Study Methods and Statistical Analysis Plan

Clinical Trial Name:
Remediation of Impaired Self-Regulation in Patients with Mild TBI

NCT #02260570

Date of Document Upload: May 12, 2022

IRB (Institutional Review Board/Human Studies Subcommittee)
DEPARTMENT OF VETERANS AFFAIRS
NORTHERN CALIFORNIA HEALTH CARE SYSTEM
SAC-5th Floor Conference Room; MTZ-Director's Conference Room

IRB APPROVAL - Continuing Review

Date: May 10, 2018
From: Jary Larsen, PhD, IRB Chairperson
Investigator: Andrew Kayser, M.D., PhD
Protocol: MERIT: Remediation of Impaired Self-Regulation in Patients with Mild TBI
ID: 00720 Prom#: 5838 Protocol#: 14-06-00720
Expiration Date: 05/01/2019

The following items were reviewed and approved at the 05/01/2018 meeting:

- Continuing Review Application (04/26/2018; 2018)
- Consent Form (05/11/2017)
- Flyer - mTBI (04/06/2017; Flyer with and without tear-off strips)
- Flyer - OIF/OEF (04/06/2017; Flyer with and without tear-off strips)
- Human Subject Enrollment Form - 03/16/2017 to 02/16/2018 (02/16/2018)
  Research Service has this on file. Nine Veterans at VANCHCS listed and six Veterans not at VANCHCS listed.
- MR/fMRI Research - Investigator Performed (04/26/2018)
- Project Data Sheet (02/16/2018)
- Research Security Plan (02/22/2018)
- Research Project Abstract (02/16/2018)
- Authorization for PHI use for Research (05/05/2016)
- Research Data Use and Security Plan - Investigator (02/22/2018)
- Offsite Data Storage Waiver (02/22/2018)
- Research Financial Conflict of Interest Statement - 2018
  Andrew Kayser (02/16/2018), Mark D'Esposito (03/21/2018)

Approval is granted for a period of 12 months and will expire on 05/01/2019. Your Continuing Review is scheduled for 04/02/2019, and the requirements are attached.

The protocol was determined to have the following level of risk:
Moderate

The following other committee reviews are scheduled:
SRS (Subcommittee for Research Safety) [05/14/2018]
Research & Development Committee [05/23/2018]

Approval by each of the following is required prior to study continuation (unless Exempt):
IRB (Institutional Review Board/Human Studies Subcommittee)
Research & Development Committee

Approval for study continuation is contingent upon your compliance with the requirements of the Research Service for the conduct of studies involving human subjects.

Jary Larsen

Digitally signed by Jary Larsen
Date: 2018.05.10 09:13:24 -07'00'

Jary Larsen, PhD, IRB Chairperson

DEPARTMENT OF VETERANS AFFAIRS
NORTHERN CALIFORNIA HEALTH CARE SYSTEM
10535 Hospital Way • Mather & Martinez, CA

Conditions of IRB Approval

What Are the Conditions of IRB Approval?

1. Adhere to ethical principles: (1) Respect for persons - consent, privacy, confidentiality, (2) Beneficence - maximize possible benefits to the subject and minimize possible harms, and (3) Justice - equitable selection.

2. Obtain informed, written consent from each human subject or his legally qualified guardian or next-of-kin, unless specifically waived by the IRB. If the subject lacks decision making capacity or has been declared incompetent, surrogate consent is required. You are required to place the original, signed consent form in the medical record (and document it in the electronic record), provide a copy to the subject, provide a copy to the Research Office (if applicable), and keep a copy for your files.

3. Promptly report all Serious Adverse Events or Serious and Unexpected Events to the IRB (both events at the VA and sponsor reports of events at other sites). The FDA defines Serious Adverse Events as: (1) death, (2) life-threatening, (3) hospitalization - initial or prolonged, (4) disability, (5) congenital anomaly, (6) required intervention to prevent permanent impairment/damage, or (7) serious and unexpected severity or frequency of expected events.

4. Promptly report all deviations (including error and accidents) from the approved protocol and do not initiate any unapproved changes (amendments, consent form modifications, advertisements) without IRB review and approval, except where necessary to eliminate apparent immediate hazard to human subjects.

5. Report Emergency Use of unapproved test articles to the IRB within 5 days.

6. If applicable, provide a copy of each subject's consent form and the Investigational Drug Information Record (VA Form 9012) to the Investigational Pharmacist prior to your request to receive, store, and dispense study medications. (The Investigational Pharmacist is responsible for the storage and dispensing of investigational drugs.)

7. Submit Continuing Review information to the IRB by the date specified and inform the IRB when your study is completed (federal law requires that every protocol must be reviewed a minimum of once per year). File a final report upon completion or termination of a study.

What Are the Penalties for Non-Compliance?

1. Non-compliance may result in suspension of approval or a particular project. Serious or continuing non-compliance may result in suspension of your privilege to conduct research at this VAMC.

D. STUDY DESIGN AND MERIT

1. **Estimated length of study:** *(in years or months)*
   VA RR&D funding has been provided for this study for 5 years.

2. **Length of each participant's time in this study:** *(in hours, days, weeks, months, or years)*
   Each participant will have 3 study visits: one screening visit for approximately 2 hours and two functional MRI visits of approximately 5 hours each.

3. **Purpose of study:**

   a. **State the research hypothesis.**
   The purpose of this application is to develop adjunctive medication options for the treatment of self-regulatory deficits. Such deficits are thought to emerge from failures of top-down control – i.e. the ability of higher-order goals to constrain impulses, habits, and other more "stimulus-driven" responses. Convergent data from multiple fields, including examples from both our own human neuroimaging work and animal studies of related processes, argue that top-down control is reflected neurophysiologically in the ability of prefrontal cortex (PFC) to influence activity in behaviorally-relevant posterior cortical and subcortical brain regions. Given the clear need for new therapeutic approaches to self-regulatory impairments, this mapping from brain to behavior identifies a potential biomarker for self-regulatory failure, and points toward a strategy for developing treatments. As we detail below, both our work and other reports suggest that the brain-penetrant, FDA-approved, catechol-O-methyltransferase (COMT) inhibitor tolcapone shows promise in improving the ability of PFC to influence posterior cortical and subcortical activity, and thus to improve self-regulation.

   b. **Describe the research objectives.**
   We propose to use behavioral tasks and functional MRI (fMRI) to directly test the hypotheses that self-regulatory deficits in veterans with mild traumatic brain injury (mTBI) result from diminished top-down control, and that administration of the FDA-approved, brain-penetrant COMT inhibitor tolcapone will improve self-regulation in human subjects. We will employ clinically-relevant tasks within a randomized, double-blind, placebo-controlled translational fMRI study to address behavioral, cognitive, and social-emotional self-regulation, respectively, including a delay discounting task to measure impulsivity, a visual perceptual task to assess attention, and a social-emotional task to evaluate social-emotional regulation. We hypothesize that these tasks will demonstrate

behavioral impairments in veterans with mTBI, that these impairments will correlate with reduced top-down control as measured by fMRI, and that tolcapone will remediate the behavior and underlying neurophysiology. In addition, we hypothesize that self-regulatory failures in each of the three domains – behavioral, cognitive, and social-emotional – will correlate with each other within subjects.

c. Describe in detail the purpose of this study.

Higher cognitive function – in particular, our capacity for self-regulation – enables us to plan for the future, to maintain our focus in the face of distractions, and to manage our emotions. Failures of self-regulation are an integral manifestation of mild traumatic brain injury (mTBI) and its comorbidities, including substance use and post-traumatic stress disorder (PTSD). Because of the importance of such functions in our daily lives, these impairments have profound effects on the lives of veterans with mTBI, who complain of poor decision making, diminished concentration, and inadequately controlled anxiety. Due to impediments to care including the severity of these comorbid symptoms, the remoteness of their homes, and concerns about disclosing the extent of their deficits, many of these veterans are poorly able to participate in behavioral/neurocognitive approaches to address these issues. In such circumstances, effective adjunctive medications to improve self-regulation are important to permit and/or to reinforce the ability of these veterans to manage their symptoms and to engage in behavioral therapies. Unfortunately, very few medications are effective for cognitive issues in patients with mTBI, and current agents are not effective for many symptoms and for many veterans.

d. Describe the importance of resulting knowledge from this study.

