STUDY PROTOCOL COVER PAGE

TITLE: Plasma Exosomal MicroRNAs as Promising Novel Biomarkers for Suicidality and Treatment Outcome

NCT NUMBER: NCT02418195

DOCUMENT DATE: July 11, 2019

Human Subjects Protocol (HSP)

Form Version: February 1, 2017

- You are applying for IRB review of the research described in this form.
- To avoid delay, respond to all items in order and include all required approvals and documents. For more tips, see the UAB IRB website.
- To complete the form, click the underlined areas and type or paste in your text; double-click checkboxes to check/uncheck.
- All responses should be Times New Roman, Bold, and Underlined.
- Submit all materials to AB 470, 701 20th Street South, Birmingham, AL 35294-0104.

Indicate the type of review you are applying for:

☒ Convened (Full) IRB ***-OR-***

☐ Expedited - See the Expedited Category Review Sheet, and indicate the category(ies) here:

☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

1. IRB Protocol Title: Plasma Exosomal MicroRNAs as Promising Novel Biomarkers for Suicidality and Treatment Outcome

2. Investigator and Contact Person

a. Name of Principal Investigator: **Yogesh Dwivedi, PhD**
Degree(s)/Title: **Professor** BlazerID: **ydwivedi**
Dept/Div: **Psychiatry & Behavioral Neurobiology** Mailing Address: **SC 1060** UAB ZIP: **0017**
Phone: **975-8459** Fax: **975-4462** E-mail: **yogeshdwivedi@uabmc.edu**

b. Name of Contact Person: **Samantha White** Title: **Clinical Trials Manager** Phone: **934-9189**
E-mail: **swwhite@uabmc.edu** Fax: **975-4462**

INVESTIGATOR ASSURANCE STATEMENT & SIGNATURE

By my signature as Principal Investigator, I acknowledge my responsibilities for this Human Subjects Protocol, including:

- Certifying that I and all key personnel comply with reporting requirements of the UAB Conflict of Interest Review Board;
- Certifying that the information, data, and/or specimens collected for the research will be used, disclosed and maintained in accordance with this protocol and UAB policies;
- Following this protocol without modification unless (a) the IRB has approved changes prior to implementation or (b) it is necessary to eliminate an apparent, immediate hazard to a participant(s);
- Verifying that all key personnel listed on the protocol have completed initial IRB training and will complete continuing IRB training as required;
- Verifying that all personnel are licensed/credentialed for the procedures they will be performing, if applicable;
- Certifying that I and all key personnel have read the *UAB Policy/Procedure to Ensure Prompt Reporting of Unanticipated Problems Involving Risks to Subjects or Others to the IRB, Institutional Officials, and Regulatory Agencies* and understand the procedures for reporting;
- Applying for continuing review of the protocol at least annually unless directed by the IRB to apply more frequently;
- Conducting the protocol as represented here and in compliance with IRB determinations and all applicable local, state, and federal law and regulations; providing the IRB with all information necessary to review the protocol; refraining from protocol activities until receipt of initial and continuing formal IRB approval.

Signature of Investigator: _____ **Date:** _____

3. Protocol Personnel

Including the PI, list all key personnel (each individual involved in the design and conduct of this protocol). See the Key Personnel Flowchart.

Complete the UAB (3.a.) and non-UAB (3.b) tables, as applicable. Use the checkboxes to show each individual's role, whether the individual has financial interests as defined by the UAB CIRB, and briefly describe the individual's protocol responsibilities and qualifications to perform those responsibilities. **Insert additional rows as needed.**

FDA: For studies involving investigational drugs, list all investigators who will be listed on FDA Form 1572 and include a copy of the 1572. Send the IRB a copy of Form 1572 any time you update the form with the FDA.

a. UAB Personnel (includes UAB affiliates and Children's of Alabama personnel)

Name, Degree, and Dept.	Blazer ID	Role	Financial Interest?*	Protocol Responsibilities and Qualifications (indicate if this person obtains consent)
Name: Yogesh Dwivedi Degree: PhD Department: Psychiatry & Behavioral Neurobiology	ydwivedi	Principal Investigator	☒No ☐Yes	Expert in studies pertaining to the neurobiology of psychiatric illnesses and molecular neuroscience
Name: Richard Shelton Degree: MD Department: Psychiatry & Behavioral Neurobiology	rshelton	☒Sub-Investigator ☐Other	☒No ☐Yes	Expert in studies pertaining to the neurobiology of psychiatric illnesses and molecular neuroscience
Name: Badari Birur Degree: MD Department: Psychiatry & Behavioral Neurobiology	bbirur	☐Sub-Investigator ☒Other	☒No ☐Yes	Experienced psychiatrist
Name: Ripu Jinda Degree: MD Department: Psychiatry & Behavioral Neurobiology	jindalr	☐Sub-Investigator ☒Other	☒No ☐Yes	Experienced psychiatrist
Name: Michael Falola Degree: MD Department: Psychiatry & Behavioral Neurobiology	mykeid	☐Sub-Investigator ☒Other	☒No ☐Yes	Experienced psychiatrist
Name: Samantha White Degree: BS, CCRC Department: Psychiatry & Behavioral Neurobiology	slwood76	☐Sub-Investigator ☒Other	☒No ☐Yes	Very experienced clinical research manager
Name: Roberta May Degree: MA Department: Psychiatry & Behavioral Neurobiology	bmay	☐Sub-Investigator ☒Other	☒No ☐Yes	Very experienced clinical research manager
Name: Nicholas Bossaller Degree: MBA Department: Psychiatry & Behavioral Neurobiology	bossalna	☐Sub-Investigator ☒Other	☒No ☐Yes	Very experienced clinical research coordinator
Name: Allison Stewart Degree: BA Department: Psychiatry & Behavioral Neurobiology	ams14	☐Sub-Investigator ☒Other	☒No ☐Yes	Experienced clinical research coordinator
Name: Kristine Pike Degree: BS	kp92lynn	☐Sub-Investigator ☒Other	☒No ☐Yes	Experienced clinical research coordinator

Department: **Psychiatry & Behavioral Neurobiology**				
Name: **Kayleigh Coleman Curry** Degree: **MPH** Department: **Psychiatry & Behavioral Neurobiology**	**kayleigh**	☐Sub-Investigator ☒Other	☒No ☐Yes	**Experienced clinical research coordinator**
Name: **David Otuada** Degree: **MPH** Department: **Psychiatry & Behavioral Neurobiology**	**daotuada**	☐Sub-Investigator ☒Other	☒No ☐Yes	**Experienced clinical research coordinator**
Name: **Bhaskar Roy** Degree: **PhD** Department: **Psychiatry & Behavioral Neurobiology**	**royb**	☐Sub-Investigator ☒Other	☒No ☐Yes	**Very experienced lab manager**
Name: **Kevin Prall** Degree: **BS** Department: **Psychiatry & Behavioral Neurobiology**	**kmprall**	☐Sub-Investigator ☒Other	☒No ☐Yes	**Very experienced lab technician**
Name: **John Samuel Irvin** Degree: **BA** Department: **Psychiatry & Behavioral Neurobiology**	**Jsi822**	☐Sub-Investigator ☒Other	☒No ☐Yes	**Experienced clinical research coordinator**

b. Non-UAB Personnel Relying on UAB IRB - If you are requesting that the UAB IRB serve as the IRB of record for anyone not affiliated with UAB, list these individuals below.

