Anti-viral Therapy in Alzheimer's Disease

NCT03282916

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Introduction

This multicenter project is funded by grant number R01AG055422 from the National Institute on Aging, P.I. Dr. Davangere P Devanand. The recipient organization is Columbia University (CU). Since many procedures are conducted at New York State Psychiatric Institute (NYSPI) through a Research Foundation for Mental Hygiene (RFMH) subcontract, the term "NYSPI" is used to refer to CU/NYSPI conduct of the protocol. By default, all policies and procedures refer to CU/NYSPI, and procedures specific to the two other sites, New York University (NYU; PI Dr. Thomas Wisniewski) and Banner Alzheimer's Institute (BAI; PI Dr. Allison Perrin), are indicated accordingly.

In this study, we will be conducting the first controlled clinical trial to directly address the long-standing viral etiology hypothesis of Alzheimer's disease (AD) which posits that viruses, particularly the very common herpes simplex virus-1 (HSV1) and herpes simplex virus-2 (HSV2), may be etiologic or contribute to the pathology of AD.

The generic antiviral drug valacyclovir at 4 g per day, repurposed as an anti-AD drug, will be compared to matching placebo in the treatment of 130 patients (65 valacyclovir, 65 placebo) with mild AD in a randomized, double-blind, 18-month Phase II proof of concept trial. Participants are required to be seropositive for HSV1 or HSV2. The targeted number of participants was reduced from 130 to 120 (60 valacyclovir, 60 placebo) because of delays due to the COVID pandemic and the funding timeline. This change was approved by the DSMB and the sponsor, NIA.

We hypothesize that patients treated with valacyclovir will show less decline in cognition and function compared to placebo; will show less amyloid accumulation than those on placebo using 18F-Florbetapir PET imaging, and less tau binding than those on placebo using 18F-MK-6240 tau PET Imaging.

Background

The viral hypothesis of Alzheimer's disease (AD) posits that viruses in the brain, specifically herpes simplex virus-1 (HSV1) and to a lesser extent herpes simplex virus-2 (HSV2), may be etiologic or contribute to AD pathology. HSV has been implicated for several reasons. HSV1 and HSV2 can trigger amyloid aggregation and their DNA is common in plaques. Anti-HSV drugs reduce Aβ and P-tau accumulation in brains of mice infected with HSV1, and HSV1 reactivation is associated with tau hyperphosphorylation. There is a strong association between HSV1 and amyloid plaques in AD brains but not normal brains. After initial oral infection, HSV1 becomes latent in the trigeminal ganglion and can enter the brain via retrograde axonal transport. Recurrent reactivation with newly produced HSV viral particles, 'drop by drop,' is supported by amino acid homology between human p-tau and VP22, a key target for phosphorylation.

Valacyclovir, a pro-drug of acyclovir, is a generic anti-viral drug. Acyclovir is converted by HSV viral thymidine kinase into monophosphate and triphosphate forms that inhibit DNA polymerase and this leads to HSV chain termination. Therefore, valacyclovir leads to death of infected cells but not non-infected cells and has efficacy against several herpes viruses.

Valacyclovir may be both symptomatic and disease-modifying because chronic use leads to prolonged HSV suppression in patients with peripheral HSV infection. In a pilot clinical trial of 24 patients with schizophrenia with positive HSV1 antibody titers, valacyclovir 3 g daily was superior to placebo with a large effect size of around 1.0 on three cognitive tests of memory from the Penn battery. Valacyclovir has been tested in multiple sclerosis (MS) with equivocal results for changes in MRI lesions; cognition was not assessed in the MS trials.

Valacyclovir is the most widely used generic antiviral drug with over 20 years of worldwide use. It is approved for the treatment of HSV1, HSV2, varicella zoster (shingles), and chickenpox. No other available antiviral drug, e.g., acyclovir (intravenous), famciclovir and ganciclovir, has been shown to be superior to valacyclovir in the treatment of HSV1 and HSV2. Recommended dose of oral valacyclovir for peripheral acute HSV infections is 1 to 3 g daily, and bioavailability is 54%. For long-term HSV suppression, the dose is 1 g daily. In patients with HIV infection and clinical AIDS, valacyclovir 8 g/day was associated with serious adverse events in 10% of patients including GI disturbances and headache, and thrombotic microangiopathy in a few cases. Doses of 6-8 g daily are tolerated in healthy young adults. The difficulty in obtaining efficacy for any drug in AD has led us to target a dose of valacyclovir 4 g daily in this proof-of-concept trial; 3 g is approved for peripheral HSV infection and was effective in the schizophrenia pilot trial.

Based on our experience to date in the conduct of this protocol, which is consistent with U.S. prevalence rates, HSV1/HSV2 seropositivity rate is estimated to be 60-65%.

Participants can continue on cholinesterase inhibitors and/or memantine, if doses are stable for 1 month prior to study entry. Major neurological and psychiatric disorders are excluded. Psychotropic and other medications will be permitted. Medication dosage may be changed if indicated by the study physician. All medication changes will be documented using the National Alzheimer's Coordinating Center (NACC) rating form for possible ancillary analyses. Valacyclovir does not have any major drug-drug/drug-food interactions.

SPECIFIC AIMS.

The aim is to evaluate valacyclovir, a repurposed generic antiviral drug, as a treatment for early AD. An additional aim is to evaluate the effect of valacyclovir on biomarkers of AD. VALAD is a Phase II, proof of concept (POC), randomized, double-blind, placebo-controlled, 18-month treatment trial with early AD and antibodies to HSV1 or HSV2.

Hypothesis 1. Patients treated with valacyclovir will show smaller decline than patients treated with placebo on the ADAS-Cog11 (primary outcome; cognitive measure, 0 to 78 weeks).

Hypothesis 2. Patients treated with valacyclovir will show smaller decline than patients treated with placebo on the ADCS-ADL (secondary outcome; function measure, 0 to 78 weeks).

Hypothesis 3. Patients treated with valacyclovir will show less accumulation than patients on placebo in PET amyloid scans' (18F-Florbetapir, 0 to 78 weeks) combining six ROIs (SUVR: cerebellar reference) that show increased uptake in AD: medial orbital frontal, anterior cingulate, parietal, temporal, posterior cingulate, precuneus.

Hypothesis 4. From baseline to 78 weeks, patients treated with valacyclovir will show smaller increase in 18F-MK-6240 binding (SUVR: combining medial temporal, lateral temporal, prefrontal, parietal, and occipital regions of interest, ROIs, with cerebellar reference) than patients treated with placebo.