By testing tractable hypotheses supported by our preliminary data, these studies address a critical barrier to progress in the fields of cognitive rehabilitation and psychotherapy. Specifically, as our own clinical experiences and exclusion criteria in published reports indicate, not all veterans are capable of participating in behavioral paradigms addressing cognition and mental health. For such patients, pharmacological approaches are a much-needed adjunct that may enable other therapies. That potentially beneficial medications are already FDA-approved for other indications increases both the rapidity with which these medications can be applied to mTBI, and the urgent need to obtain high quality, proof of principle results. Moreover, by using fMRI to evaluate the influence of tolcapone on brain activity related to relevant tasks, we gain insights into mechanism of action that can guide the development of other agents, whether pharmacological or otherwise (e.g. transcranial magnetic stimulation). This proposal thus represents an innovative, pragmatic approach to a problem – self-regulatory failure after mTBI – that is widespread, under-treated, and for which veterans desperately want new therapies.

4. Check types of study design:

- ☐ **Chart/Medical Records Review**
  - ☐ Prospective
  - ☐ Retrospective
- ☐ **Observational (the investigator observes the events without altering them):**
  - ☐ Cross-sectional study (each participant examined only once)
  - ☐ Longitudinal study (each participant followed over a period of time)
- ☒ **Experimental Intervention (the investigator observes the effect of the intervention on outcome):**
  - ☒ Randomized
  - ☒ Blinded
  - ☐ Retrospective
  - ☒ Prospective

5. **Describe statistical methods** *(For example: sample size estimation, power calculation, statistical tests or descriptive statistics, data analysis tools, etc.)*
Given our primary outcomes and preliminary data, we specify a sample size of 40 subjects per group, consistent with both seminal neuroimaging papers and our previous work. This number assumes certain standard estimates of signal-to-noise, spatial smoothing, and BOLD time series duration that are well-established in the fMRI literature across studies including perceptual, attentional, language-related, and executive tasks. Our sample size will provide 80% power to detect a difference between treatment groups with a standardized effect size (observed effect divided by the standard deviation of the signal noise) of 0.71 at a corrected significance level (alpha) of 0.05 (two-tailed). This effect size corresponds to a 0.25% difference in the BOLD signal change between tolcapone / placebo conditions. We note that differences in BOLD signal in our tasks can sometimes be reliably present at higher levels (e.g. 0.5%), so it is possible that our estimated requirement for 40 subjects may be unduly conservative. Statistical analyses of neuroimaging results will be conducted within the AFNI suite of fMRI analysis programs.

6. **Describe appropriateness and rationale for elements warranting special attention** *(placebo, washout period, challenge study, radiation exposure, deception study, deviation from accepted standard of care).*
Subjects will receive both tolcapone and placebo in a randomized, double-blind, counterbalanced, cross-over design. The use of a placebo will permit each subject to serve as his/her own control, an important point given known individual differences in dopamine tone that can be obscured if only across group comparisons are possible. A washout period between the two fMRI sessions will be used. Tolcapone concentration peaks at 90 minutes, and when used for the treatment of Parkinson's disease (its FDA-approved indication), it is dosed three times per day. To ensure that the one-time dose of the drug is eliminated from each subject's system prior to the second scan, at least 5 days will elapse between MRI scans. Finally, MRI scanning is used because it noninvasively permits excellent spatial and temporal resolution of brain activity without the use of ionizing radiation.

7. **Have there been IRB approved protocol amendments modifying the study** *(including sponsor amendments)* **since the last review?**
☒ Yes ☐ No
- *If "YES", list approval date and summarize the nature and purpose of all protocol amendments made since the time of last Initial or Continuing Review:*

[redacted]

E. AMENDMENT REQUEST AT CONTINUING REVIEW

1. **Are any protocol amendments modifying the study** *(including sponsor amendments)* **being proposed at the time of this continuing review?**
☐ Yes ☒ No
- *If "YES", complete the rest of this section, If No, skip the rest of this section*

2. **Purpose and/or reason for modifying the protocol.**

3. **Brief Description of Amendment.**

F. SUBJECT POPULATION

1. Human Subject Enrollment

a. How many total participants did VANCHCS IRB originally approve for accrual (sign consent forms) at VANCHCS/VACCHCS? **40**

b. How many total participants are currently approved for accrual at VANCHCS/VACCHCS? **80**

c. How many total participants did VANCHCS IRB originally approve for accrual at other sites under your responsibility? **40**
List other initial site names **The UCSF Research Clinic, located at UC Berkeley**

d. How many total participants are currently approved for accrual at other sites under your responsibility? **80**
List other current site names **The UCSF Research Clinic, located at UC Berkeley**

e. If this is a Multicenter trial with different sites and different PIs, how many total participants are currently planned to be enrolled for the entire project? **N/A**

f. No contact with participants, authorization and consent waived: ☐

1) Enter total number of samples or charts originally approved _____

2) Enter total number of samples or charts currently approved _____

3) Enter total number of records extracted from VA Data Mart or VA Data Warehouse (National, Regional, or VISN) originally approved _____

4) Enter total number of records extracted from VA Data Mart or VA Data Warehouse (National, Regional, or VISN) currently approved _____

2. Status of subjects

a. Number of subjects, samples or charts entered into study **since project began**? **55**

b. Number of subjects, samples or charts entered into study **since last report** to the IRB? **15**

3. Since the **last report**, to the IRB indicate:

a. Number of female subjects:**2**

b. Number of male subjects: **13**

c. Number of subjects in each of the following groups:

Caucasian: **5**	African-American: **3**	Hispanic: **4**
Asian: **2**	Other: *(indicate minority status and number)* **1 - American Indian**	

d. Number of subjects in each of the following vulnerable groups:

☒ None	Children:	Persons with HIV:
Economically Disadvantaged:	Employees:	Prisoners:
Educationally Disadvantaged:	Homeless/Shelter:	Students/Trainees:
Impaired Decision Making Capacity:	Mentally Disabled:	Terminally Ill Patients:
Pregnant Women & Fetuses:	Non-English Speaking:	Others:

e. Number of subjects who signed consents but were dropped from study ("screen failures"):**3**

f. Total number of patients who withdrew or were withdrawn from the study: **1**
1) Summarize the reasons for withdrawal. **Subject unable to complete study tasks**

g. Did all research subjects give written informed consent? ☒ **Yes** ☐ **No** ☐ **N/A - consent waived**
1) If no, provide explanation:

4. **Which of the following groups will be recruited for this study?** *(check all that apply)*		
☐ Inpatients	☒ Outpatients	☐ Pre-Operative patients
☐ Nursing home patients	☐ Non-VA participants *	☒ Healthy volunteers

Recruitment of Non-VA Participants

a. *Non-veterans may be entered into VA-approved research studies only when there are insufficient veterans available to complete the study in accordance with 38 CFR 17.45 and 38 CFR 17.92.*

b. *You must document how you will attempt to enroll veterans and outline how you will provide verification to Research Service that recruitment resulted in insufficient veteran enrollment.*

5. Are you recruiting and enrolling Non-VA participants?

☐ Yes ☒ No

- *If "YES", complete the following information:*

a. Document how you will attempt to enroll veterans.

b. Outline how you will provide verification to Research Service that recruitment resulted in insufficient veteran enrollment.

6. Selection Criteria

a. What are the inclusion/exclusion criteria?

Inclusion Criteria:

Ages 18-50 and in general good health
Able to read English at a 6th grade level (as determined by WTAR)
Able to provide written informed consent
* Mild TBI (GCS 13-15, LOC < 30 min, and/or PTA < 24 hours from onset) as confirmed by structured clinical history (TBI SUJECTS ONLY)
* Greater than 6 months from the time of brain injury (TBI SUBJECTS ONLY)
Normal or corrected-to-normal visual acuity
Stable doses of all medications (2 weeks or greater)

Exclusion Criteria:

Contraindications to MRI (e.g. unremovable ferromagnetic metals, claustrophobia)
Inability to complete basic fMRI requirements (e.g. making button presses, minimizing movement < 5mm)
History of major brain surgery or penetrating brain injury (i.e. violating brain parenchyma)
Severe low blood pressure or uncontrolled high blood pressure
* History of mild, moderate, or severe TBI (CONTROL SUBJECTS ONLY)
Contraindications to tolcapone use, including liver function tests (AST, ALT, Total Bilirubin, Direct Bilirubin, Alkaline Phosphatase) more than 2 times normal ranges, pregnancy, previous adverse reaction to tolcapone, or significant liver impairment including but not limited to chronic hepatitis, cirrhosis, hepatocellular carcinoma, parasitic liver infection, autoimmune hepatitis, primary biliary cirrhosis, hemochromatosis, or any other liver condition obtained from patient history (and/or the medical record, if available) that is identified by the reviewing clinician
Current use (within previous 30 days) of pharmacological agents with dopaminergic actions, including but not limited to tolcapone, levodopa/carbidopa, entacapone, amantadine, bromocriptine, pergolide, pramipexole, ropinirole, selegeline, isocarboxazid, phenelzine, tranylcypromine, clozapine, olanzapine, quetiapine, risperidone, ziprasidone, aripiprazole, fluphenazine, haloperidol, perphenazine, pimozide, thiothixene, trifluoperazine, loxapine, molindone, chlorpromazine, mesoridazine, thioridazine, promethazine, dextroamphetamine, dexmethylphenidate, dextroamphetamine, methylphenidate, cocaine, or methamphetamine
Active alcohol dependence or alcohol abuse by DSM-IV-TR criteria (within previous 30 days)
Active substance dependence or substance abuse by DSM-IV-TR criteria (including marijuana, opiates, stimulants (cocaine, amphetamines), hallucinogens within previous 30 days)
Positive urine drug screen for illicit substances
Past schizophrenia, ADHD, and/or other psychiatric diagnosis except depression or PTSD
History of psychiatric hospitalization (last 1 year), suicide attempt (last 5 years), or current suicidal ideation
Clinically severe medical illness requiring treatment
Subject has received an investigational drug within 30 days of screening visit
Seizures greater than 4 weeks after injury or requiring active pharmacological treatment
History of brain tumor, stroke, demyelinating disease, encephalitis, or aneurysm rupture
Diagnosis of Alzheimer's disease or other primary neurodegenerative disorder

A history of substance abuse will be assessed via patient history, consistent with our previous studies in healthy and substance-abusing patient populations. As noted elsewhere in the protocol, we will also screen the urine for drugs of abuse in order to ensure that subjects are not engaging in active use of amphetamine, cocaine, and other drugs as listed in the protocol. A history of psychiatric illness will be assessed via patient history, consistent with our previous studies in healthy and substance-abusing patient populations. As noted elsewhere in the protocol, our questionnaires will also augment these data (e.g. the PCL to assess symptoms of post-traumatic stress disorder).

b. How do the inclusion/exclusion criteria reflect the purpose of the study?
The challenges of designing studies with a mTBI population in mind are many, not least of which is selecting as reasonably homogeneous a group of patients as possible. Our study will enroll mTBI and matched control OEF/OIF veterans between 18 and 50 years old who live independently and are in the chronic, stable phase of recovery -- at least 6 months removed from the time of their traumatic brain injury. These criteria reflect our goal of looking at patients in the chronic phase of mTBI whose symptoms are not potentially confounded by other significant neurological or psychological comorbidities.

c. How do inclusion and exclusion criteria impose fair and equitable burdens and benefits?
These criteria attempt to balance the need to be broad enough to make the results generally applicable, but specific enough to ensure that other factors do not confound or negate possible results. For individual subjects, the inclusion and exclusion criteria balance safety, given the use of both MRI and tolcapone, with possible improvements (or not) in decision making.

d. Describe the science and ethics of excluding groups that might benefit from the research. *(If women or minorities are excluded, explain reasons for exclusion.)*
Gender and ethinicity/race do not interact with any of our hypotheses, and we will not exclude any subjects on either basis.

7. Research Setting:

a. Describe the research setting in context of equitable selection of subjects.
Subjects will be screened on either the VA Martinez campus or at the UCSF Research Clinic located at U.C. Berkeley, depending on subject convenience. Both settings are designed to be accessible and available to subjects with a variety of backgrounds. By a similar token, the MRI scanner setting at U.C. Berkeley does not impact equitable selection of subjects.

b. Where will participants be screened, enrolled, and followed?

☐ **VANCHCS Outpatient Clinics - Check all that apply:**
- ☐ Chico VA Outpatient Clinic - Specify Clinic:
- ☐ Fairfield VA Outpatient Clinic - Specify Clinic:
- ☐ Mare Island VA Outpatient Clinic - Specify Clinic:
- ☐ McClellan VA Outpatient Clinic - Specify Clinic:
- ☐ Martinez VA Outpatient Clinic - Specify Clinic:
- ☐ Oakland VA Outpatient Clinic - Specify Clinic:
- ☐ Oakland VA Mental Health and Substance Abuse Clinic - Specify Clinic:
- ☐ Redding VA Outpatient Clinic - Specify Clinic:
- ☐ Sacramento VA Mental Health Clinic - Specify Clinic:

☐ **Sacramento VA Medical Center – Check all that apply:**
- ☐ Outpatient Clinic: Specify:
- ☐ Inpatient Ward: Specify:
- ☐ UC Davis CTSC Clinical Research Center (CCRC)

☐ **VANCHCS Martinez: Center for Rehabilitation and Extended Care (CREC)**

☐ **VANCHCS Martinez: UC Davis Alzheimers Disease Center (UCD ADC)**

☒ **VANCHCS Research Space - Specify Site:** Building 4

☐ **UC Davis Medical Center - Specify:**

☐ **University or College Campus - Specify:**

☐ **VACCHCS Outpatient Clinic - Specify Clinic:**

☐ **VACCHCS Research Space - Specify Site:**

☒ **Other - Specify:** the UCSF Research Clinic, located at UC Berkeley; UC Berkeley Brain Imaging Center

8. How will participants be recruited for taking part in the study? *Please review "Important Information for Researchers" for more information about acceptable recruitment methods.*

a. Check all that apply:

☒ **Investigator's patient population:** Study investigators recruit their own patients directly in person and/or nurses working with researchers approach patients.

☐ **Scheduled visit:** Study investigators provide their colleagues with an IRB approved "Dear Patient" letter describing the study. This letter can be signed by the treating health care provider and would inform the patients about how to contact the study investigators. The study investigators may not have access to patient names and addresses.

☒ **Physician referral:** Study investigators send an IRB approved letter to colleagues asking for referrals of eligible patients interested in the study. The investigators may provide the referring physicians an IRB approved Information Sheet about the study to give to patients. If interested, the patient will contact the PI. Or, with documented permission from the patient, the PI may be allowed to talk directly with patients about enrollment.

☒ **Direct advertising:** Interested participants will initiate contact with study investigators. *(Submit an electronic copy of all recruitment media listed in this section to the IRB Coordinator who will forward it to VANCHCS Public Affairs Officer (PAO) for review prior to IRB review and approval.)*

☐ Newspaper: Name(s)

☒ Bulletin Board Poster: Posting Location(s) **VA Martinez, Concord and Oakland Vet Centers**

☒ Flyers: Posting Location(s) **VA Martinez, UCSF Research Clinic located at UC Berkeley, UC Berkeley, Concord and Oakland Vet Centers, see attached approved amendment(3/14/16) for additional sites**

☒ Internet: Web site address **Craiglist**

If using the media above, see VANCHCS Policy Statement PS-00-9 "Local Publications" or call VANCHCS HRPP at 916 366-5369.

☐ Radio: Station Name(s)

☐ Television: Station Name(s)

If using the media above, see VANCHCS Policy Statement PS-00-7 "Public Affairs Program."

☐ Other:

☐ **Waiver of Authorization and Consent for recruitment purposes:** This waiver is an exception to the policy but may be requested in exceptional circumstances such as:

☐ Minimal risk studies in which participants will not be contacted, for example chart/database review only (Describe who and how):

☐ Review of charts/database is needed to identify prospective participants who will then be contacted (Describe who and how):

☐ Large-scale epidemiological studies and/or other population-based studies when participants may be contacted by someone other than personal health care provider (Justify and describe by who and how):

☒ **Direct contact:** Potential participants have previously given consent to be contacted for participation in research. Clinic or program develops an IRB approved recruitment protocol that asks patients if they agree to be contacted for research (a recruitment database) or consent for future contact was documented using the consent form from a different study that was approved by the IRB.

☐ **Potential participants unknown to investigators:** Study investigators recruit potential participants who are unknown to them. Examples include direct approach in public situations, random digit dialing, use of social networks, Please explain here:

☐ **NO contact:** This study does not involve participant contact for recruitment. Examples include record review, use of specimens.

b. Are participants being paid *(includes all types of reimbursement, such as parking fees, etc.)* **for participation?**

☒ Yes ☐ No

Note: VA policy prohibits paying human subjects to participate in research when the research is integrated with a patient's care and when it makes no special demands on the patient beyond those of usual medical care.

- *If "YES", continue to question 1), 2), 3), 4), 5) and 6) below.*
- *If "NO", skip to Section F.9.*

1) Payment may be permitted in the following circumstances
Check all that apply

☒ **No Direct Subject Benefit:** When the study to be performed is not directly intended to enhance the diagnosis or treatment of the medical condition for which the volunteer participant is being treated, and when the standard of practice in affiliated non-VA institutions is to pay participants in this situation.