Name and Degree	From Institution with or without own IRB?	Financial Interest?*	Protocol Responsibilities and Qualifications (indicate if this person obtains consent)
Name: _____ Degree: _____ Institution: _____ Email: _____	☐Has own IRB but requests that UAB IRB serve as IRB of record?-***OR***- ☐Does not have own IRB and needs to rely on UAB IRB.	☐No ☐Yes	_____

***Financial Interest** – for each individual listed above, answer **Yes** or **No** as to whether the individual or an immediate family member has any of the following:

- An ownership interest, stock options, or other equity interest related to the investigator's institutional responsibilities of any value.
- Compensation greater than $5,000 in the previous two years when aggregated for the immediate family
- Proprietary interest including, but not limited to, a patent, trademark, copyright, or licensing agreement.
- Board of executive relationship, regardless of compensation.
- Any other Financial Interest as defined by the UAB CIRB.

UAB Personnel: If the individual or his/her spouse or dependent child has a Financial Interest, a disclosure has to be made to the UAB CIRB. A completed CIRB evaluation has to be available before the IRB can complete its review.

Non-UAB Personnel: If the individual has a Financial Interest, ***include a copy of the report from his/her own institution's conflict of interest review with this submission to the UAB IRB.***

c. Do the investigators listed above include any students using this research for their thesis or dissertation?

☒ No, continue with Item 3.d.

☐ Yes, complete the following

Student Name	Thesis/Dissertation Title

d. Is the principal investigator a student, fellow, or resident? ☐Yes ☐No

If Yes, complete items below and obtain signature of faculty advisor or supervisor:

Supervisor's Name: _____

Degree(s) / Job Title: _____

Additional Qualifications pertinent to the protocol: _____

Telephone: _____
E-Mail: _____
Signature: _____

e. Describe the principal investigator's activities related to this protocol and provisions made by the PI to devote sufficient time to conduct the protocol: **Dr. Dwivedi will oversee all aspects of the protocol including supervision of the research team. He will ensure that the data is maintained appropriately and will communicate with the UAB IRB in a timely manner.**

f. Is medical supervision required for this research? ☒Yes ☐No

If Yes, who will provide the medical supervision?

☐ PI will provide ***-OR-***

☒ Other:

Name: **Richard Shelton, MD** Telephone: **975-9295**

If other than PI, obtain signature of person providing medical supervision:

Signature _____

g. Describe your process for ensuring all key personnel are adequately informed about the protocol and their research-related duties and functions: **The research team all have IRB certification. In addition, prior to study initiation, a meeting will be held with all co-investigators and research staff to review the protocol procedures for obtaining informed consent, procedures that ensure accurate and reliable data collection, and roles and responsibilities of each person. Weekly meetings will be held to discuss issues which arise during the course of the study.**

4. Funding

Is this protocol funded? ☒Yes ☐No

If No, specify that costs of the protocol will be covered by funds from the UAB department or other source named: _____

If Yes, attach one copy of completed application or request for funding sent to sponsor, and complete a-d.

a. Title of Grant, Contract, or Agreement: **Plasma Exosomal MicroRNAs as Promising Novel Biomarkers for Suicidality and Treatment Outcome**

b. UAB PI of Grant, Contract, or Agreement: **Yogesh Dwivedi, PhD**

c. Office of Sponsored Programs (OSP) Assigned Number: **000507208**
(If not yet available, enter "Pending" and provide upon receipt from OSP.)

d. Sponsor, Funding Route:
(Check and describe all that apply)
(If subaward, list both the funding source and the institution receiving the direct award)

☒ Gov't Agency or Agencies—Agency name(s): **NIMH. The Data and Safety Monitoring Board (DSMB) will act in an advisory capacity to the National Institute of Mental Health (NIMH) Director to monitor participant safety, data quality and evaluate the progress of the study. Drs. Dwivedi and Shelton, University of Alabama at Birmingham, is conducting the NIH supported study above under a grant funded by the National Institute of Mental Health.**

☐ Department of Defense (DoD): Identify DoD component: _____
☐ Department of Energy (DOE)
☐ Department of Justice (DOJ)
☐ Department of Education
☐ NIH Cooperative Group Trial - Group name: _____
☐ Private Nonprofit (e.g., Foundation) - Name: _____
☐ Industry, investigator-initiated - Name: _____
Describe the funding arrangement: _____

NOTE: The UAB IRB typically only reviews industry-sponsored protocols that are investigator initiated or when the protocol qualifies for expedited review or involves gene therapy.

☐ UAB Departmental/Division Funds—Specify: _____

5. Locations Involved

a. Indicate all performance sites that will provide space, services, or facilities for the conduct of this protocol.

☒ UAB Hospital
☐ UAB Hospital - Highlands
☐ The Kirklin Clinic of UAB Hospital
☐ The Kirklin Clinic at Acton Road
☐ UAB Callahan Eye Hospital
☒ UAB Clinical Research Unit
☐ Children's of Alabama
☐ Birmingham Veterans Affairs Medical Center
☐ Jefferson County Department of Health
☒ Other (i.e., any performance site not listed above, including those covered by subawards related to this protocol) - Describe: **OPCR, Sparks Center 10th floor; Dr. Dwivedi's Lab, 7th floor Sparks Center; UAB Emergency Department, Center for Psychiatric Medicine; Heflin Center for Genomic Sciences, UAB Genomics Core Facility.**
NOTE: Documentation of IRB approvals from sites receiving subawards must be received by the UAB OIRB before funding will be released for that subaward.

b. Describe the space, service, or facilities available for the conduct of the research in the performance sites listed in Item 5.a (For research on UAB campus, include building names): **OPCR, Sparks Center (SC) 10th floor; Dr. Dwivedi's Lab, 7th floor Sparks Center (SC); UAB Emergency Department, Center for Psychiatric Medicine (CPM); Heflin Center for Genomic Sciences, UAB Genomics Core Facility.**

c. Is this protocol a clinical trial requiring clinical services at one of the performance sites listed in Item 5.a above? ☒Yes ☐No

If Yes, will any of the services be billed to either participants/their insurance or to the study account through the Hospital Billing Office (PFS) or the HSF Billing Office (MSO)? ☒Yes ☐No

If Yes, submit a Full Fiscal Approval Process (FAP)-designated unit submission to s complete a FAP submission and send to fap@uab.edu. For more on the UAB FAP requirements, go to FAP - SiteMinder Processes.