18F-MK-6240 PET imaging was funded by a grant supplement within the first year after study initiation and conducted in a subset of the overall sample.

In exploratory analyses, we will compare valacyclovir to placebo for changes in global cognition (MoCA), verbal memory (Craft story delayed verbatim recall), and examine age, sex and apolipoprotein E e4 genotype as a potential moderator of outcome. We will explore the AD "signature" of regional cortical thinning and whole brain cortical thinning on MRI for

valacyclovir compared to placebo. We will evaluate plasma acyclovir levels. In the subsample with CSF acyclovir levels, we will examine CSF acyclovir levels and if a sufficient number of participants has LPs done for CSF, plasma/CSF acyclovir correlations will be examined.

Inclusion Criteria:

1. Females must be postmenopausal defined as 12 consecutive months without menstruation.
2. Diagnosis of probable AD by NIA clinical diagnostic criteria.
3. Folstein Mini Mental State (MMSE) score 18 to 28 (inclusive) out of 30.
4. Clinical Dementia Rating (CDR) score of 1 (mild dementia).
5. A family member or other individual who is in contact with the patient and consents to serve as informant during the study.
6. Patient retains capacity to consent for him/herself or retains the capacity to identify a surrogate who will consent on his/her behalf.
7. At screening, patients must test positive for serum antibodies to HSV1 or HSV2. Patients that test equivocal (index between 0.90-1.09; < 0.90 is negative and > 1.09 is positive) will repeat the test within 6 weeks at a repeat visit. If the results are negative at the second test, the patient will not enter the study. If the results are equivocal or positive at the second test (first test was equivocal), we will enroll the patient in the study because "equivocal" indicates the presence of antibodies that do not reach the minimum threshold.
8. Use of cholinesterase inhibitors and memantine, and concomitant psychotropic medications (other than high- dose benzodiazepines), will be permitted throughout the trial. Doses of these medications will need to be stable for at least 1 month prior to study entry. Any changes to the medication will be documented in the participant research chart. Medications given for other medical reasons, e.g., anti-diabetic or antihypertensive medications, will not be altered for the purposes of this trial and the patient's primary physician may adjust such medications as medically indicated throughout the trial. Details of concomitant medication use will be documented at all visits and will be available for statistical analysis.
9. For patients diagnosed with Mild Cognitive Impairment and CDR score of 0.5 (questionable dementia), if these patients have biomarkers of AD neuropathology with either a positive amyloid PET scan, positive fluorodeoxyglucose (FDG) PET scan of the brain, or positive findings for AD in CSF (low ABeta42 and high tau, p-tau protein levels) they will be eligible for the study. This applies to patients who already had an amyloid PET scan, FDG PET scan of the brain, or lumbar puncture, prior to recruitment into the protocol.

Exclusion Criteria:

1. Caregiver and/or participant is unwilling or unable to comply with study instructions.
2. Patient has dementia predominantly of non-Alzheimer's type, including vascular dementia, frontotemporal dementia, Lewy body dementia, substance-induced dementia.
3. Modified Hachinski scale score greater than 4
4. Current clinical diagnosis of schizophrenia, schizoaffective disorder, other psychosis, bipolar disorder or current major depression by DSM-5 criteria. Prior history of major depression will not be exclusionary (25% of older adults have a lifetime history of major depression).
5. Active suicidal intent or plan based on clinical assessment.

6. Current or recent (past 6 months) alcohol or substance use disorder (DSM-5 criteria).
7. Current diagnosis of other major neurological disorders, including Parkinson's disease, multiple sclerosis, CNS infection, Huntington's disease, and amyotrophic lateral sclerosis.
8. Clinical stroke with residual neurological deficits. MRI findings of cerebrovascular disease (small infarcts, lacunes, periventricular disease) in the absence of clinical stroke with residual neurological deficits will not lead to exclusion.
9. Acute, severe, unstable medical illness. For cancer, patients with active illness or metastases in the last 12 months will be excluded, but past history of successfully treated cancer will not lead to exclusion.
10. Sitting blood pressure > 160/100 mm Hg Physician Evaluation
11. Renal failure as determined by an estimated Glomerular Filtration Rate (GFR) < 44 ml/min/1.73m^2.
12. Serum vitamin B12 levels below the normal range.
13. Patients with thrombotic thrombocytopenic purpura/hemolytic uremic syndrome will be excluded.
14. Use of benzodiazepines in lorazepam equivalent doses equal to or greater than 2 mg daily.
15. For patients consenting to lumbar puncture (40% of sample), this procedure will be conducted if there is no lower spinal malformation or other contraindication to lumbar puncture.
16. For MRI, metal implants and pacemaker, and claustrophobia such that the patient refuses MRI. In our experience, these exclusions occur in less than 5% of patients with mild AD. MRI is required for VALAD.
17. Radiation exposure in the prior 12 months that, together with 18F- Florbetapir and 18F-MK-6240 PET, will be above the FDA annual radiation exposure threshold. This will be determined through study staff (i.e. Principal Investigator, Study Physician) discussion with potential subjects at Screening, documenting inquiry about radiation history. If there is any history of additional radiation exposure in the past year; it will be reviewed with PET Center staff for their approval before proceeding. The combined radiation exposure from the maximum doses used for 18F- Florbetapir and 18F-MK-6240 is within the FDA limits for annual radiation exposure and the second scan in each patient will be done 18 months after the initial PET scan (for both radioligands).
18. Severe vision or hearing impairment that would prevent the participant from performing the psychometric tests accurately. This will be a clinical determination by the study physician without formal testing or audiometry.
19. Olfaction component: current upper respiratory infection (patient tested as soon as this improves), current smoker > 1 pack daily (past smoking has been shown not to affect UPSIT scores, UPSIT score < 12/40 (10 out of 40 is scored by chance in this multiple-choice test) indicating congenital anosmia. In our experience, less than 3% of cases are excluded for having one or more of these exclusionary criteria. If a patient is excluded from the olfaction component, the patient will still be eligible for the main protocol and all other study procedures.

In the study sample, we anticipate 55% female and 45% male participants, 25% minorities comprising 12% African American, 12% Hispanic and 1% Asian.