☐ **Others Being Paid:** In multi-institutional studies, when human participants at a collaborating non-VA institution are to be paid for the same participation in the same study at the same rate proposed.

☐ **Comparable Situations:** In other comparable situations in which payment of participants is appropriate. Describe:

☒ **Transportation Expenses:** When transportation expenses are incurred by the participant that would not be incurred in the normal course of receiving treatment and which are not reimbursed by any other mechanism.

2) Payment Amount:
Total Amount $ **Approximately $316, assuming study completion**
Prorated as follows: **$12/hour for non-scanner time, $20/hour for scanner time, up to $40 for task-related payments, and a $100 completion bonus to encourage returning for all 3 visits**

3) Method of Payment:

☐ Cash	☒ Check	☐ Gift certificate	☐ Other:

4) Payment Schedule:

☐ Each visit	☒ Study completion	☐ Other:

5) Substantiate that proposed payments are reasonable and commensurate with the expected contributions of the participant.
We anticipate that subjects will be present for 2 hours for the screening visit, and 5 hours for each of the MRI visits, of which 2 hours will consist of MRI scanner time. 8 hours of behavioral time x $12/hour = $96. 4 hours of MRI scanner time x $20/hour = $80. Including $40 related to performance of the economic games and the $100 completion bonus, the total payment would be $316.

6) Substantiate that proposed payments are fair and appropriate and that they do not constitute undue pressure or influence to participate.
These payments are consistent with our previous IRB-approved protocols at U.C. Berkeley and U.C. San Francisco. Payments of $12/hour for behavioral testing and $20/hour for MRI scanner time reflect ongoing subject payment rates at U.C. Berkeley. The maximum of $40 for bonus payments related to economic task performance is necessary to encourage veridical participation in the economic tasks. Finally, the $100 completion bonus ensures that subjects return for all 3 sessions, while balancing the concerns of undue influence to participate.

9. Which of the following vulnerable populations will be recruited for this study? *(Check all that apply).*

☒ None	☐ Children*	☐ Non-English Speaking
☐ Economically Disadvantaged*	☐ Employees	☐ Persons with HIV
☐ Educationally Disadvantaged*	☐ Fetuses*	☐ Prisoners*
☐ Impaired Decision Making Capacity*	☐ Homeless/Shelter	☐ Students/Trainees

☐ Pregnant Women*	☐ Mentally Disabled*	☐ Terminally Ill Patients
☐ Others:		
** listed in the Federal regulations; VHA Handbook 1200.5 Appendix D lists special requirements*		
a. Describe the scientific and ethical reasons for including vulnerable populations in the research. *(Why are vulnerable populations necessary in this research study?)* N/A		
b. Describe the extra protections and additional safeguards that protect the rights and welfare of vulnerable groups. *(How are the vulnerable populations being protected?)* N/A		
c. Describe the procedures that you have devised to ensure that participant's representatives are well informed regarding their roles and obligations to protect incompetent participants or persons with impaired decision making capacity. N/A		

G. RESEARCH PROCEDURES

1. Check all procedures to be performed on human participants, samples or charts:	
☐ Analysis of Existing Biological Specimens	☒ Interview
☐ Analysis of Existing Data	☐ Invasive Procedures – Diagnostic (e.g. biopsy, catheters, etc.)
☒ Biological Specimen Collection (urine, sputum, tissue, etc.)	☐ Invasive Procedures – Therapeutic (e.g. infusions, catheters, etc.)
☒ Blood Collection	☒ fMRI: Clinical Research
☒ Chart Review	☒ MRI: Clinical Research
☒ Cognitive or Perceptual Experiment	☐ MRI: Diagnostic
☐ Commercial Product Development Potential from Human Biological Specimens	☒ Placebo
☐ Deception	☒ Physical Measurements: Non-Invasive (e.g. vitals signs)
☐ Device(s): FDA approved	☐ Public Behavior Observation
☐ Device(s): Investigational	☒ Questionnaire
☒ Drug(s): FDA approved	☐ Radiation: Clinical Research (e.g. PET)
☐ Drug(s): FDA approved Controlled Substance	☐ Radiation: Diagnostic (e.g. X-ray)
☐ Drug(s): Investigational	☐ Radiation: Therapeutic
☐ Drug(s): Investigational Controlled Substance	☐ Specimen Collection for Future Use (tissue banking)
☐ ECG	☐ Specimen Use from Tissue Bank (stored samples)
☐ EEG	☐ Surgery
☐ EMG	☐ Survey
☐ Evaluation of Program or Services	☐ Taste Test
☐ Gene therapy	☐ VA Data Record Search (Data Mart, Data Warehouse, etc.)
☒ Genetic/DNA Research	☐ Other

2. **Describe research procedures to be performed on participants, samples or charts.**
   a. **Describe all interactions with participants or their identifiable samples or data in detail.**

For subjects who potentially meet eligibility criteria, we will use the initial phone screening performed by Dr. Kayser, Dr. D'Esposito, their postdoctoral fellows, graduate students, or research assistants to verify that subjects meet the criteria specified in the advertisement. Specifically, interested subjects will contact the study via the contact information provided in the study advertisements. Dr. Kayser, Dr. D'Esposito, or their research associates will then contact each potential subject by phone (or by each subject's preferred method of communication) in order to set up a brief phone interview, during which the requirements for the study will be reviewed. For control subjects, research assistants, graduate students, or postdoctoral fellows may perform the initial phone screening. Information collected during this phone screening is not written down.

For subjects who state that they are potentially eligible for enrollment, we will arrange an initial visit, at the subject's convenience, to perform further screening and to gather initial behavioral data. The Subject Health screening sheets will be filled out immediately (and only) after obtaining written informed consent. We will additionally administer an extensive questionnaire listing contraindications to MRI scanning. Because the MRI scanner attracts certain metals, subjects who may have metallic objects in their bodies will be excluded. (As an additional measure of protection, we will use a hand-held metal detector to screen subjects before entering the scanner. This screening visit will take place either at the VA NCHCS Martinez campus or at the U.C.S.F. Research Clinic located at U.C. Berkeley, whichever is more convenient for subjects.

After the study is explained to them and informed consent is obtained, subjects will participate in a blood draw in order to determine liver function tests. A hepatic screen will assay total protein, albumin, globulin, A/G ratio, bilirubin (total, direct, and indirect), alkaline phosphatase, AST (SGOT), and ALT (SGPT). These tests will be performed in the VA NCHCS system or at Quest Diagnostics. Elevation of plasma bilirubin, AST (SGOT), ALT (SGPT), or alkaline phosphatase consistent with liver disease and greater than 2.5 times the upper limit of normal will be grounds for subject exclusion. (Note that ongoing monitoring of liver enzymes will not be necessary, as only a single, counterbalanced dose of tolcapone will be administered to each subject.) If subjects have had liver function tests evaluated within the previous 6 months, subjects may sign a waiver to allow us to obtain those laboratory results. This step has the benefit of minimizing the use of even minimally invasive procedures for each subject. Subjects will also provide a salivary sample so that COMT genotype -- specifically, SNPs within the COMT gene -- can be obtained. Importantly, COMT genotype may modulate the effect of tolcapone, which inhibits COMT, and will therefore provide additional information that may potentially impact how the drug affects each subject. DNA extraction and analysis will be conducted using standard methods on saliva samples obtained just prior to the first MRI session. The UC Genomics Core will carry out genotyping of the COMT gene using Taqman and other assays with which they have extensive experience. Examiners and researchers outside of the Genomics Core will remain blinded to genotype until the end of the study.

Female subjects will also be screened for pregnancy, as the effects of the drug during pregnancy are not adequately known and the drug can appear in breast milk. (Pregnancy is also a contraindication to MRI scanning; see below.) Since subjects may not know they are pregnant, all female subjects recruited to participate in the study will be required to have a urine pregnancy test prior to each session of the study. They will self-administer the test after coming into the research lab. These pregnancy tests have been in reliable use at the UC Berkeley Brain Imaging Center and Research Clinic for approximately 20 years without any reported failures. These requirements will not apply to any female subjects who are post-menopausal.

Finally, at the screening visit subjects will complete a number of questionnaires (attached). They will also complete the VA NCHCS multi-center core TBI protocol.

b. Describe the research methods, including how the study will be implemented locally.

This study is a randomized, double-blind, counterbalanced, crossover, behavioral and resting state fMRI study designed to test the effect of tolcapone on decision-making and neural activity. Tolcapone is an orally active, selective and reversible inhibitor of catechol-O-methyltransferase (COMT), an enzyme that catabolizes extracellular dopamine. Consequently, tolcapone prolongs the effect of endogenous dopamine release. It was FDA-approved in 1998 for treatment of Parkinson's disease as an adjunct to levodopa-containing medications Following screening, subjects will participate in two sessions (on separate days), and will be administered either placebo or tolcapone at the start of each session. Each session will last approximately 5-6 hours. Combining tolcapone challenge with task-active fMRI allows us to examine the impact of tolcapone on the neural circuits underlying decision-making during task performance.