d. Is this a field study? ☐Yes ☒No

If Yes, describe the community and include information about how the community will be involved in the design, implementation and analysis of the research. This would include focus groups, training local facilitators/community health advisors: _____

e. Has this protocol been rejected or disapproved by another review board (another IRB, similar review board, or departmental review committee(s)) that authorizes the use of its patient populations? ☐Yes ☒No

If Yes, provide name(s) of the review board(s) and reason(s) not approved: _____
Attach copies of the disapprovals.
NOTE: If this protocol is subsequently rejected or disapproved by another review board, promptly notify UAB IRB.

f. Will the protocol be conducted at or recruit participants from the Birmingham Veterans Affairs Medical Center (BVAMC)? ☐Yes ☒No

If Yes, describe the involvement of the BVAMC: _____

Attach the VA IRB approval and VA IRB-stamped consent form(s), if applicable.
NOTE: See the BVAMC section of the IRB Guidebook for more information.

g. Will the protocol be conducted at or recruit participants from the Jefferson County Department of Health (JCDH)? ☐Yes ☒No
If Yes, describe the involvement of the JCDH and list the JCDH clinics being used: _____
Attach the JCDH Research Review Panel approval, if applicable.
NOTE: Human subjects research conducted at certain JCDH clinics requires review by the JCDH Research Review Panel. See the JCDH section of the IRB Guidebook for more information.

6. Clinical Trial

Does this protocol meet the following definition of a clinical trial? ☒Yes ☐No
**A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes. For more information, see the full definition of clinical trial here.*
If Yes, you will need to fulfill the following requirements (regardless of funding):

a. All key personnel must complete the Good Clinical Practices (GCP) training. For information on this requirement, visit the IRB website here.

b. This protocol must be registered on ClinicalTrials.gov. Provide the National Clinical Trial (NCT) identifier number: **NCT02418195**
If you have any questions regarding registering a study on ClinicalTrials.gov, email the UAB Center for Clinical and Translational Science at ccts@uab.edu.

7. Multi-Site Studies

a. Is this a multi-site study with the UAB investigator as the lead investigator? ☐Yes ☒No

b. Is this a multi-site study with UAB as a coordinating site? ☐Yes ☒No

c. If Yes to a or b, describe the management of information obtained in multi-site research that might be relevant to the protection of participants. Include, at a minimum, how the following items are managed:
- IRB approvals from other sites
- Unanticipated problems involving risks to participants or others. (For example, if there is an unanticipated problem involving risks to participants or others, which site is responsible for reporting it?)
- Interim results
- Protocol modifications

_____

8. Drugs

Will any drugs or supplements be *used or studied* in this protocol? ☒Yes ☐No
If Yes, attach the completed Drug Review Sheet.

9. Devices

a. Will any devices be *studied* in this protocol? ☐Yes ☒No

b. Will any *not FDA-approved* devices be *used or studied* in this protocol? ☐Yes ☒No
If Yes to a or b, attach the completed Device Review Sheet.

10. Special Approvals

a. Does this protocol involve the use of radioisotopes? ☐Yes ☒No
If Yes, attach documentation of approval from the Radiation Safety Division.

b. Does this protocol include patients with contagious infections (e.g., mumps, measles, chickenpox, TB, meningitis)? ☐Yes ☒No
If Yes, attach documentation of approval from the Infection Control Committee of the appropriate facilities.

c. Does this protocol involve obtaining remnant biopsy or surgical material from the Department of Pathology or any other source? ☐Yes ☒No
If Yes, attach documentation of approval from the entity or individual providing the materials (e.g., the UAB Division of Anatomic Pathology Release of Pathologic Materials).

d. Does this protocol require obtaining any remnant clinical laboratory specimens, body fluids, or microbiological isolates from the Department of Pathology or any other source? ☐Yes ☒No
If Yes, attach documentation of approval from the entity or individual providing the materials (e.g., the UAB Division of Laboratory Medicine Release of Pathologic Materials).

e. Does this protocol use stored (existing) specimens from a repository? ☐Yes ☒No
If Yes, attach documentation of approval for use of specimens, and describe how existing specimens are labeled: _____

11. Use of Specimens
Does this protocol involve the collection of specimens? ☒Yes ☐No
If Yes, complete 11.a-11.h.
If No, skip to Item 12.

a. How will specimens be obtained, processed, distributed, and stored? **Whole blood samples (60 ml, about 4.5 tablespoons for controls and 160mLs over 3 days for MDD participants) will be collected by phlebotomy by a very experienced health care professional. The DNA, RNA, and microRNAs will be extracted and stored in the Dr. Dwivedi lab. The RNA and microRNA samples will be sequenced at the Heflin Center for Genomic Sciences, UAB Genomics Core Facility. The DNA will be analyzed in the Dwivedi lab for genomic methylation. For those with MDD without safety labs completed within the previous 10 days, an additional 10 ml will be drawn and analyzed at the UAB Outreach Labs prior to the infusion for safety.**

b. How will specimens be labeled (e.g., unique identifier, medical record number, Social Security number, name, date of birth)? **The biological sample will be labeled with a unique identifier number.**

c. How will clinical data associated with the specimens be collected and stored? **Clinical data will be obtained from the participant by specially trained clinical coordinators/raters and stored on an encrypted database. Hard copies of interviews will be stored in the research office.**

d. What participant-identifying information will be collected and linked to the specimens? **When an individual is enrolled in the study, each person is assigned a unique identification number that is used to identify all data associated with that person, including hard copy, biological data, and computerized data.**

e. What steps will be taken to maximize the confidentiality of linked identifiers? For example, procedures could include using a password-protected computer database to link identifiers, with limited personnel knowledgeable of the password, or coded identifiers released without the ability to link to clinical data (also called "stripped" or "anonymized" specimens). **The PI will maintain a code which links identification numbers to personal identifiers. At no point during or after the study will the PI provide this linkage code to any other investigator outside the project staff. Laboratory technical assistants who process the samples have no access to the clinical data. To further protect the confidentiality of participants, all information about participants in these studies will be stored in areas specially secured for keeping participant records. Data will be entered into an encrypted database, which will be online in a confidential, password-protected, HIPAA-compliant, anonymized file.**

f. Is genetic testing planned as part of this protocol? ☒Yes ☐No

If Yes, describe the planned genetic testing here. **Participants in the MDD groups will undergo ketamine 0.5 mg/kg IV infusion over 40 minutes. Blood will be collected at baseline (40mL), 30min (40mL), 180min (40mL), 24 hours post-infusion (20mL), and 14 days post-infusion (20mL) from which micro RNAs will be extracted and sequenced. Participants in the control group will have blood collected (60mL) from which micro RNAs will be extracted and sequenced.**

g. Will specimens be stored for future use? ☒Yes ☐No

If Yes, indicate whether they will be used for the disease under study in this protocol or research on other diseases. **The biological samples may be used for future studies of mental illness with documentation of IRB approval.**

h. Will specimens be shared with other investigators in the future? ☒Yes ☐No

If Yes, answer i. and ii.

i. What identifiers, clinical information and demographic information will be shared; or will the specimens be stripped of identifiers (i.e., anonymized)? **The samples will be anonymized, unless other investigators receive appropriate IRB approval.**

ii. Outline your procedure for assuring IRB approval for release and use prior to release of specimens. **Other investigators may request permission to use the de-identified samples and must provide documentation of IRB approval before the samples will be released.**

NOTE: Investigators who receive and/or use these specimens must document approval from the appropriate IRB(s) before the specimens may be released.