Table 1. Study Procedures for the 78-week valacyclovir-placebo (VALAD) trial

Procedure	Screening	0 weeks	2 weeks	12 weeks	26 weeks	52 weeks	78 weeks
Clinical assessment/physical exam/vital signs	X	X	X	X	X	X	X
Diagnosis (Consensus Dx at Weeks 0, 52,78)	X	X				X	X
ADAS-Cog11		X		X	X	X	X
MMSE	X						
MoCA		X				X	X
CDR	X			X	X	X	X
ADCS-ADL		X		X	X	X	X
CIBIC-plus		X		X	X	X	X
NACC/UDS		X				X	X
Modified Hachinski (from NACC)	X						
Adverse Events		X	X	X	X	X	X
Serum anti-HSV antibodies with quantitative IgG and IgM	X						X
SMAC blood chemistry	X			X	X		X
Complete Blood Count	X			X			X
Plasma acyclovir levels				X			X
*CSF acyclovir levels				X			X
*CSF Neurofilament Light (NFL), ABeta, tau, p-tau		X		X			X
UPSIT olfaction test		X					X
Apolipoprotein E genotype		X					
MRI scan of brain		X					X
18F-Florbetapir Amyloid PET Scan		X					X
18F-MK-6240 tau PET scan		X					X

*** patients who agree to CSF studies**

Statistical Analysis Plan

1. Introduction.

The aim of the study was to evaluate the efficacy of Valacyclovir treatment in a 78-weeks, multicenter, randomized, double-blind, placebo-controlled, parallel-group treatment trial in participants with early Alzheimer's Disease (AD) and positive serum antibodies (IgG or IgM) to HSV1 or HSV2.

This statistical analysis plan provides more detailed descriptions of the statistical analyses conducted in the paper.

2. Study Design

One hundred and twenty participants with clinical diagnosis of probable AD or mild cognitive impairment (MCI), confirmed by a positive amyloid PET or FDG PET scan or a CSF AD profile,

were randomized to Valacyclovir or placebo at 1:1 ratio. Block randomization with varying block sizes (2 and 4) was used to reduce the risk of treatment allocation prediction by clinicians. Participants were evaluated at five scheduled visits (weeks 0, 12, 26, 52, and 78). As a proof-of-concept study, the target dose of Valacyclovir was 4 g per day -- at the higher end of the usual oral dosing range. Treatment began at 2 g per day (1 g twice daily), with the dose increased by 1 g per day every two weeks until reaching either 4 g per day or the participant's maximum tolerated dose.

3. Outcome Measures.

1) Cognitive and functional measures:

- **Alzheimer's Disease Assessment Scale – Cognitive Subscale 11 (ADAS-Cog 11)**, assessed at weeks 0, 12, 26, 52, 78; scoring range 0-70, higher scores indicate greater cognitive impairment. (Primary)
- **Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale (ADCS-ADL),** assessed at weeks 0, 12, 26, 52, 78; scoring range 0-78, higher scores indicate better daily functioning. (Secondary)
- **Craft story delayed verbatim recall**, assessed at weeks 0, 52, 78; scoring range 0-44, higher scores indicating better memory. (Secondary)
- **Montreal Cognitive Assessment (MoCA),** assessed at weeks 0, 52, 78; scoring range 0 to 30, higher scores indicating better global cognition. (Secondary)

For all cognitive and functional measures, the outcome of interest is the change from baseline at each follow-up time point. The primary endpoint is the change from baseline to 78 weeks.

2) Imaging measures:

- **^{18F}Florbetapir PET SUVR:** Mean standardized uptake value ratio (SUVR) from the medial orbitofrontal cortex, anterior cingulate, parietal lobe, posterior cingulate, temporal lobe, and precuneus, normalized to cerebellar gray matter.
- **^{18F}MK-6240 PET SUVR (Medial Temporal):** SUVR averaged across medial temporal regions including the amygdala, hippocampus, entorhinal cortex, and parahippocampus.
- **^{18F}MK-6240 PET SUVR (Global Mean):** SUVR global mean normalized to cerebellar gray matter.
- **MRI Cortical Thickness:** Mean cortical thickness across nine predefined brain regions.
- **MRI Hippocampal Volume:** Volume of the hippocampus.

All imaging measures were collected at baseline and 78 weeks. The outcomes are defined as the change in each measure from baseline to 78 weeks.

4. Sample Size Calculation.

The sample size calculation was based on the primary outcome: change in ADAS-Cog11 scores from baseline to 78 weeks, using the RMASS program for longitudinal studies. Assuming a within-subject correlation of r=0.3 (moderate correlation) for repeated measures and a uniform dropout rate reaching 15% by 78 weeks, a total sample size of 130 participants (65 per arm) was

originally projected to detect Cohen's d of 0.50 with 80% power at 5% significance level. With approval from sponsor (NIA) and DSMB, the recruitment target was reduced to 120 participants due to pandemic-related recruitment delays and required study completion within the extended funding timeline. For n=120, the minimum detectable effect size increased slightly to a Cohen's d of 0.52.

5. Statistical analysis

The analyses were conducted on the Intent-to-treat (ITT) sample, i.e., all randomized participants according to the treatment that they were assigned. All hypotheses were tested at level of significance of 5%. There was no adjustment for multiple statistical comparisons in this trial. All analyses were conducted using R.

We first examined patients' baseline characteristics to ensure that covariates were balanced between treatment and placebo arms. Continuous variables were summarized using means and standard deviations, while categorical variables were summarized using counts and percentages.

Linear mixed effects models were used to evaluate the efficacy of Valacyclovir as compared to placebo on cognitive and functional outcomes. Specifically, for each outcome measure, we considered the following model

$$\Delta Y_{it} = \beta_0 + \beta_1 * Group_i + \boldsymbol{\alpha} * Time_{it} + \boldsymbol{\gamma} * Group_i * Time_{it} + \delta Y_{i0} + b_i + \epsilon_{it}, \qquad (1)$$

where ΔY_{it} is change of the outcome measure (week t minus baseline) for subject i at timepoint t, $Group_i$ is the treatment group indicator for subject i (1= Valacyclovir and 0=placebo), $Time_{it}$ is the visit time point (treated as a categorical variable), Y_{i0} is baseline value of the outcome measure for subject i, b_i is a subject-specific random intercept, and ϵ_{it} is the unexplained residual error term. $(\beta_0, \beta_1, \boldsymbol{\alpha}, \boldsymbol{\gamma}, \delta)$ are fixed effects parameters. The efficacy of Valacyclovir versus placebo at each time point was tested by forming contrasts of the fitted model. The model was further adjusted for key demographic and genetic variables, including age, sex, and apolipoprotein E ε4 carrier status. Missing data on outcome variables were dealt with by using (longitudinal) linear mixed effects models which do not require complete measurements under the "missing at random" assumption.