In keeping with our previous protocols and published reports, the randomization of drug across subjects (tolcapone versus placebo) is accomplished via a true random number generator utilizing atmospheric noise and accessible at the website www.random.org. The dispensing record is now attached. Utilizing the (blinded) medication assignment, the clinician identifies the study drug, logs the drug into the dispensing record, notes the drug administered in the subject's documentation, and administers the drug to the subject.

c. Provide detailed information about all study procedures, including the approximate duration and frequency of each procedure. It is not necessary to repeat descriptions of non-human related procedures from the protocol narrative *(e.g. you should describe how much and how frequently blood is drawn, but not the methods for performing tests on the blood, if already stated elsewhere).*

For the MRI component of the study, subjects will participate in 2 days of testing – one each for tolcapone and placebo administration. The structure of each session of the 2 days will be identical: subjects will participate while seated in a well-lit, comfortable room in the Brain Imaging Center on the UC Berkeley campus where the MRI scanner is located. Light snacks and reading material will be provided. The sequence of events during a session will be as follows:

-10 minutes: Subjects will be urine-screened for illicit drug use (Biotechnostix) and for alcohol intoxication via breathalyzer (Lifeloc Technologies). Female subjects will be screened for pregnancy as described above. Active use of substances other than alcohol or tobacco, use of alcohol on the day of the study as assessed by breathalyzer testing, and/or a positive pregnancy test, will be grounds for exclusion.

-5 minutes: Subjects perform a baseline testing mini-battery and have their blood pressure taken. The mini-battery will consist of the backwards digit span, visual analog scales (anxious, happy, sad, nauseous, drowsy, jittery, fatigued, and dizzy), a time perception task, and/or a motor tapping test, all of which are designed to assess changes in dopaminergic tone.

0 minutes: Subjects will be administered either 200mg of tolcapone or placebo, prepared by the compounding pharmacy to match tablet appearance, in randomized, double-blind, counterbalanced fashion. Because tolcapone can discolor the urine, and therefore unblind participants, both tolcapone and placebo will be co-administered with riboflavin, a naturally-occurring B-vitamin that also discolors the urine and therefore masks this tolcapone effect.

+60 minutes: Tolcapone concentration is known to peak in the bloodstream at approximately 90 minutes after oral ingestion. At approximately 60 minutes, subjects will be brought to the MRI scanner suite. They will be provided with ear protection, lumbar support, and head cushioning to ensure that they are comfortable in the scanner. They will also be given a response box in order to respond during task performance, and they will be provided with a mirror in order to see a rear-projection screen. These procedures will be performed in time for subjects to be ready for testing that includes the time of peak drug concentration. Behavioral and MRI tasks are described in more detail below.

+210 minutes: Subjects will undergo additional behavioral testing outside the scanner.

+300 minutes: Subjects will complete the testing day.

The primary cognitive tasks are three. The first is a computer-based delay discounting task in which subjects choose between hypothetical monetary rewards available immediately versus lesser ("discounted") rewards available at one of a range of future time points or "delays". The second is a computer-based visual attention task in which subjects respond to pictures of faces and houses. The third is a computer-based social-emotional task in which subjects view pictures of emotional faces and from the IAPS set. They are required to react to the images, or to reframe the context of the picture to reduce the emotional response. Other tasks to measure impulsivity or decision-making may also be employed. Specifically, we will measure reaction time and response inhibition (i.e. motor impulsivity) directly, assess memory and higher-order problem-solving, ask subjects game theory-style decision-making questions, or determine how cognitive set modifies decisions about monetary reward and risk.

d. Distinguish procedures that are for research from those that are clinically indicated and/or standard of care.

All of the procedures included in this protocol are employed for research purposes only.

e. **Will any study procedures** *(including analysis of subject samples or data)* **be conducted at any site other than VANCHCS/VACCHCS?** ☒ Yes ☐ No • *If "YES", complete the following information:*
1) Site(s): UCSF Research Clinic, located at UC Berkeley, and UC Berkeley Brain Imaging Center
2) What study procedures will be performed there? Screening visits will be performed at the UCSF Research Clinic, located at UC Berkeley, for subjects who find the site more convenient than the VA Martinez campus. The U.C. Berkeley Brain Imaging Center represents the site for MRI scanner visits. Blood testing for liver function and complete blood counts may be performed at Quest Diagnostics. The UC Genomics Core will perform genetic analyses.

H. RISK

1. Expected risks

- *Describe all known risks to subjects of study-related procedures and products and their expected frequency and severity.*
- *Assess the likelihood and seriousness of identified risks.*

a. Physical Risks: There are no known risks of functional MRI studies. This noninvasive technique involves no catheterizations or introduction of exogenous tracers. A multitude of subjects have now undergone magnetic resonance studies without apparent harmful consequences. Radiofrequency power levels and gradient switching times used in these studies are within the FDA-approved ranges. Some people become claustrophobic while inside the magnet, and in these cases the study will be terminated immediately at the subject's request. The only absolute contraindications to MRI studies are the presence of either intracranial or intraocular metal, or a pacemaker. Relative contraindications include pregnancy and claustrophobia. Participants who may be pregnant, who may have metallic foreign bodies in the eyes or head, or who have cardiac pacemakers will be excluded because of potential contraindications of MRI in such subjects. A negative pregnancy test will be required for female subjects.

b. Tolcapone, the medication being used in these studies, has previously been associated with one very serious adverse effect. Three elderly parkinsonian women who were also taking tolcapone suffered fatal fulminant hepatic failure when liver function tests were either unmonitored or not used to discontinue the medication. Since this issue was raised in 1998, during 40,000 subsequent patient years of treatment only 3 cases of severe but reversible liver injury have occurred with chronic use. Reviews have concluded that "severe liver injury as a result of tolcapone is not greater than that observed with other routinely prescribed drugs such as carbamazepine, valproate and phenytoin". We note that this study will involve only a one-time dose of this medication, and that it will only be administered to subjects with liver function tests within a defined range prior to participation. Additionally, the current study population is significantly younger and has been selected to be physically healthy. No case reports or other studies have reported abnormalities in liver function that have developed after one dose. It is therefore very likely that our current study population will be at much less risk. Nonetheless, all subjects will be informed of this risk, and subjects with liver function tests elevated above twice the normal range will be excluded from participation. Notably, the other drug in its class – entacapone – works only peripherally, as it does not cross the blood-brain barrier. In placebo-controlled trials of tolcapone, common side effects that occurred at a greater rate than for placebo included nausea, anorexia, orthostasis, and fatigue. Each of these side effects is uncommon at the single dosage being utilized in these studies, and subjects with contraindications to tolcapone use are excluded in our screening procedures. Moreover, in our sample of greater than 100 subjects who have taken tolcapone for other studies, no subject has reported such side effects, and subjects have been unable to identify placebo versus tolcapone.

c. Psychological Risks: There are no risks associated with cognitive testing except for the occasional possibility of fatigue or frustration with poor performance. Testing will stop if a subject becomes too tired or frustrated. Subjects who become anxious during testing (e.g. due to PTSD symptoms) will have access to drop-in Mental Health care within the VA system, and a physician or nurse practitioner will be on-site at all facilities.

d. Social Risks: There are no known social risks of these studies.

e. Economic Risks: There are no known economic risks of these studies. Subjects will be reimbursed for their travel and participation.

f. Legal Risks: There are no known legal risks of these studies.

2. Risk minimization

a. Describe the impact of study design on risk. *(e.g. does observational design impact on risk; or does observational design only impact privacy risks; or does placebo controlled design impact risk, or do all patients receive therapy; or does single blind placebo washout period increase risk of uncontrolled symptoms?)*

Because the study is performed in double-blind fashion, researchers will not be immediately aware of the drug condition should subjects have a side effect. If in the judgment of the on-site clinican this side effect requires knowledge of the medication provided, the blind can be broken .

b. Describe study procedures that minimize risks.