12. Gene Therapy

Does this protocol involve gene therapy or administering recombinant materials to humans? ☐Yes ☒No

If Yes, submit the Gene Therapy Project Review Panel Report ***-OR-*** the Protocol Oversight Review Form For Clinical Vaccine Trials, as applicable.

13. HIPAA Privacy and Security

Will the PI or others obtain, review, or make other use of participants' "protected health information" (i.e., information, whether oral or recorded in any form or medium that (a) is created or received by a health care provider and (b) relates to past, present, or future physical or mental health or condition of an individual; or provision of health care; or payment for provision of heath care)? ☒Yes ☐No

If Yes, complete Items 13.a-13.f.

If No, skip to 14.

a. Will the data/information be stored or managed electronically (on a computer)? ☒Yes ☐No

b. Is the principal investigator requesting that the UAB IRB waive patient HIPAA authorization from another institution or entity (e.g., insurance company, collaborating institution)? ☐Yes ☒No

If Yes, attach copies of the privacy notices from each institution/entity, and provide the name of each institution/entity: _____

c. Indicate which of the entities would provide health information for this protocol, maintain health information as it was collected for this protocol, and/or store health information after it has been collected for this protocol.

☒ UAB Hospital or UAB Hospital - Highlands
☐ The Kirklin Clinic of UAB Hospital or Acton Road (and/or associated clinics)
☐ UAB Callahan Eye Hospital
☐ Children's of Alabama
☐ Jefferson County Department of Health
☐ School of Dentistry
☐ School of Health Professions

☒ School of Medicine
☐ School of Nursing
☐ School of Optometry
☐ University of Alabama Health Services Foundation
☐ UAB Health Centers
☐ Viva Health
☐ Ophthalmology Services Foundation
☐ Valley Foundation
☐ Medical West - UAB Health System Affiliate
☐ None - **If None, skip to Item 14.**

d. Indicate any information systems that will be the sources of information used for the protocol.

☒ A system maintained centrally by UAB Health System (these include the following: HealthQuest for registration, billing, and patient administration; PowerInsight (clinical data warehouse); Cerner IMPACT for PowerNotes for meds, Lab, Radiology, UED, Surgery

NOTE: If a researcher needs information in a specified format or a specified time, the researcher must confirm with the unit who can supply the information/service that the request can be met before writing the information/service into the research protocol. In addition, the researcher must be aware that these services may have a cost attached that should be considered in the research budget.

To request access to clinical systems for research purposes, visit https://www.oneuabmedicine.org/web/hsis/technical-support, click "Accounts Request" and complete the form indicating access for research purposed.

☐ Another system on a UAB server - Describe: _____

e. Indicate which of the listed identifiers will be accessed, associated and/or linked with the protected health information (PHI) used for this protocol.

☒ Names
☒ Geographic subdivisions smaller than a state
☒ Elements of dates (except year) related to an individual
☐ Telephone numbers
☐ Fax numbers
☐ Email addresses
☒ Social security numbers
☒ Medical record numbers
☐ Health plan beneficiary numbers
☐ Account numbers
☐ Certificate/license numbers
☐ Vehicle identifiers and serial numbers
☐ Device identifiers and serial numbers
☐ Biometric identifiers
☐ Web universal resource locators (URLs)
☐ Internet protocol address numbers
☐ Full-face photographic images
☐ Any other unique identifying number - Describe: _____
NOTE: Codes are not identifying as long as the researcher cannot link the data to an individual
☐ None - **If None, skip to Item 14.**

f. Choose one plan to describe your use of the personal health information:

☐ The data collected meet the specifications for a "limited data set" (LDS)

-If the LDS will leave the covered entity or will be received from another covered entity you will need a Data Use Agreement

☒ Research staff will obtain authorization from each participant to use the information
-Include the HIPAA Authorization form, complete except for participant name and IRB protocol number, as the final page of the consent form

☐ PI requests waiver of authorization to use the information
-Attach Waiver of Authorization and Informed Consent form

PROPOSED RESEARCH

- The IRB will not accept grant applications and/or sponsor's protocols in lieu of the items as outlined below.
- Do not separate responses from items. Instead, insert your response to each item below the item, keeping the information in the order of this form.

14. Purpose - in nontechnical, lay language

a. Summarize the purpose and objectives of this protocol in one short paragraph. **We aim to examine whether neural-derived exosomal miRNAs are differentially expressed that are specific to suicidal ideation or behavior, and which by affecting specific miRNA targets and pathways, are associated with suicidal behavior and response to ketamine. We will examine the following groups of subjects: 1) major depressive disorder (MDD) with a recent suicide attempt (in past 2 weeks), 2) MDD with serious ideation without recent suicide attempt (in the past 6 months), 3) MDD without clinically significant suicidal ideation or suicide attempt in the past 6 months, and 4) healthy controls. Both suicidal and non-suicidal MDD will be given ketamine (0.5mg/kg, IV) and blood drawn at 30 and 180 min post-infusion to measure changes in miRNAs. This is a Phase II study. We will also include 15 participants who have a primary psychiatric diagnosis, other than MDD, and have made a recent suicide attempt or recent suicidal ideation (Group 5) for the following reason: Rationale: To date, this study has assessed micro RNAs as potential biomarkers for suicidality in the context of major depression (MDD). However, any identified biomarker could be specific for suicidality in the specific context of MDD, and may not be valid in other instances of suicidality, for example, in the context of bipolar disorder, psychosis, substance use disorders, or personality disorders. The purpose of this revision is to determine if the identified biomarkers extend to instances of suicidality other than the MDD context. Benefit: The identification of a suicidality biomarker (sometimes called a "biosignature") may be helpful to both researchers and clinicians to identify risk for suicide. However, it is critical at this juncture to determine if suicidality in other clinical diagnostic contexts have the same or different biosignatures. Group 5 participants will not receive the ketamine infusion.**