For the primary outcome (ADAS-Cog 11), a series of sensitivity analyses were conducted to evaluate the robustness of the findings across key clinical subgroups and under different analytic assumptions. These included: 1) a per-protocol analysis limited to participants who completed the study; 2) a subgroup analysis of participants who received cholinesterase inhibitors or memantine; and 3) a subgroup analysis of participants with a baseline 18F-Florbetapir PET SUVR ≥ 1.15 (amyloid positive for AD).

Linear regression analyses were performed to evaluate the effect of Valacyclovir on changes in imaging outcomes from baseline to 78 weeks. Each model included the baseline value of the corresponding imaging measure as a covariate to control for initial differences. The models were

further adjusted for key demographic and genetic variables, including age, sex, and apolipoprotein E ε4 carrier status. To assess the robustness of the findings and address potential bias due to missing data at follow-up, sensitivity analyses were conducted using weighted linear regression. In these models, the weights were calculated as the inverse probability of a subject being a completer, with probabilities estimated using logistic regression with ridge regularization to handle potential collinearity among baseline variables.

To assess safety, adverse events were systematically evaluated. For each type of adverse event, number and proportion of participants who experienced the adverse event was reported and compared by treatment arms using Fisher's exact test. In addition, plasma acyclovir and CSF acyclovir concentrations obtained at 12 weeks and 78 weeks were summarized using means and standard deviations.

Coordination of Trial:

The National Institute on Aging (NIA) has issued funding for the project to Dr. Devanand at Columbia University (CU). CU is the prime recipient with subcontracts to RFMH, NYU and BAI. Procedures are conducted at both CU and NYSPI, as well as at NYU and BAI as described in this manual. The research teams at NYSPI, NYU and BAI are responsible for the proper conduct of project and data management. Coordinating Center (CU/NYSPI) staff will oversee all research operations in collaboration with NYU and BAI. NYSPI staff will be responsible for communications with the NYSPI Institutional Review Board (IRB), Data Coordinating Center (DCC), Research Pharmacy, and other involved personnel and organizations.

The project began before NIH instituted sIRB requirements for NIH-supported multicenter trials. Therefore, the three sites at Columbia/NYSPI, NYU and Banner have their own IRBs for each of their sites participating in this protocol.

NYU staff will be responsible for communication with the NYU IRB on an independent basis (with notification/report provided to the Coordinating Center team before and after their IRB submissions. Coordinating Center staff will notify the NYU team of any new material or amendment to be submitted to the NYU IRB.) The team at NYU will first communicate with the program manager and other team members at Coordinating Center in order to establish that there is any question or issue requiring the collaboration of the DCC, Research Pharmacy, and other involved personnel and organizations. As the Coordinating Center, Columbia University/NYSPI must be made aware of any issues transpiring at a subsite in order to oversee and collaborate on the appropriate solution.

BAI staff will be responsible for communication with the WIRB on an independent basis (with notification/report provided to the Coordinating Center team before and after their IRB submissions. Coordinating Center staff will notify the BAI team of any new material or amendment to be submitted to the WIRB.) The team at BAI will first communicate with the program manager and other team members at Coordinating Center in order to establish that there is any question or issue requiring the collaboration of the DCC, Research Pharmacy, and other involved personnel and organizations. As the Coordinating Center, Columbia University/NYSPI must be made aware of any issues transpiring at a subsite to oversee and collaborate on the appropriate solution.

Regulatory compliance

ALCOA-C principles are implemented. When errors are made on source documents or CRFs, corrections should be made using a single line through, signed, and dated. Investigators should sign and date source documents in wet ink; signature stamps or signature images generated in Word or other software programs should not be utilized.

All research staff will be required to complete courses on the following NYSPI internal website, including the course on "Essential Documentation and Regulatory Binders".

- OMH HRPP Research Education Course Library: intranet.nyspi.org/research/hrpp/education

Specific trainings for the PI, study physicians, and other patient-interfacing research staff (research assistants, research coordinators, program managers) are listed as follows:

- PI: CITI training, HRPP training, RFMH C-SSRS Training, IRB protocol training
- Study physician: CITI training, HRPP training, RFMH C-SSRS Training, IRB protocol training
- Other staff: CITI training, HRPP training, RFMH C-SSRS Training, neuropsychological assessment training, phlebotomy training, MRI training, PET training, IRB protocol training

NYSPI Institutional Review Board

The NYSPI Institutional Review Board (IRB) will review this protocol on an annual basis and must be kept up to date on any changes made to protocol throughout the lifecycle of the study (from start up to close out). Serious Adverse Event (SAE) reports and follow-up correspondence relevant to SAE reports will need to be submitted as well. Any reports from the Data Safety and Monitoring Board (DSMB) or significant notifications from sponsor/NIA program officer will need to be reviewed by the IRB. The Columbia University IRB agreed to accept the transfer of this NYSPI protocol based on NYSPI IRB protocol approved procedures during the research pause that began in June 2023 due to circumstances unrelated to this protocol. The NYSPI IRB permitted this protocol to continue because this is a clinical trial with active participants but required the remaining active participants to be transferred to the NYU site to complete their final study visit procedures. The Columbia University IRB agreed with this plan and all annual renewals will henceforth be done through the Columbia University IRB.

For all IRB protocol submissions, all relevant documents must be attached when submitting the Protocol Summary Form (PSF) and consent forms. During the review process, coordinators should attach all documents previously submitted, to allow the IRB to consider the entire document history in the current review cycle.

NYU Institutional Review Board

The NYU IRB will review this protocol on an annual basis and must be kept up to date on any changes made to protocol throughout the lifecycle of the study (from start up to close out). Serious Adverse Event (SAE) reports and follow-up correspondence relevant to SAE reports will need to be submitted as well. Any SAE taking place with an NYU subject will first be reported to the NYU IRB, then to the NYSPI IRB (see "SAE" section for full details) if appropriate. Any reports from the DSMB or significant notifications from sponsor/NIA Program Officer will need to be reviewed by the NYU IRB. NYU must send NYSPI stamped copies of all material approved by NYU IRB for this protocol. Though a single IRB will not be used, the NYSPI IRB may still request to review any and all documents approved by the NYU IRB.

Since this protocol is now transferred to the Columbia IRB under WCG with a reliance agreement, annual IRB renewals will henceforth take place through Columbia and WCG.