All subjects will be screened by the experimenter to ensure they do not have any metallic implants, shrapnel, pacemakers, or other contraindications to MRI. All subjects will be under close supervision on the days of the study. Also, for each subject's protection, access to the scanner is restricted to members of the research team. Information obtained from the studies in the research plan will be strictly confidential, except as required by law, but will be made available to the subject and his/her physician in response to a specific request from the participant. There will be no personal identification of subjects in scientific communications. fMRI studies are not given a clinical interpretation. In the event that a significant abnormality is detected on an anatomical MRI scan, a recommendation to seek further medical consultation will be made. However, it is stressed that the MRI evaluation performed for these studies does not represent a complete clinical MRI evaluation, and it is not being performed for clinical diagnostic purposes. All complications of treatment, as well as adverse and severe adverse events, will be promptly reported to the local institutional review board for human subjects. Timely contact will be made with the subject's physician, and care will be provided within the VA system, where applicable.

c. Describe standard of care procedures that minimize risks.

As described in section (b) above, study procedures will minimize risks. These research studies are operating in an area of study for which standard of care procedures are otherwise defined.

I. RISK BENEFIT RATIO

1. Risks in Relation to Benefits

a. What are the direct benefits to the participants?

Healthy adults and TBI patients may gain some insight into the scientific process of learning about human cognitive function; they may also note changes in their performance on the behavioral tasks. In addition, subjects may benefit psychologically from knowing that they are participating in research designed to benefit veterans. In addition, subjects will be reimbursed for their participation. The potential benefits anticipated in improved treatment and management of patients with cognitive disorders are expected to far outweigh the minimal associated risks.

b. Why do you believe the risks are reasonable in relation to the potential benefits to the participants?

The behavioral and MRI procedures are well-known to subject participants to minimal risks. The study drug has been very well tolerated in our previous studies of greater than 75 subjects. Study procedures described above minimize risks of each of these exposures. Given these small risks, and the above benefits, we believe the benefits outweigh risks.

c. What are the benefits to society?

Both awareness and incidence of mTBI have increased dramatically in recent years. To date the pharmacological treatments of mTBI are extremely limited. If this study points toward a benefit of tolcapone, this drug could improve the treatment of these individuals. We anticipate that the results of these studies will help in the overall understanding of cognitive function and may lead to improved treatments for patients with traumatic brain injury and other brain injuries.

Why do you believe the risks are reasonable in relation to the potential benefits to society? As above, minimal risks and potentially significant benefits argue that the risk-benefit analysis represents a reasonable tradeoff.

2. **Alternatives to participation**
   a. **Describe appropriate alternative procedures or courses of treatment, if any, which might be advantageous to the participant.** *(If no alternatives exist or if this is not a treatment study, state so.)* Because this study is a research study, not a treatment study, the alternative for subjects would be not to participate.

J. MONITORING SAFETY

1. **Describe the Data and Safety Monitoring Plan that ensures the safety of participants in this research study.** *(e.g. what labs to monitor for abnormalities, what questionnaire responses to monitor for suicide)*

Subjects will be closely monitored while MRI scans are underway, and they will be able to communicate with the scanner operator at any time. Only scanner operators who have received both MRI safety and operator training will be allowed to scan subjects. Tolcapone administration will be observed, and subjects will remain in the laboratory setting for 6 hours after tolcapone (or placebo) ingestion so that any immediate side effects will be noticed. The drug is only administered in the UCSF Research Clinic located at UC Berkeley, and only under the supervision of an on-site study physician (currently either Dr. Kayser or Dr. D'Esposito). Currently either Dr. Kayser or Dr. D'Esposito (both neurologists within the VA system), or in the future another trained prescribing clinician, will be on-site whenever a subject is administered a medication. Tolcapone will be kept in a secure, locked location in the UCSF Research Clinic located at UC Berkeley, and all use will be logged. Finally, a monitoring board headed by a physician independent of the study will review study procedures and outcomes.

Numerous procedures ensure that the study drug is safe for use. All ingredients used are weighed and compared with the weight of the final product to ascertain that the strength of the drug in milligrams is as expected. Tolcapone is supplied as 100mg tablets, allowing the pharmacist to easily verify that the final weight of the compounded product is equal to the weight of the 2 x 100mg tablets, the incorporated riboflavin, and inert compounding ingredients. Tolcapone is supplied with a 2-year expiration date. The compounded bottles are labeled with a standard six month expiration date after compounding to ensure stability even though the tablets are given a two years expiration by the manufacturer. Consistent with the package insert for tolcapone, the original tolcapone tablet is not specially formulated (e.g. as some delayed-release formulations of other medications may be). Similarly, it is not resolubilized during the compounding process. Tolcapone is currently purchased by Abbotts Compounding Pharmacy from Bellco, a licensed wholesaler and subsidiary of AmerisourceBergen Corp. The placebo capsule contains microcrystalline cellulose and riboflavin that are both obtained from Medisca, an FDA-registered chemical wholesaler. Both tolcapone and placebo will be stored in a locked cabinet, in a secured office, away from light and moisture sources, in space occupied by the UCSF Research Clinic located at UC Berkeley.

2. **Does this study have a Data and Safety Monitoring Board (DSMB)?**
   ☒ Yes ☐ No
   - *If "YES":*

   a. **What is the nature and expected role of the DSMB?** An independent DSMB will examine accumulating data to assure protection of patients' safety while the study's scientific goals are being met. The DSMB is responsible for conducting periodic reviews of accumulating safety and efficacy data. It will determine whether there is support for continuation of the trial, whether there is evidence that study procedures should be changed, or whether the trial should be halted for reasons relating to the safety of the study patients. Adverse event data and other data intended for safety monitoring will be reported through the study Principal Investigator to the DSMB. After each meeting, the DSMB will communicate its recommendations and a summary report of all 'possibly' related serious adverse events (SAEs) to the Principal Investigator, to be conveyed to the IRBs involved in the study. While interim efficacy analysis is not planned, the DSMB may request such analysis to permit proper evaluation of safety data. If an unscheduled interim efficacy analysis is necessary, the DSMB will specify the question, the analysis required, the critical values for a decision, and the statistical procedures necessary to control the overall type 1 error at $p<0.05$. A protocol amendment will be included in the DSMB report of the analysis describing the necessary changes in the statistical plan.

   b. **How often will the findings of the DSMB be reported to the IRB?** Our first subject was enrolled in July of 2015, a report will be generated yearly from this date.

3. **Explain how researchers will manage adverse events and research-related injuries.**

   Serious adverse events related or unrelated to the research, and serious unanticipated problems related to the research, will be reported directly to the Director of the Office for Protection of Human Subjects. These problems or events will be reported as soon as possible, and at most within one week (seven calendar days) of the Lead Investigator learning of the incident. All MRI studies performed at the UC Berkeley Brain Imaging Center are part of research protocols and are not intended to provide comprehensive clinical MRI examinations of the brain. If, however, a potential abnormality is identified on the MRI scan, one of the two study neurologists – Dr. Kayser or Dr. D'Esposito – will notify the subject and the subject's physician.

4. **Describe the circumstances under which a participant may be withdrawn prematurely from the study and the potential risks of such early withdrawal.**

   Subjects who do not return for follow up visits or who are unable to otherwise comply with study procedures will be withdrawn from the study. In addition, if subjects do not wish to continue with the study or suffer a severe adverse event, they will be removed from the study. There are no risks in this study of early withdrawal per se.

5. **Describe the procedures for reporting adverse events.**

   Serious adverse events related or unrelated to the research, and serious unanticipated problems related to the research, will be reported directly to the Director of the Office for Protection of Human Subjects. These problems or events will be reported as soon as possible, and at most within one week (seven calendar days) of the Lead Investigator learning of the incident.

K. SAFETY REPORT *(refer to OHRP "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events" dated January 15, 2007)*

1. **Adverse Events**

   a. **Local (Internal) Adverse Events and Serious Adverse Events (AE/SAE):** Have ALL complications, untoward side effects, or adverse events related or possibly related to research at this site been reported to the IRB since the last review?

   ☐ **Yes** ☐ **No** ☒ **N/A = none occurred**

   - *If "YES":*
     Attach a Local Adverse Event spreadsheet summarizing all AE/SAE's which occurred at this site since the last report to the IRB.
   - *If "NO":*
     Submit the missing report to the IRB and attach a Local Adverse Event spreadsheet summarizing all AE/SAE's which occurred at this site since the last report to the IRB.

   b. **Global (External) Adverse Events and Serious Adverse Events (AE/SAE):** Have any complications, untoward side effects, or adverse events been reported at other sites (SAE or IND Safety Reports) since last report?

   ☐ **Yes** ☐ **No** ☒ **N/A**

   - *If "YES":*
     Attach a Global Adverse Event spreadsheet summarizing all AE/SAE's which occurred at other sites since the last report to the IRB.