b. Describe how outcomes will be measured for this protocol. _____

15. Background - in nontechnical, lay language

Summarize in 2-3 paragraphs past experimental and/or clinical findings leading to the design of this protocol. Include any relevant past or current research by the PI. For drug and device studies, summarize the previous results (i.e., Phase I/II or III studies). **Suicide is the 3rd leading cause of death in the US ages between 15-34 years and about one million people commit suicide every year world-wide. Thus, there is a desperate need for identifying risk factors and for noninvasive, reliable biomarkers that can be used for early detection of suicidality and treatment response. Recently, microRNAs (miRNAs) have emerged as an important class of small non-coding RNAs that bind to 3'UTR of mRNAs and suppress the translation and/or stability of specific target genes. Since miRNAs show a highly regulated expression, they contribute in the development and maintenance of a specific transcriptome and thus have the unique ability to influence physiological and disease phenotypes. Our recent studies show that the expression of a group of miRNAs is altered in brain of depressed subjects and that they are involved in coping response to stress. In addition, our preliminary data indicate that a subset of miRNAs is specifically altered in brain of suicide subjects regardless of psychopathology, suggesting**

that miRNAs can distinguish suicidality. Recently, circulating miRNAs are under intense investigation and have been extremely useful in detecting and following the course of various diseases. Neural miRNAs are responsive to environmental, synaptic, and pathological changes and can be actively secreted by cells such as exosomes from brain into blood. These exosomes bear cell-type specific surface markers. Using a neural specific surface marker, we successfully isolated neural-derived exosomes and found that these exosomes are enriched with miRNAs/mRNAs that are expressed in brain. Using this novel approach we aim to examine whether neural-derived exosomal miRNAs are differentially expressed that are specific to suicidal ideation or behavior, and which by affecting specific mRNA targets and pathways, are associated with suicidal behavior and response to ketamine. We will examine the following groups of subjects: 1) major depressive disorder (MDD) with a recent suicide attempt (in past 2 weeks), 2) MDD with serious ideation without recent suicide attempt (in the past 6 months), 3) MDD without clinically significant suicidal ideation or suicide attempt in the past 6 months, and 4) healthy controls. Both suicidal and non-suicidal MDD will be given ketamine (0.5 mg/kg, IV) and blood drawn prior to infusion and at 30 min, 180 min, 24 hours, and 14 days post-infusion to measure changes in miRNAs. We also propose a parallel human postmortem brain study to examine whether changes in miRNAs in suicidality correspond to miRNA changes in brain by comparing dlPFC and hippocampus from MDD suicide, MDD non-suicide, and control subjects. With this we attempt to achieve: 1) whether suicidal ideation or behavior is associated with differences in the expression of specific miRNAs, 2) whether anti-suicidal/antidepressant effects of ketamine is associated with miRNAs changes, and 3) whether miRNA/mRNA-regulatory pathways contribute to suicide pathogenesis and treatment response. Our study will provide a novel avenue for the development of miRNAs as "molecular tool" to identify suicidality and treatment response and in generating target based therapies to treat this devastating disorder.

16. Participants (Screening and Selection)

a. How many participants are to be enrolled at UAB (if other sites relying on UAB IRB, list the number for each site)? **340**

If multi-site study, total number at all sites/institutions: _____

b. Describe the characteristics of anticipated or planned participants (if multiple groups, repeat list for each group).

Sex: **Male and Female**

Race/Ethnicity: **all**

Age: **18-65. Participants over the age of 65 have been excluded because this is a study of depressed subjects, some of which, in this age group, may also have cognitive impairments. Those over 65 have been excluded in order to not confound the results by inadvertently including those with cognitive impairment.**

Health status: **There will be four groups of participants (n=60 per group) enrolled/randomized: 1) major depressive disorder (MDD) with a recent suicide attempt (in past 2 weeks), 2) MDD with serious ideation without recent suicide attempt (in the past 6 months), 3) MDD without clinically significant suicidal ideation or suicide attempt in the past 6 months, and 4) healthy controls. There will be also be a fifth group (n=15) 5) Diagnosis of other primary psychiatric disorder as determined by the MINI, such as: bipolar disorder, personality disorders, psychotic disorders, post-traumatic stress disorder, obsessive-compulsive disorder, dissociative disorders, without any history of MDD diagnosis, with recent suicide attempt or suicidal ideation (past 2 weeks).**

c. From what population(s) will the participants be derived? **Patients with Major Depressive Disorder or other psychiatric disorder diagnosis will be recruited from individuals in the UAB Emergency Department, Center for Psychiatric Medicine, or UAB-Highlands. Others will be recruited from the outpatient psychiatric and/or research clinics, Community Psychiatric Clinic, or self-referred.**

Describe your ability to obtain access to the proposed population that will allow recruitment of the necessary number of participants: **As a psychiatrist in the Department of Psychiatry, the co-**

principal investigator, Dr. Richard Shelton, sees many people in his practice that meet eligibility criteria for the study. In addition, recruitment materials will be posted for the general public so that potential participants may self-refer.

d. Describe the inclusion/exclusion criteria: **Inclusion Criteria**

All Participants:

1. Age 18-65
2. Physically healthy and capable of undergoing ketamine infusion
3. Willing and able to provide informed consent

Healthy Controls:

4. HAM-D 21 score < 8

MDD Participants:

5. Diagnosis of MDE as determined by the MINI
6. HAM-D 21 score ≥ 16

MDD or Group 5 Participants with Suicide Attempt:

7. Suicide attempt occurred within past 2 weeks

MDD or Group 5 Participants without Suicide Attempt, with SI:

8. For the time frame of the past 7 days, C-SSRS score ≥ 3

(If subject had a suicide attempt in past 6 months, discuss with PI. Allowed on case-by-case basis).

MDD Participants without Suicide Attempt without SI:

9. For the time frame of the past 7 days, C-SSRS score < 3

(If subject had a suicide attempt in past 6 months, discuss with PI. Allowed on case-by-case basis).

Group 5 Participants:

10. Diagnosis of other primary psychiatric disorder as determined by the MINI, such as: bipolar disorder, personality disorders, psychotic disorders, post-traumatic stress disorder, obsessive-compulsive disorder, dissociative disorders.

Exclusion Criteria

MDD Participants:

1. Systolic blood pressure > 150 and/or diastolic blood pressure > 90 at screening
2. A QTc > 480 as determined by an ECG

All Participants:

3. Pregnancy or lactation (women of reproductive potential must have a negative urine pregnancy screen)
4. Post-partum state (being within 2 months of delivery or miscarriage)
5. Homicide risk as determined by clinical interview
6. A lifetime history of psychotic disorder (included Group 5)
7. Any history of dissociation or dissociative disorder (included Group 5)
8. Bipolar disorder (included Group 5)
9. Pervasive developmental disorder
10. Cognitive disorder
11. Cluster A personality disorder (included Group 5)
12. Anorexia nervosa
13. Treatment with one of the following medications, known to affect the glutamate-NMDA receptor system (specifically:lamotrigine, acamprosate, memantine, riluzole, or lithium)
14. Alcohol or drug dependence (except nicotine and caffeine) within the last month or the use of any hallucinogen (except cannabis), including phencyclidine in the last month (NOTE that a positive UDS is not exclusionary except for hallucinogens, methamphetamine, or cocaine. People presenting intoxicated with alcohol may be included when a Breathalyzer test (Alco-Sensor IV) is negative as long as there is no history of recent dependence. (included Group 5-consult Dr. Shelton)
15. Any known hypersensitivity or serious adverse effect associated with ketamine treatment
16. Any clinically-significant medication condition or therapy that would preclude treatment with ketamine, to include: Recent myocardial infarction