Western Institutional Review Board (WIRB, the IRB of record for BAI)

The WIRB will review this protocol on an annual basis and must be kept up to date on any changes made to protocol throughout the lifecycle of the study (from start up to close out). Serious Adverse Event (SAE) reports and follow-up correspondence relevant to SAE reports will need to be submitted as well. Any SAE taking place with BAI subjects will first be reported to the WIRB, then to the NYSPI IRB (see "SAE" section for full details) if appropriate. Any reports from the DSMB or significant notifications from sponsor/NIA Program Officer will need to be reviewed by the WIRB. BAI must send NYSPI stamped copies of all material approved by WIRB for this protocol. The NYSPI IRB may still request to review any and all documents approved by the WIRB.

National Institute on Aging Progress Reports

This trial is funded by a federal grant awarded by the National Institute on Aging (NIA). An annual grant progress report to the NIA will be generated by site staff each spring.

Research coordinators (RC) are responsible for generating the following components of the NIA progress report and sending it to the program manager, who will edit the documents and send them to the PI. Sections can be copied from the prior progress report, if there was one, and there have not been major changes in project aims:

1. **Progress Report:**
   a. *Aims*: This section should be copied verbatim from the grant and reviewed for accuracy against amendments to the protocol.
   b. *Studies and Results*: This section contains a detailed list of all substantial IRB-approved changes to the protocol. This information should be copied directly from the memos accompanying amendments submitted to the IRB and reviewed for accuracy. Summarize this section if it exceeds one page.
   c. *Subject Recruitment*: This section contains the number of subjects screened and recruited, as well as demographic information about recruited subjects. This section also includes information about SAEs and AEs. Specify SAEs in detail, summarize AEs.
   d. *Significance*: This section should be copied verbatim from the grant and reviewed for accuracy against amendments to the protocol.
   e. *Plans*: This section discusses plans for the next year; specifically pertaining to recruitment.
   f. *Publications*
   g. *Project generated resources*

2. **Human Subjects Section:** This section of the grant must be reviewed for accuracy against amendments to the protocol.

3. **Inclusion Enrollment Report**: Contains demographic information about enrolled patients.

Contact information:

NIA Program Officer: Laurie Ryan, PhD 301-496-9350 ryanl@mail.nih.gov	**NIA Research Program Analyst:** Alvin McKelvy Phone: 301-827-5492 alvin.mckelvy@nih.gov

Data Coordinating Center

Dr. Howard Andrews will chair the DCC. Tejal Shah will also work as part of the Data Coordinating Center (DCC). The DCC will standardize the data entry procedures and provide consultation to all study staff during the trial. The DCC will have the following responsibilities: develop and implement data forms and collection procedures; lead data management and data security; carry out quality control for data entry; produce reports to the NIA, DSMB, and lead site; assist with statistical analyses; assist with trial closeout.

Contact information:

DCC chair: Howard Andrews, PhD 646-774-5468 andrews@nyspi.columbia.edu	Tejal Shah 732-668-7706 tcs2113@cumc.columbia.edu

Database Management

Study coordinators at NYSPI, NYU and BAI will enter deidentified data collected in this study. Each study coordinator who will be entering data will have their own account login through the Citrix access gateway. The database for this study will be monitored and administrated by the DCC at NYSPI and the program manager.

Data entry must be completed within 3-5 days of study visit completion. Data entry must be double checked and verified with the source documents by another coordinator and the program manager. The study coordinator running a second check of data entered should flag and correct any errors noted in the database and/or source documents. The second data check should be run 1-2 days after the initial data entry by the first RC. The program manager will run source document verification against what is entered into the database for all protocols on a rotating basis (acting as a third check) and log any discrepancies on a protocol specific spreadsheet. All discrepancies noted by the program manager will be followed up on within 3 days.

Questions regarding the study database from NYSPI study coordinators should be directed to our contact at the DCC, Tejal Shah. Questions regarding the study database from NYU study coordinators should be directed to one of the NYSPI study coordinators, who will then reach out to Tejal Shah. There will be one NYSPI study coordinator delegated the task of consistently sending database queries from both NYSPI and NYU to Tejal.

All changes to the database should be recorded in the 'Changes to the ANTIVIRAL Database' log kept in the geriatric psychiatry server, maintained by NYSPI staff.

Data Safety and Monitoring Board

Dr. Gary Small will chair the Data Safety and Monitoring Board (DSMB). The DSMB will consist of Dr. Gary Small (Hackensack Meridan Health), Dr. Jeffrey Cummings (Cleveland Clinic), and Dr. Richard Whitley (University of Alabama).

The DSMB responsibilities are to:

- Review the research protocol, amendment, informed consent documents and plans for data safety and monitoring;
- advise the NIA on the readiness of the study staff to initiate recruitment;
- evaluate the progress of the trial, including periodic assessments of data quality and timeliness, recruitment, accrual and retention, participant risk versus benefit, and other factors that can affect study outcome;
- consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants, the ethics of the trial, or trial conduct;
- review study performance, make recommendations and assist in the resolution of problems reported by the PI;
- protect the safety of the study participants;

- report to NIA on the safety and progress of the trial;
- make recommendations to the NIA and the PI concerning continuation, termination or modifications of the trial based on the observed beneficial or adverse effects of the treatment under study;
- ensure the confidentiality of the study data and the results of monitoring; and,
- assist the NIA by commenting on any problems with study conduct, enrollment, sample size and/or data collection.

The DSMB will discharge itself from its duties when the last participant completes the study.

The DCC will be responsible for preparing data and completing data analyses requested by the DSMB. The study team will hold teleconferences with the DSMB every 6 months (or more frequently based on subject recruitment and/or participant safety concerns) at the call of the chairperson and/or NIA program official. The DSMB will be notified of SAE reports from the study site on an ongoing basis. The program manager will be responsible for scheduling DSMB teleconferences as well as generating an agenda for those calls.

To schedule DSMB teleconferences, the program manager will send a Doodle poll to all required attendees: Coordinating Center and sub-site PIs, Dr. Howard Andrews, NIA Program, DSMB Chair and members, as well as DSMB members' assistants if needed (with the DSMB members cc'd in the initial scheduling email). Try to schedule at least 3 months out, as required staff tend to be very busy and often in different time zones. Either Dr. Laurie Ryan or Dr. Alvin McKelvy from NIA must be on the call.