NOTE: Definition of SAE and AE:

- *Serious Adverse Event – any adverse experience that results in the following: Death; Hospitalization; Disability/Incapacity; Congenital Anomaly/Birth Defect; Requires Intervention; or is Life-threatening*
- *Adverse Event – any adverse experience temporally associated* with the investigational treatment not meeting the definition of serious adverse event.*

* ***temporally associated*** *– during the time period the subject participates in the study*

2. **Have unanticipated problems*** *(local or global)* **involving risks to subjects or others, or significant new findings** *(that have not been previously reported)* **been discovered since the previous IRB review that might affect the subject's willingness to continue participation?**

   ☐ Yes ☒ No

   - *If "YES", complete the following:*

   a. **Attach a spreadsheet summarizing all unanticipated problems which occurred since the last report to the IRB.**

   b. **Explain the risks or findings in detail:** *(a clear explanation of why the adverse event or series of adverse events has been determined to be an unanticipated problem)*

   c. **Describe any proposed protocol changes or other corrective actions to be taken by the investigators in response to the unanticipated problem:**

   d. **Do these risks or findings require modification of the informed consent form?**

   ☐ Yes ☐ No

   - *If "YES", have the modifications been submitted to the IRB?*

   ☐ Yes ☐ No

   e. **Were subjects notified of these risks or findings?**

   ☐ Yes ☐ No

   f. **Were subjects re-consented?**

   ☐ Yes ☐ No

3. Have other unanticipated problems (not related to adverse events) been discovered since the previous IRB review?

☐ Yes ☒ No

- *If "YES", complete the following:*

a. Attach a spreadsheet summarizing all unanticipated problems which occurred since the last report to the IRB.

b. Explain the findings in detail:

c. Describe any proposed protocol changes or other corrective actions to be taken by the investigators in response to the unanticipated problem not related to an adverse event:

*** NOTE: Unanticipated problems are any incident, experience, or outcome that meet all of the following criteria:**

- *Is unexpected in terms of nature, severity, or frequency*
- *Is related or possibly related to participation in the research*
- *Suggests that the research places the subject or others at a greater risk of harm than was previously known or recognized*

4. Describe any complaints about the research since the last IRB review.

☒ N/A – none occurred

5. Describe any unanticipated protocol deviations (including errors and accidents) since the last review.

☒ N/A – none occurred

L. PRIVACY AND CONFIDENTIALITY

1. Research Data

a. Identifiers: Please indicate all identifiers that may be used by researchers or included in study research records.

☐ NO identifiers used by researchers (*skip to item L.1.d. "Medical Records or Health Information"*)

Check all that apply:

☒ Names	☒ Social Security Number	☐ Device Identifiers
☒ Dates	☒ Medical Record Number	☐ Web URLs
☒ Postal Addresses	☐ Health Plan Numbers	☐ IP Address Numbers
☒ Phone Numbers	☐ Account Numbers	☐ Biometric Identifiers
☐ Fax Numbers	☐ License/Certificate Numbers	☐ Photos and Comparable Images
☒ Email Addresses	☐ Vehicle ID Numbers	☐ Any Other Unique Identifier

b. Source of Identifiers Listed Above: Please indicate the sources of the information listed in part 1(a) above

Check all that apply:

☒ Medical Records (created as part of health care, collected as part of health care, added to the medical record, extracted from the medical record, or used to make health care decisions)

☒ Directly from the Participant, including Interviews, Questionnaires

☐ Records Open to the Public

☐ Other:

c. Describe how identifiers will be used to screen and/or recruit participants for the trial.

These identifiers will be used to contact subjects and to pay subjects. In addition, as indicated below, subjects may also allow researchers to obtain recent (previous 6 months) laboratory results for liver function testing.

d. Medical Records or Health Information: Please indicate all information that may be used by researchers or included in study research records.

☐ NO medical record or health information used by researchers (*skip to Section M. "Research Data Security"*)

Check all that apply:

☐ History and Physical Exam	☒ Progress Notes
☐ Operative Report(s)	☐ Discharge Summary(ies)
☒ Diagnoses	☒ Drugs/Medications
☐ Radiology Images	☐ Radiology Reports
☐ Pathology Reports	☒ Laboratory Reports
☐ ECG Reports	☐ Consult Reports
☒ Drug Abuse	☒ Alcoholism or Alcohol Abuse
☐ Testing for or Infection with HIV	☐ Sickle Cell Anemia
☐ Psychological Tests	☒ Mental Health (not psychotherapy notes)
☐ Patient Demographics	☐ Only the following records of types of health information:

e. Describe who will access protected health information (PHI) *(i.e. medical record)* **and for what purpose.**

Researchers will not access PHI except in one circumstance. During the screening procedures, a blood draw is required in order to assess liver function tests (AST, ALT, T.Bili, D.Bili, Alk Phos). Some subjects may have obtained liver function tests within the previous 6 months, and may therefore be able to avoid an unnecessary venipuncture. If so, subjects may sign a disclosure of PHI form so that the research team may obtain a record of these results for determination of eligibility. Dr. Kayser will access the PHI

In keeping with their roles in monitoring the study, the following entities may access or use PHI: VA RR&D, UC Berkeley IRB, UC San Francisco IRB, the FDA, and the VA NCHCS IRB.

f. Disclosure of Protected Health Information (PHI): Please indicate to whom or where you may disclose any of the information listed above as part of the study process.

Check all that apply:

- ☐ We do not plan to share any of the PHI listed above outside the research team.
- ☒ VANCHCS/VACCHCS Research & Development Committee and Subcommittees
- ☐ VANCHCS/VACCHCS Designated Non-Profit Corporation
- ☒ U.S. Food and Drug Administration (FDA)
- ☐ U.S. Department of Health and Human Services Office for Human Research Protection (OHRP)
- ☐ U.S. Government Accounting Office (GAO)
- ☐ Participant's Medical Record
- ☒ Study Sponsor: **VA RR&D**
- ☒ Others **UCSF and UC Berkeley Institutional Review Boards**

g. Identify who will disclose information.

If required by the organizations noted in (f), Dr. Kayser will disclose the requested information.

2. **Data Protection**

a. **Describe the provisions that exist to protect participant privacy during and after the research.**

We will collect only the minimum amount of the individual's private information required to complete our study. To protect privacy, we will advise potential subjects of the minimum amount of personal information that would be required of them in order to participate in our study. Furthermore, we will provide information about the logistics of participating in our research study (e.g., location of testing) to ensure that each subject can decide whether logistics will impinge on his/her privacy. Finally, all participants will be informed regarding how information is secured and stored to protect confidentiality. Based on this information, the potential subject can determine for him/herself if he/she wishes to provide this information to us and whether he/she wishes to participate in our research study

b. **Describe the provisions in place to protect participant confidentiality during and after the research.**

Identifiable personal information will be obtained from each subject. Each participant will then be given a unique identifier that will not contain any identifying personal information. Information gathered using this unique identifier will be kept in a separate locked file cabinet. Only members of the research team who have been identified as key research personnel will have access to the subject information and study data. In the event that a potential subject is deemed ineligible for the study, all personal, identifiable information will be destroyed.

Questionnaire data are stored in a separate cabinet in Dr. Kayser's office, and do not include subject personal identifiers. Behavioral, imaging, and genetic data do not include personally identifiable information. Data are stored in password-protected data files. The fMRI data are collected at U.C. Berkeley and are temporarily stored in a password protected directory on the UCB Brain Imaging Center network, which is also behind a firewall. No subject personal identifiers are ever associated with these data on either network.

The data are to be presented in tables or MRI scans in peer-reviewed publications. Individual subjects are never identified. We have found that some subjects are interested in the published data and we provide them with copies of publications where their data is included. The consent forms and screening sheets of subjects excluded from the study will be destroyed.

M. INTERIM FINDINGS

1. **Provide a summary description of study progress, subject experiences, research results obtained thus far, and any new information since the IRB's last review.**

Currently we are actively recruitng potentially eligible subjects. Because we are still in the process of collecting data there are no research results at this time.

2. **Provide a summary of any relevant recent literature since the IRB's last review.** *(Attach copies of any relevant publications.)*

3. **Attach any relevant multi-center trial reports.**

N. INFORMED CONSENT PROCESS

1. **Will all participants taking part in this study be consented on VA Form 10-1086?**

☒ Yes ☐ No

- *If "YES", continue to question #2 and #3 below.*
- *If "NO", submit the document entitled "Request to Waive Consent and Authorization for a Research Study" and skip Sections O2 and O3.*

2. Describe the process of obtaining informed consent.

a. Describe who conducts the consenting process.

Andrew Kayser, M.D. Ph.D., Mark D'Esposito M.D., or Nick Rodriguez, BA in conjunction with their post-doctoral fellows, graduate students, and/or research assistant(s), will obtain informed consent from the subjects. All researchers participating in the consent process, and in the study as a whole, will be certified to work with human subjects.

b. Describe when it occurs.