17. Unstable angina
18. Active neoplasm in the past 6 months
19. Immunosuppressive or corticosteroid therapy within the last month, with the following exceptions: any inhaled, intranasal, topical or vaginal corticosteroids are allowed.
20. Chemotherapy
21. Head injury of loss of consciousness in the past 6 months.
22. any of the following disorders:
a) Rheumatoid arthritis
b) Lupus erythematosus
c) Autoimmune hepatitis (other hepatitis is OK if stable)
d) Autoimmune peripheral neuropathy (other peripheral neuropathy is OK)
e) Autoimmune pancreatitis (history of alcoholic pancreatitis is OK if resolved)
f) Behcet's disease
g) Crohn's disease (IBS is OK)
h) Autoimmune glomerulonephritis
i) Grave's disease
j) Guillain-Barre syndrome (if active)
k) Hashimoto's thyroiditis
l) Autoimmune polymyositis or polymyalgia (fibromyalgia is OK)
m) Myasthenia gravis
n) Narcolepsy
o) Polyarteritis nodosa
p) Scleroderma
q) Sjogren's syndrome
r) Transverse myelitis
s) Wegener's granulomatosis
t) History of seizures (only childhood febrile seizures are allowed)
HIV and Hepatitis are OK if stable

e. If participants will comprise more than one group or stratification, describe each group (e.g., treatment/intervention, placebo, controls, sham treatment) **and** provide the number of participants anticipated in each group. **There will be four groups of participants (n =60 per group) enrolled/randomized 1) major depressive disorder (MDD) with a recent suicide attempt (in past 2 weeks), 2) MDD with serious ideation without recent suicide attempt (in the past 6 months), 3) MDD without clinically significant suicidal ideation or suicide attempt in the past 6 months, and 4) healthy controls. There will be also be a fifth group (n=15) 5) Diagnosis of other primary psychiatric disorder as determined by the MINI, such as: bipolar disorder, personality disorders, psychotic disorders, post-traumatic stress disorder, obsessive-compulsive disorder, dissociative disorders, without any history of MDD diagnosis, with recent suicide attempt or suicidal ideation (past 2 weeks).**

f. Indicate which, if any, of the special populations listed below will be involved in the protocol. Include the Special Populations Review Form (SPRF) if indicated.

☐ Pregnant Women: Attach SPRF—Pregnant Women, Fetuses, Neonates/Nonviable Neonates
☐ Fetuses: Attach SPRF—Pregnant Women, Fetuses, Neonates/Nonviable Neonates
☐ Neonates/Nonviable Neonates: SPRF—Pregnant Women, Fetuses, Neonates/Nonviable Neonates
☐ Prisoners: Attach SPRF—Prisoners
☐ Minors (<18 years old): Attach SPRF—Minors
☒ Employees or students at institution where research conducted
☐ Persons who are temporarily decisionally impaired
☐ Persons who are permanently decisionally impaired
☐ Non-English Speakers

For each box checked, describe why the group is included **and** the additional protections provided to protect the rights and welfare of these participants who are vulnerable to coercion: **Employees and students at the institution where research is conducted may be included in the study. Students will be informed they may withdraw from the study at any time, for any reason, before it is completed. They will be informed their participation will not affect their class standing or grades at UAB. They will not be offered or receive any special consideration if they take part in the research. Employees will be informed that taking part in the research is not part of their UAB duties and refusing to be a part of the study will not affect their job or relationship with UAB. They will not be offered or receive any special job-related consideration if they take part in this research.**

g. List any persons other than those directly involved in the protocol who will be at risk. If none, enter "None": **None**

h. Describe the recruitment process (e.g., medical record review, referrals, letter of invitation, existing patients) that will be used to seek potential participants (e.g., individuals, records, specimens). Research recruitment by non-treating physicians/staff may require completion of Partial Waiver of Authorization for Recruitment/Screening. **We plan to recruit potential participants from UAB/UAB-Highlands Emergency Department, Center for Psychiatric Medicine, Community Psychiatry Program (CPP), UAB psychiatric outpatient clinics, and the co-PI's patients seen in his UAB outpatient office. Clinicians working at these outpatient facilities will be approached for referrals. These clinicians will only be asked to introduce the study's goals and our research team, and to obtain verbal or written permission from their patients to be contacted directly by the research team. Additionally, self-referral as a response to flyer coverage has proven, in the past, to provide a rich source of potential participants. Because we are looking for depressed subjects with and without suicidal ideation, and normal controls, three different flyers have been developed. Once a prospective participant gives permission to be contacted by our research staff, he/she will be contacted immediately to determine potential eligibility to participate in this study. A telephone pre-screen interview will be designed to capture the most obvious exclusion criteria so that potential screen failures can be eliminated prior to an office visit.**

i. If you will use recruitment materials (e.g., advertisements, flyers, letters) to reach potential participants, attach a copy of each item. If not, identify the source (e.g., IRB Protocol Number for approved databases) from which you will recruit participants. **No new materials. Flyers and advertisments have been previously approved for use.**

j. Describe the screening process/procedures for potential participants. **Patients seen in the above described settings with a current or recent prior diagnosis of Major Depressive Disorder, or other psychiatric diagnosis will be informed of the study by the treating clinician. The clinician will ask the patient's permission to be contacted by a study coordinator who will administer the pre-screen telephone interview and schedule the screening visit, if appropriate. Self-referred potential subjects will also have a pre-screen telephone interview. During this pre-screen telephone interview, an oral overview of the study will be described. Thus the participant will have more than 24 hours between the phone call and the first office study visit. If potential subjects meet criteria from this pre-screen telephone interview, a screening/study appointment will be scheduled. During the consent process, the purpose of the study, its risks and benefits, the rights of the participants, and what will be required of participants will be discussed. The participants will be given time to ask questions and have their questions answered by trained research staff. After the consent has been signed, participants will then be clinically interviewed and administered the Hamilton Rating Scale for Depression (HRSD) and the C-SSRS to determine initial eligibility.**

17. Protocol Procedures, Methods, and Duration - in nontechnical, lay language

a. Describe the procedures for all aspects of your protocol. Tell us what you are doing. ***Visit 1.*** **Following the informed consent process, a medical evaluation and physical will be conducted to assess for the inclusion and exclusion criteria. Approximately 10mL of blood will be obtained for screening labs**

(chem, CBC, TSH, UDS, pregnancy) and urine will be obtained for drug screen and pregnancy test. If safety labs have been conducted within the previous 10 days, these will not be repeated. Vital signs including height, weight, and BMI will be assessed. An ECG will be performed at the screening visit. Controls and Group 5 will not have the screening labs, physical exam, or ECG, but they will have vital signs and 60mL of blood drawn for the miRNA analysis.