Contact information:

Chair of DSMB **Gary Small, MD** Gary.Small@hmhn.org Hackensack Meridian Health 30 Prospect Ave, Hackensack, NJ,07601 Assistant: Melissa Fermin Melissa.Fermin@hmhn.org Melissa: 551-996-2008 Dr. Small: 201-294-3132	DSMB Member Jeffrey Cummings, MD cumminj@ccf.org Cleveland Clinic Las Vegas, NV cumminj@ccf.org Assistant: Mary Kay Tarkanian tarkanm@ccf.org 702-701-7926	DSMB Member Richard Whitley, MD rwhitley@peds.uab.edu University of Alabama Birmingham, AL rwhitley@peds.uab.edu Assistant: Sara Davis, sdavis@peds.uab.edu 205-996-7804

The study team is responsible for compiling a blinded report prior to each DSMB teleconference. This report needs to be approved by Dr. Devanand and submitted to Howard Andrews at least 2 weeks before the scheduled teleconference. This report will include:

1. **Project Summary**
    a. *Major Activities*: This section lists all IRB-approved changes to the protocol since the previous teleconference.
    b. *Subject Recruitment*: This section contains the number of subjects screened and recruited, as well as demographic information about recruited subjects.
2. **Serious Adverse Events**: Each SAE report must be included in its entirety, including any information from follow-up correspondence with the IRB after the initial report.
3. **Patient Flow Charts**
4. **Recruitment Rate by Month**
5. **Baseline Demographic and Clinical Summary Statistics**: This section is completed by Dr. Howard Andrews from the database.

6. **Unblinded DSMB report**. Dr. Howard Andrews generates the unblinded report directly to DSMB members with participant data by treatment assignment. Blinded study staff are not privy to this information.

DSMB Communications
All key communications (including protocols, manual of procedures, reports, recommendations and other study-related correspondence) will be distributed by Dr. Devanand and/or the data management team led by Dr. Howard Andrews to DSMB board members and NIA program officials.

In between meetings, the DSMB would like to be notified of, and review key changes to the protocol requiring IRB approval. These communications should be generated by site staff (i.e. NYSPI program manager, who will produce official reports for coordinating center and sub sites), reviewed by Dr. Devanand, then sent to the DSMB chair and members. An example of this would be amendment to protocol: the DSMB would like to be notified of any amendments to protocol after they have been submitted and approved by the local IRB. Report of amendment should be coalesced with supporting documentation for the DSMB's review by the NYSPI program manager, reviewed by Dr. Devanand, then disseminated by NYSPI program manager to DSMB members in turn.

In the case of an SAE, an expedited report of each SAE will be submitted by email to the DSMB chair and members, and NIH Program Officer, within 24 hours of the event being reported to the PI.

A note on scheduling and confirming Dr. Howard Andrews for DSMB Teleconferences: To ensure Dr. Andrews's timely attendance at DSMB Teleconferences, the study team members (lead by the program manager) should follow these steps:

1. Send Dr. Andrews an Outlook invitation stating the date and time of the teleconference. Ensure Dr. Andrews accepts the invitation at least 2 weeks prior to the teleconference.
2. Place 2 reminder calls to Dr. Andrews the week of teleconference (one call the day before, and another call 3 days before the conference. Ensure that you receive verbal confirmation from Dr. Andrews.
3. Keep Dr. Andrews on all reminder emails pertaining to the teleconference.

Recruitment:

Recruitment is multifaceted and involves a variety of sources. Each source must be managed meticulously, and the relationships involved with each must be maintained accordingly. A focus on recruitment for this study is a high priority.

At all stages of recruitment, two key points should be emphasized:
1. This study has a simple **two-step screening and consent process**. Potential patients may not be eligible due to HSV seronegativity based on a blood draw in the clinic followed by the sample being assayed at Quest diagnostics for HSV1 IgG and IgM, and HSV2 IgG and IgM levels.
2. Patients will have an hour to discuss the study procedures with a physician at their screening visit.

Recruitment Sources (Recruitment Closed at this time)

1. Advertisements (NY Daily News, NY Post,) (NYSPI and NYU)
2. Community Advertising (NYSPI and NYU)
3. DPO (Neurological Institute) Physician Referrals (NYSPI Specific)
4. MDC (NYSPI Specific)
5. CEAD (NYSPI Specific)
6. TOPAD Cross Referral between Dr. Luchsinger/Yefrenia Henriquez and Dr. Devanand
7. NIA Email Blast (NYSPI and NYU)
8. Registries (NYSPI and NYU)
9. NYU's Primary Referral Sources

- **Advertisements**

StudyKik **ended 05/10/2022** • **Site:** https://studykik.com/login • **Accountable Party / Timeline:** PM/monthly plan • **Process:** Reviews and sends Studykik rep IRB approved Ad language for listing -> Loop in Cileyn and Ed for payment -> Check if listing is active -> Review new sign-up daily -> Assign potential participants to RAs for phone screen -> Check in with RA about contact status -> Update in Studykik & Recruitment tracker **Contact:** • Ricky May • 1315 Lincoln Blvd, Suite 270, Santa Monica, CA 90401 • (919) 257-6675 • ricky.may@studykik.com • **Facebook (Qualtrics) **stopped 05/10/2022**** • **Site:** https://login.qualtrics.com/login?lang=en • **Accountable Party / Timeline:** PM / Monthly • **Process:** Ads need to be renewed monthly-> PM reviews new sign up daily -> Assign potential participants to RAs for phone screen -> Check in with RA about contact status -> Update in recruitment tracker **Contact:** • Gabriella Dishy, MA • New York State Psychiatric Institute (NYSPI) • (646) 774-5388 • gabriella.dishy@nyspi.columbia.edu **Metro **stopped 05/10/22**** • **Accountable Party / Timeline:** PM & BO / Monthly • **Process:** Ads need to be renewed monthly by email -> Betty's desk phone number is on the ad, BO gets calls -> BO assigns potential participants to RAs for phone screen -> Check in with RA about contact status -> Update in recruitment tracker **Contact:** • Peter J. Blankenstein (*Healthcare Sales Director Schneps Media)* • One Metrotech Center North, Third Floor. Brooklyn, NY 11201 • Phone: (973) 454-2412 • Email: peter.blankenstein@metro.us	

As with all studies in the Memory Disorders Clinic, we have created an advertisement for this Anti-viral study. Advertising is confirmed by the program manager and department administrator. All accounts are already in place. At the end of each month, the program manager will reach out to the primary contact for each respective newspaper to renew the advertisement for the following month. The frequency and size may be adjusted. Once the program manager has given the specifics, they will send an insertion order form (a one-page summary of the order). The program manager will have to print this form, sign it, scan it, and send it back to the primary

contact. Hard copies of all records will be maintained. The Metro financial teams will send an email at the end of each month with the invoice for the advertisements and the program manager is responsible for paying them in a timely manner.