Informed consent will take place at the beginning of the screening visit.

c. Describe where it occurs.

Informed consent will be obtained at the research lab in Martinez or in the UCSF Research Clinic located at UC Berkeley.

d. Describe how you will assure an acceptable level of comprehension before consent.

If a subject has difficulty reading, the researcher will read the consent to the participant in the presence of a spouse, family member, or other subject-designated individual. As in our other active protocols outside the VA, subjects will be asked to repeat in their own words what goals and procedures the study involves, including risks and benefits of participation. As in our other active protocols outside the VA, all subjects will be given the opportunity to ask any questions about the goals and procedures the study involves, including risks and benefits of participation. If the subject indicates that s/he cannot adequately understand the study goals and procedures, or the researcher believes that s/he cannot adequately understand the study goals and procedures, the subject will be excluded from participation.

e. For participants who may have impaired decision-making capacity to give informed consent:

1) Describe the likely range of impairment.

Subjects with impaired decision-making capacity to give informed consent will not be enrolled in the study.

2) Describe how the participants' decision-making capacity to consent will be determined.

As noted in section 2d, subjects will be required to demonstrate an understanding of the goals and procedures of the study, including risks and benefits.

3) Who will determine whether or not the participant has decision-making capacity to consent?

We will not recruit patients who have impaired decision-making capacity. If such a subject is inadvertently screened and the researcher who is obtaining consent notes that the subject cannot explain goals, procedures, risks, and benefits of the study, the researcher will be instructed to call Dr. Kayser or Dr. D'Esposito to confirm. If confirmed, these subjects will be excluded.

f. If any vulnerable populations will be recruited, describe what precautions will be taken to insure their protection from undue influence.

No vulnerable populations will be recruited.

g. If surrogate consent is likely to be required, describe your procedure for obtaining consent from the legally authorized representative.

Surrogate consent will not be required.

3. After Hours Contact Information *(to be included in the consent form)*

a. The VA approved after-hours telephone number for research studies is (916) 843-7000 extension 6051.

b. This study will use the VA approved after-hours telephone number for research studies.

☒ Yes ☐ No

- *If "YES", complete the following:*

1) Designated Service (department):

OR

1) Designated Contact Person: **Andrew Kayser MD**

2) After-hours telephone number for the designated contact person (to be given to the VA after-hours operator): **415-302-0303**

b. This study will use a Designated Contact Person.

☒ Yes ☐ No

- *If "YES", complete the following:*

1) Designated Contact Person: **Andrew Kayser MD**

2) After-hours telephone number for the designated contact person: **415-302-0303**

O. PRINCIPAL INVESTIGATOR'S KNOWLEDGE ATTESTATION

Initial beside each statement to confirm your knowledge and agreement.

AK **1.** I assure that the rights and welfare of human subjects participating in this research project will be protected at all times and that the benefits to be gained from this study are commensurate with the risks involved.

AK **2.** I will obtain, (unless a waiver of consent and authorization is approved) an authorization to use PHI for research and a fully documented research informed consent on a VA Form 10-1086 for each subject enrolled.

AK **3.** I will document the consent process in the progress notes for each research subject, unless a waiver of consent and authorization is approved.

AK **4.** I certify that I will report all serious adverse events and unexpected adverse experiences as required.

AK **5.** I acknowledge that I will immediately report any complications arising from this study to the Human Studies Subcommittee/IRB through the Research Office.

AK **6.** I understand that any research project utilizing VA resources (i.e. space, personnel, services) must be approved by VANCHCS/VACCHCS Research and Development (R&D) Committee prior to commencement of the project.

AK **7.** I understand that any research involving VANCHCS/VACCHCS patients must be approved by VANCHCS/VACCHCS R&D Committee.

AK **8.** I will not begin any research project using human subjects before it has been fully approved by VANCHCS IRB and VANCHCS/VACCHCS R&D Committees.

AK **9.** I understand that I am required to annually complete an educational course or web-based training on **both** the protection of human subjects in research **and** Good Clinical Practice (GCP). ORD and Collaborative IRB Training Initiatives (CITI) have developed a VA training curriculum to satisfy this annual training requirement. (http://www.appc1.va.gov/resdev/fr/PRIDE/training/)

AK **10.** I understand that the research staff working for me who are involved in human studies are required to annually complete an educational course or web-based training on **both** the protection of human subjects in research **and** Good Clinical Practice. A single combined course will satisfy this requirement.

AK **11.** I understand that there may be specific training requirements for me and my research staff regarding animal research, laboratory safety, and security.

AK **12.** I understand that I am to cooperate fully with VANCHCS Research Compliance Officer regarding compliance in research.

AK **13.** I understand that any research involving radiation must be approved by VANCHCS Radiation Safety Committee.

AK **14.** I agree to abide by the requirements of VHA Handbook 1200.18, *Intellectual Property*. (http://www.va.gov/publ/direc/health/Handbook/1200-18hk.pdf)

AK **15.** I agree to abide by the requirements of VANCHCS PS-151-9, *Publication of Professional Papers* (http://vaww.northern-california.med.va.gov/policies/ResearchIndex.html) and VHA Handbook 1200.19 *Presentation of Research Results Handbook*. (http://www.va.gov/publ/direc/health/handbook/1200.19hk.pdf)

AK **16.** I agree to abide by the requirement of VANCHCS PS-151-7, *Administration of Non-VA Funded Research Grants*. (http://vaww.northern-california.med.va.gov/policies/ResearchIndex.html)

AK **17.** I agree to abide by the requirements of VANCHCS PS-151-2, *Detecting and Managing Conflicts of Interest in Research* (http://vaww.northern-california.med.va.gov/policies/ResearchIndex.html).

AK **18.** I agree to abide by the requirements of VHA Handbook 1200.8, *Safety of Personnel Engaged in Research* and the *Chemical Hygiene Plan* for Medical Research. (http://www.va.gov/publ/direc/health/Handbook/1200.8hk.pdf)

P. PRINCIPAL INVESTIGATOR'S ASSURANCE

As the Principal Investigator, I have ultimate responsibility for the performance of this study, the protection of the rights and welfare of the human subjects, and strict adherence by all co-investigators and research personnel to all requirements of the Human Subjects Subcommittee (IRB), the Research and Development Committee, federal regulations, and state statutes for human subjects research.

I hereby assure the following:

All named individuals on this project have read and understand the procedures outlined in the protocol. All experiments and procedures involving human subjects will be performed under my supervision or that of another qualified professional listed on this protocol.

I understand that, should I use the project described in this application as a basis for a proposal for funding (either intramural or extramural), it is my responsibility to ensure that the description of human subjects used in the funding proposal(s) is identical in principle to that contained in this application.

I will submit modifications and/or changes to the IRB as necessary to ensure these are identical.

I and all the sub-investigators and research personnel agree to comply with all applicable requirements for the protection of human subjects in research including, but not limited to, the following:

- Obtain legally effective informed consent of all human subjects or their legally authorized representatives, and use only the currently approved, stamped consent form (if applicable);
- Make no changes to the approved protocol or consent form without first having submitted those changes for review and approval by VANCHCS Institutional Review Board;
- Within 24 hours of investigator awareness, communicate any Local Research Subject **Deaths** to the IRB and submit a written follow-up report to the IRB within 5 working days;
- Communicate other Local Serious Adverse Events, except death, in writing to the IRB within 5 working days after investigators learn of the event;
- Promptly provide the IRB with any information requested relative to the project;
- Promptly and completely comply with an IRB decision to suspend or withdraw its approval for the project;
- Submit an application for continuing review within 60 days prior to the date on which the approval for the study expires. I understand if I fail to apply for continuing review, approval for the study will automatically expire, and study activity must cease until IRB current approval is obtained;
- Submit a final report, within 60 days, to VANCHCS Research Office at the conclusion of this project;
- If I am unavailable to direct this research personally, I will arrange for an investigator to assume direct responsibility as principal investigator in my absence. I will submit a protocol amendment to the IRB in advance of such arrangements requesting this modification.

I understand my obligations as an investigator and agree to fulfill them.
The information contained in this application is complete to the best of my knowledge.
By signing this document, I attest that all the information I have provided is accurate to the best of my knowledge.

Principal Investigator Andrew Kayser Digitally signed by Andrew Kayser DN: cn=Andrew Kayser, o=UCSF, ou=Neurology, email=akayser@gallo.ucsf.edu, c=US Date: 2018.04.26 16:05:26 -07'00' **Date** 04-26-2018