The following psychiatric assessments and scales will be done by all participants. *The Mini International Neuropsychiatric Interview (MINI)* adapted for DSM-will be the primary instrument for diagnosis. It is a semi-structured interview with excellent reliability and validity. Participants that have a completed a MINI within the past 6 months of screening will not have to repeat this scale.

Screening for inclusion will be done using the 21-item *HRSD* by the clinician using a structured interview with defined anchor points and aims to quantify the degree of depression

The *Montgomery-Åsberg Depression Rating Scale (MADRS)* revised to reflect shorter timeframes will be the primary measure of change in depression. The *MADRS* has been used successfully in prior ketamine studies. We will assess positive and negative affect using the *Positive and Negative Affect Schedule – Expanded Form (PANAS-X).* The revised *Beck Depression Inventory (BDI-II)* and *Beck Anxiety Inventory (BAI)*, 21-item self-report inventories, will be used for depression and anxiety, respectively.

Current suicidal ideation, plans, intent, and behaviors will be assessed using the *Columbia Suicide Severity Rating Scale (C-SSRS,* Baseline and Screening versions). The Baseline version assesses lifetime suicidal ideation and behavior, while the Screening version assesses suicidality during a predefined time period (here, the last week). The effects of treatment on suicidal potential will be assessed using the *Beck Scale for Suicide Ideation (BSSI).* The *BSSI* is a 21-item, self-report rating scale that measures the current intensity of specific attitudes, behaviors, and plans to commit suicide. Each item consists of 3 options graded according to intensity on a 3-point scale (0-2). All items will be assessed at each time point. The first 19 items are summed to yield a total score (range 0-38). Individual items assess risk factors such as the duration and frequency of ideation, sense of control over suicidal impulses, deterrents, preparation for an attempt, as well as the incidence and frequency of previous suicide attempts. The *BSSI* has been standardized with adult psychiatric in inpatient, outpatient, and ED settings, and across a range of ages, languages, and races and ethnicities. The *BSSI* has high internal consistency, concurrent validity, and inter-rater reliability. The *BSSI* also is sensitive to change in clinical trials, including ketamine studies. Change in the *BSSI* with treatment is only moderately correlated with change in depression (r=0.65).

Suicide is not a unitary construct and there are a number of characteristics associated with suicide risk; for example, hostility/irritability, impulsiveness, and aggression. Hostility and irritability will be measured using the *Buss-Durkee Hostility Inventory (BDHI)* which is a self-rated scale yielding seven subscale scores which assess the cognitive, affective, and behavioral components of hostility and irritability. Impulsivity will be measured using the *Barratt Impulsiveness Scale, 11th version (BIS-11)* a self-report measure of impulsiveness. This scale provides 3 measures of impulsivity: motor, cognitive, and non-planning. The *Brown-Goodwin History of Aggression* (BGHA) is an interview that assesses lifetime aggressive behaviors across three separate stages of life (childhood, adolescence, and adulthood).

Suicidal behavior or impulses themselves range from more impulsive/reactive to more deliberate phenotypes. Impulsive suicide attempts tend to be unplanned, follow an immediate stressor (particularly interpersonal conflict), use more violent means, and often with prior attempts. A more deliberate phenotype is characterized by planned attempts, often with a suicide note or other preparation, and an association with neuroticism and introversion Although in our preliminary data we found *BIS-11* scores to be relatively high on average in suicidal patients (mean total score=74.94), we found a wide range of impulsivity (total score 61-96); 66.3% of our acutely suicidal patients fell within the normative range (mean 64.2+10.7).91 In addition, the BIS-11 total and subscale scores were stable across ketamine infusion (e.g., baseline total=74.94, 180 minutes=77.19). Planning and intent will be assessed using the Beck Suicide Intent Scale (SIS)

which consists of 15 questions which are scaled from 0-2, which take into account both the planning of the suicide attempt as well as the intent to die.

We will assess temperament using the *NEO-Five-Factor Inventory (NEO-FFI)*, Revised. The focus of the *NEO-FFI* analysis will be neuroticism and extraversion subscales. Categorical personality disorders (PD) per se are not the focus for this project, and most are not relevant to suicide; Turecki et al. found that PD comorbidity was found largely in participants with higher impulsiveness and aggression, which may be the more relevant personality constructs. However, Keilp et al. found that these personality features are confounded with the categorical construct of borderline personality disorder (BPD), which was closely associated with trait impulsivity and hostility but not aggression. Taxometric and latent class analyses indicate that borderline personality disorder can be best understood dimensionally than categorically. Participants with BPD will be included if MDD is present. The Personality Assessment Inventory – Borderline Personality subscale will also be conducted to gather further information. Those with a history of dissociation or psychosis will be excluded because of the risks of ketamine infusion. We will assess hopelessness using the *Beck Hopelessness Scale (HS)*, a 20-item self-report index of pessimism about the future, loss of motivation, and negative expectations. Our prior experience with ketamine indicates that infusion significantly reduces HS scores (mean reduction=36%). Life stress, including early trauma and recent stressors, will be measured. Early life trauma will be measured using the *Childhood Trauma Questionnaire (CTQ)*. The *CTQ* yields a total score and subscale scores in five areas of adversity: emotional, physical, and sexual abuse, emotional neglect, and physical neglect. Recent stressors will be measured using the *Perceived Stress Scale (PSS)*.This will complete the study for the controls. For the convenience of the MDD participants or time constraints, if the above assessments cannot be completed at the screening visit, the following will be allowed at the infusion visit: *ATRQ-M, CTQ, PSS, BDHI, BIS-II, SIS, NEO-FFI.* If the screening visit cannot be completed in one visit due to logistics, the participant may return to complete the visit.

*Visit 2.*Participants in all MDD groups will undergo ketamine 0.5 mg/kg IV infusion over 40 minutes. Blood (40mLs) will be collected at baseline, 30 and 180 min post-infusion from which micro RNAs will be extracted and sequenced. Safety, tolerability, and adverse events assessments will be done prior to the infusion and at 30, 60, 120, 360 minutes. The presence of psychotic symptoms both pre and post infusion will be evaluated using the 4-item *Brief Psychiatric Rating Scale (BPRS). This 4-item version assesses conceptual disorganization, suspiciousness/persecution, hallucinatory behavior, and unusual thought content.* The presence or absence of dissociative symptoms will be ascertained by the *Clinician-Administered Dissociative States Scale (CADSS).* Manic symptoms will be queried several times using the *Young Mania Rating Scale, (YMRS). The BPRS, CADSS, and YMRS will be conducted prior to the infusion as well as 30 minutes, 180 minutes, and 24 hours after the infusion. The Systematic Assessment for Treatment Emergent Events (SAFTEE)*, a 56 item, self-report inventory along with spontaneously reported adverse events will be recorded. Vital signs will be recorded based on schedule in chart.