- **Community Advertising: (NYSPI and NYU)**

Advertisement in the form of fliers, posters, print, etc. anti-viral RC will compose various advertising material (in English and Spanish) for review by Dr. Devanand then complete submission to NYSPI IRB. All fliers and brochures must be approved by NYSPI IRB first and must have an IRB stamp placed on them. Advertising material will be sent to sub sites from coordinating center for review and approval by sub site IRB. Sub sites will add their appropriate contact information to recruitment material prior to submission to IRB and once material is approved, post in locations as approved by institution.
Ads (primarily the 1-page VALAD flier) should not be placed in the Neurological Institute (NI3) unless specifically approved by Dr. Lawrence Honig and team. They may be placed around PI, the AIM East Clinic, and approved areas in Presbyterian Hospital. They should also be handed out at any aging lecture.

- **DPO (Neurological Institute) Physician Referrals: (NYSPI Specific)**

Primary Contact: Lamprine N. Whitney (Nitsa) MS, RD, RN
Email: lnw2109@cumc.columbia.edu **Phone:** (212) 342-5615

Taub Recruitment and Referral Procedure:
For referred patients who are potentially eligible for multiple studies: Taub staff will initiate contact, discuss options, and send study information to patients. Taub staff will offer patients the possibility of hearing more about the study from the study team. If the patient(s) agree to hear more, Taub staff will refer accordingly and will follow up on which study the patient(s) decided to participate in.
For referred patients who are potentially eligible for one study: Taub staff will forward the referral directly to the study team to avoid multiple contacts. The Taub staff will follow up with the team regarding screening outcome.
For patients who were identified as potentially eligible but were not referred to us:
Taub staff will not contact the patient. If the clinician agreed that the study team may contact the patient(s), the study team will inform Taub staff prior to contacting the patient so that Taub staff can make sure that the patient is not being recruited or participating in other studies. No patient will be contacted without the knowledge of the treating clinician. Taub staff must be informed regarding the outcome of research staff contact to patient so that they may document and track study recruitment.
For outside referrals: Taub staff will prescreen any interested participant, recruit for all potential studies, and refer to the study team accordingly, and will follow up on regrading which study the patient decided to participate in.
Monthly updates to PI and study team: A monthly report will be sent to the PIs with the status of referred patients per study.

In-person Recruitment

When a referring physician has a potential research patient and their caregiver(s) in the office for a scheduled visit, they may call Dr. Devanand and/or the RC to come over and discuss the study. RC's should always be ready for an in-person presentation as this is a highly effective resource for recruitment. Dr. Devanand and/or the RC will be ready with a consent packet and some basic screening forms including the MMSE and calendar. This is an opportunity to build rapport and explain the study in detail. We may find out that a patient/family is not interested, that they need more time to think about their involvement, or that they would like to schedule an evaluation as soon as possible. After this interview, the RC needs to follow up within the week and finalize the decision about whether the patient joins the study based on communications with the patient/caregiver/referring physician as appropriate.

As a rule, if a patient with whom a RC has previously discussed the VALAD protocol (by phone, over email, etc.) is going to be seen at the NI3 for a DPO appointment, the coordinator who previously spoke with that patient must meet with the patient before or after their appointment, to follow up, further discuss VALAD

screening and plan an in-person screen. Consents and a 1-page ad will be brought to the patient for reference. We know when patients are being seen based on patient names reviewed during weekly pre-screening EPIC review, and corresponding email sent to Nitsa Whitney. If old medical records cannot be found in EPIC, CROWN records are still available for review.

The RC will email or call the DPO provider 1-2 days prior to the patient's appointment, and let the MD know that we would like a few minutes to discuss VALAD with the patient. If the MD isn't interested in the RCs visit to NI3, we offer the patient the opportunity to come to NYSPI with us after their appointment, for an in-person screen (patient must come with a caregiver in this case). Outcomes will be presented at the Tuesday Research Meeting.

Prescreening

To comply with the Health Insurance Portability and Accountability Act (HIPAA) regulations, the site applied for a partial waiver of HIPAA. The study team at NYSPI was granted a Request for HIPAA Waiver Authorization and/or Waiver of Consent. The NYSPI team was granted a partial waiver for telephone screens and a full waiver for the purpose of accessing an existing database or records to identify potential research subjects. Recruitment for this study depends on this waiver and ability to prescreen because it is not practical for the attending physicians to screen for their patients' eligibility themselves. Therefore, the research study staff needs to identify potential research participants before suggesting that the attending physicians and Nitsa discuss the study with their patients. Recruitment ended before IRB protocol transfer from the NYSPI IRB to the Columbia IRB. Therefore, the Columbia IRB did not require their own HIPAA waiver documentation and approval for recruitment of participants in this protocol.

Prescreening patients for potential eligibility is a necessary practice for effective recruitment in this study. What follows is a general description of how to prescreen based on practices at NYSPI.

Procedure: Communication with Nitsa and DPO Providers

- The RC reviews possible participants from lists of patients scheduled to see DPO Providers in the week to come. Pre-screen eligibility is determined through comparing EPIC records against key inclusion/exclusion criteria.

Procedure: Responding to Direct Referrals from Physicians

Note: This procedure applies when a physician directly emails patients to Dr. Devanand or a research coordinator. When physicians refer through Nitsa, all further communication and updates should follow the 'Communication with Nitsa and DPO Providers' procedure above.

