document Name	Document Version #
LMIL Telephone Screening Form.doc	0.01

ID: IRB#14-001827 View: NEW 19.3 - Oral Consent - For Screening Procedures

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

Oral Consent - For Screening Procedures

You indicated that you are obtaining oral consent for the screening procedures (Section 19.2/Item 2). Please provide the following information.

1.0 ***Indicate the reason that you are requesting to conduct an oral consent process and/or parental permission instead of obtaining signed consent.**

- (●) The research is minimal risk and does not involve any procedures for which written consent is normally required outside the research setting (e.g., in everyday life written consent is not needed for minimal risk surveys, non-invasive health measurements, etc.) (45 CFR 46.117 c2)
- ( ) The only record linking the participants and the research would be the consent document, and the main risk of research would be a breach of confidentiality (45 CFR 46.117 c1).

  e.g., Participants could suffer from social stigma, embarrassment, or other harms if it became known that they participated in research that identified them as having issues including, but not limited to, risky sexual behaviors, HIV, or mental health problems.

If you indicated that the **main risk is a breach of confidentiality**, answer 1.1 if appropriate.

- 1.1
- **According to DHHS regulations at 45 CFR 46.117(c1) when the main risk of the research would be a breach of confidentiality and an oral consent process is used, each participant should be asked whether he/she wants documentation linking the subject with the research and the subject's wishes will govern.**
- **Check here if you want the IRB to consider allowing a waiver of this regulation so that you do not need to ask each subject if he/she wishes documentation.**

- ☑ Request to waive documentation linking the participant with the research

2.0 *__Provide a description of the oral screening procedures for the study.__

When a subject makes initial contact with the study team, the researchers will ask the subject to provide oral consent to undergo the telephone screening interview that is designed to determine initial eligibility. If the subject offers verbal consent, the telephone interview screen will commence and eligibility for an in-person screening interview will be determined. Telephone screens will only be performed by certified study staff or the PI.

ID: IRB#14-001827 View: NEW 20.1 - Informed Consent Process

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:

☑ **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#14-001827 View: NEW 20.3 - Description of the Consent Process

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

☑ 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.

- [x] 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.
- [x] 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
- [x] 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 #
LMIL Informed Consent Form 10-22-2015.doc	0.01
LMIL Informed Consent Form 10-22-2015_marked.doc	0.01

ID: IRB#14-001827 View: NEW 22.1 - Cultural Considerations

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.
- [x] **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.**
-

ID: IRB#14-001827 View: NEW 24.0 - Additional Information and/or Attachments

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 #

There are no items to display

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.**

ID: IRB#14-001827 View: NEW 100.0 - Instructions for Study Submission

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.

ID: IRB#14-001827 View: Display - Method Description

Audio, Visual or Digital Recordings

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

ID: IRB#14-001827 View: Display - Method Description

Behavioral Observations (only applicable if you selected Exempt Category 2 in section 5.3)

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

ID: IRB#14-001827 View: Display - Method Description

Certificate of Confidentiality

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. The project does not need to be funded by NIH to obtain a Certificate of Confidentiality. For additional information see http://grants.nih.gov/grants/policy/coc/

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

ID: IRB#14-001827 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#14-001827 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#14-001827 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#14-001827 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#14-001827 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#14-001827 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

Click "OK" below to return to the SmartForm page where you can select the appropriate response.
ID: IRB#14-001827 View: Display - Method Description

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.
ID: IRB#14-001827 View: Display - Method Description

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.
ID: IRB#14-001827 View: Display - Method Description

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

Click "OK" below to return to the SmartForm page where you can select the appropriate response.
ID: IRB#14-001827 View: Display - Method Description

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.

Click "OK" below to return to the SmartForm page where you can select the appropriate response.
ID: IRB#14-001827 View: Display - Method Description

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).

Click "OK" below to return to the SmartForm page where you can select the appropriate response.
ID: IRB#14-001827 View: Display - Method Description

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.

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

ID: IRB#14-001827 View: Display - Method Description

Radiation (Standard of Care or Investigational use of radioactive materials or ionizing radiation)

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

ID: IRB#14-001827 View: Display - Method Description

Substance Abuse Research (with Medication)

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

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

ID: IRB#14-001827 View: Display - Method Description

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

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

ID: IRB#14-001827 View: Display - Method Description

None of the above

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