Visit 3. 24 hours post infusion (visit window +1 day, that is to mean the visit may occur between 1 and 2 days post infusion), participants will return to the OPCR clinic if outpatient, or staff will conduct visit on inpatient unit. The *MADRS, BDI-II, BAI, BSSI, BHS, PANAS-X, BPRS, CADSS, YMRS*, vital signs, *SAFTEE* will be performed, *and 20mL blood will be collected.* If the 24 hours post infusion visit cannot be completed in one visit due to logistics, the participant may return to complete the visit.

Follow-up. Research staff will contact the participants who received the ketamine on Days 3 (+1 day window, that is to mean contact may occur between 3 and 4 days post infusion), and 7 (+ or - 1 day window, that is to mean contact may occur between 6 and 8 days post infusion) post-infusion to ensure safety and transition to the next level of care.

Visit 4. 14 days post-infusion (visit window + or - 3 days, that is to mean the visit may occur between 11 and 17 days post infusion), participants will return to the OPCR clinic for the last follow-up visit. The MADRS, BDI-II, and BSSI will be completed. A 20mL blood sample will be

collected. If the 14 days post-infusion visit cannot be completed in one visit due to logistics, the participant may return to complete the visit.

Schedule of Assessments									
Assessment	Controls /Group 5	Screen	Pre-Dose	Hours Post Ketamine				24 Hours Post Dose	14 Days Post Dose
			0	.5	1	2	3		
Informed Consent	X	X							
Demographics	X	X							
Medical History	X	X							
Concomitant Medications	X	X	X					X	X
MINI	X	X							
HAM-D 21	X	X							
MADRS	X		X	X	X	X	X	X	X
C-SSRS-R/L	X	X							
Suicide History	X	X							
SIS (Most Recent & Most Serious Attempt)		X							
BGHA	X	X							
ECG		X							
Vital Signs	X	X	X	X	X	X	X	X	
Labs (chem, CBC, TSH)		X							
Urine drug screen		X	X						
Urine pregnancy		X	X						
Physical Exam		X							
Diagnostic Clinical Evaluation		X							
Clinical Eval Progress Note			X						
Inclusion/Exclusion	X	X							
ATRQ		X							
PANAS-X	X	X						X	
BDI-II	X	X	X		X		X	X	X
BAI	X	X	X		X		X	X	
BHS	X		X				X	X	
BSSI	X	X	X	X	X	X	X	X	X
PAI-BOR	X	X							

BDHI	X	X							
BIS-11	X	X							
CTQ	X	X							
NEO-FFI	X	X							
PSS	X	X							
BPRS			X	X			X	X	
CADSS			X	X			X	X	
YMRS			X	X			X	X	
SAFTEE			X		X		X	X	
Research Blood Draws	X		X	X			X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X

Dr. Neil Smalheiser, with the University of Illinois Chicago, will act in a consultant role overseeing the Bioinformatics Facility. He is an expert in studies pertaining to the neurobiology of psychiatric illnesses and molecular neuroscience. His laboratory has networked storage servers with a total 40 TB disk space for archiving experimental data and databases. One G5 Mac and one Windows server (with 12 G memory) serve as web servers for bioinformatics applications and databases.

b. What is the probable length of time required for the entire protocol (i.e., recruitment through data analysis to study closure)? **5 years**

c. What is the total amount of time each participant will be involved? **Participants with MDD: Four visits totaling about 9 hours, plus contact at Day 3 and 7 to ensure safety and transition to the next level of care. Controls or Group 5: One visit about 2-3 hours long.**

d. If different phases are involved, what is the duration of each phase in which the participants will be involved? If no phases are involved, enter "None." **Participants with MDD: The initial visit will take about 4 hours; the infusion visit will be 3 hours; the 24 hour and 14 days post infusion visits will take 1 hour. Controls or Group 5: Initial visit only.**

e. List the procedures, the length of time the procedure takes, the total # of times the procedure is performed, and indicate whether each is performed solely for research or would already be performed for treatment or diagnostic purposes (routine care) for the population.
-Insert additional table rows as needed.
-If procedure is sometimes research and sometimes routine care, include on separate lines with number of times as each.

Procedure	Length of Time Required of Participants	Total # of Times the Procedure is Performed	Research (Res) – OR- Routine Care
Informed Consent	**15 minutes**	**1**	☒Res ☐ Routine
Medical Evaluation	**10 minutes**	**1**	☒Res ☐ Routine
Physical Exam	**10 minutes**	**1**	☒Res ☐ Routine
Mini International Neuropsychiatric Interview (MINI)	**30 minutes**	**1**	☒Res ☐ Routine
Labs (chem, CBC, TSH, UDS, pregnancy (if indicated))	**10 minutes**	**2**	☒Res ☐ Routine
ECG	**10 minutes**	**1**	☒Res ☐ Routine
ATRQ-M	**5 minutes**	**1**	☒Res ☐ Routine

Hamilton Rating Scale for Depression	**15 minutes**	**1**	☒Res ☐ Routine
C-SSRS	**15 minutes**	**1**	☒Res ☐ Routine
CTQ	**5 minutes**	**1**	☒Res ☐ Routine
PSS	**5 minutes**	**1**	☒Res ☐ Routine
MADRS	**20 minutes**	**7**	☒Res ☐ Routine
BDI-II	**5 minutes**	**6**	☒Res ☐ Routine
BAI	**5 minutes**	**5**	☒Res ☐ Routine
BGHA	**5 minutes**	**1**	☒Res ☐ Routine
BSSI	**5 minutes**	**8**	☒Res ☐ Routine
BHS	**5 minutes**	**3**	☒Res ☐ Routine
BDHI	**5 minutes**	**1**	☒Res ☐ Routine
BIS-II	**5 minutes**	**1**	☒Res ☐ Routine
SIS	**5 minutes**	**1**	☒Res ☐ Routine
NEO-FFI	**10 minutes**	**1**	☒Res ☐ Routine
PAI-BOR	**5 minutes**	**1**	☒Res ☐ Routine
BPRS	**5 minutes**	**4**	☒Res ☐ Routine
CADSS	**10 minutes**	**4**	☒Res ☐ Routine
YMRS	**15 minutes**	**4**	☒Res ☐ Routine
Vital Signs	**5 minutes**	**15**	☒Res ☐ Routine
SAFTEE	**5 minutes**	**4**	☒Res ☐ Routine
Blood draws	**3 minutes**	**5**	☒Res ☐ Routine
Follow-up contact	**15 minutes**	**3**	☒Res ☐ Routine
Ketamine IV Infusion	**40**	**1**	☒Res ☐ Routine

f. Will an interview script or questionnaire be used? ☒Yes ☐No

If Yes, attach a copy.