1. First, review in EPIC whether or not the patient is eligible or close to being eligible. MMSEs from 18-28 are acceptable.
   a. If a patient is clearly not eligible, include that in your response to the physician.
   b. If the patient is eligible, gather as much information as possible about the patient from EPIC. This includes where they live, who the informant is, and whether there are any practical issues affecting recruitment (e.g. the patient is living in Florida for 3 months).
2. Respond to the physician email.
   a. Dr. Devanand and all relevant study staff.
   b. Contact the patient/caregiver as appropriate.
   c. Update the provider within 24 hours regarding the patient's status: the patient is not interested; the patient is scheduled for a screening visit; the patient is considering the study but has not made a final decision.
   d. For patients who are yet to make a final decision, the process of follow up (calls and email) needs to be completed within the week. The following steps are suggested:

- Inform the patient/caregiver that they may speak with an MD to discuss study participation if they wish. If patients would like to speak with the aforementioned providers, phone numbers will be provided.
- For patients who do not wish to speak with an MD, inform them that you will reach out again in 3 days to follow up.
- When reaching out 3 days later, be ready to answer any follow up questions. If the patient still needs more time, inform them that you will contact them again in 2 days. If the patient is still unsure at that point, defer to investigational staff regarding additional follow up and continued contact. We do not want to keep potential patients in a pending status for more than 5 business days.
- In all phone calls, offer the option of coming in for a screening visit to meet with the research team and discuss any issues. We must always stress that we as the research team are here to address issues/concerns, whatever they may be. Be as specific as possible when offering to schedule the screening visit (i.e. "I have just had an opening free up for this Thursday at 1:00pm. Would you be available to come in for a screening visit then?"). In cases where the RC has not been able to schedule a screen for a patient despite reaching out on multiple occasions (at least 3 times with no success), the RC will send out a follow up letter with investigator approval. Ideally the screening visit should involve the patient and caregiver. In some cases, the caregiver may want to come alone to discuss the study, and that is also acceptable.
- Update the tracker accordingly and provide an update to the referring provider after each contact with an unsure patient (within 24 hours). When the research coordinator is unable to schedule a patient for a screening visit, the patient should be taken off the "Pending Screening" section of the tracker and moved onto the "Archived" tracker.

Very important: When a DPO provider directly refers one of their patients to the VALAD study, we screen for VALAD first and do not consider the respective patient(s) for any other protocol at MDC. In the case of VALAD screen failure the RC must first ask the referring provider whether or not he/she approves of his/her patient being considered for any other study. We can query the referring provider about other protocols his/her patient may be eligible for as soon as VALAD screen failure is fully elucidated.

Phone Screens: <u>The following phone screening script will be used:</u>

*Verbal consent must be obtained before continuing with phone screening. All patients/informants who discuss participation in the trial need to be recorded on a phone-screen log. Coordinators should express to callers that we are offering a free screening evaluation to a research study without any initial commitment required.

During the phone screen, staff must explain compensation details to subjects and/or caregivers. "We are required to mention the total compensation for participation in the protocol. For subjects who complete Lumbar Puncture the total compensation will be $880.00; for those who do not complete LP, the total compensation will be $580.00. We will also reimburse for transportation."

Contact information for informants should be collected during phone screening as well, we will implement this by using and completing the "Patient Tracking Form" in full during in person screening.

Whenever calling a patient directly the RC should ask the patient if they can also speak to their family member or other caregiver if applicable. If they say yes, then speak to the family member as well to make sure everyone is on board and to identify the informant and to confirm appointments, etc.

<u>Initial Phone Call:</u>

First make sure that you are speaking to the correct person, or ask for the correct person, e.g., patient or patient's spouse, at the start of your phone call.

Hello. My name is _____. I am calling from Columbia University Medical Center (or NYU) I understand that you called in response to an advertisement for a research study for Alzheimer's disease treatment.

If referred by another source, state that explicitly and start by identifying who you are in relation to the referral source, *e.g., I work with Dr._____ as a research coordinator, and I understand that he spoke with you about our antiviral treatment study in patients with Azheimer's disease.*
I am looking for Mr/Mrs/Ms._____.
(We must identify who will be the interviewee: patient or caregiver? If caregiver, we need to state their name and relationship to the patient).
*Do you have a few minutes to discuss this with me***?** (*if yes*)
Great, let me start by asking you a few brief questions related to you/your loved one's health. If these questions are difficult to answer, or you need to take a break, please let me know.
(if no) *Ok, let me know a good time and number to call you back.*

The following scripted section applies to patients responding to advertisements only and should be skipped for patients referred from the DPO/other known evaluation source, e.g., MDC.

Do you/your loved one have a diagnosis of Alzheimer's disease?
[If no*, are you concerned about your memory?]*
[When did the concerns begin?]
[Specific memory concerns:]
Have you been evaluated by a neurologist? If so, for what reason?
(If patient has completed neuropsych measures within 3 months, the scores can be used for initial visits in the study)
Have you been evaluated by a psychiatrist? If so, For what reason?
Are you taking any medications?
[If yes, duration & reason:]
MRI*: Claustrophobia or metal implants*
If female: *still menstruating? Approximate date for LMP?*
Do you ever use alcohol or other substances, including marijuana? I understand that some of these questions are very personal. All information discussed during this call is kept confidential.
(If yes, how often?)
Are you involved in any other research studies?
(If yes, take note)

For DPO/MDC/other known referral source:
The conversation needs to be resumed here after skipping the above questions. Reminder: if speaking with a patient who comes from the DPO, state: *"I work with Dr. Huey, Dr. Bell, etc."* or with whomever that patient sees clinically in DPO. <u>There needs to be a sense of clinical cohesion set forth in script.</u>

Screening Script
*Based on our discussion today (*or *based on DPO referral), it seems like this study may be a good fit for you. Our screening and consent is a two-step process. The first step is simple. We can schedule you and your loved one (*dependent upon if speaking with the patient directly or family member/caregiver*) to come into our clinic for a simple blood test that checks whether you have been exposed to the common viruses treated by the antiviral medication used in this study. About half of the population is positive for the virus. If the results of the blood test are positive you may be eligible to participate in the study and a study physician will discuss the details with you. If the results are negative, you will not be eligible, and we will review other available studies for which you may be eligible, or we will give you an appropriate referral.*
If you are interested, we have the following appointment slots available for you (list 3 possible dates and times). *Which one of these openings works best for you and your* (insert either patient info or informant info depending on who is speaking)*?*

Study description:
In this study, which is funded by the National Institutes of Health, we are evaluating a new therapy for mild Alzheimer's disease: valacyclovir, which is a widely used generic and safe, FDA approved anti-viral medication. We are conducting the first-ever clinical trial to address the theory that viruses, particularly

herpes simplex virus, may cause or contribute to the pathology of Alzheimer's disease. Basic science studies show that anti-viral drugs are effective in lowering brain amyloid and tau, which are hallmarks of Alzheimer's disease.

The blurb below is only to be read to those patients who directly inquire regarding additional information: it is better to leave these points to be discussed in person and stick to the main points of the 2-part screen on the phone, seeing as the study design, procedures, and medications may not be relevant to those who won't qualify, and could serve as a deterrent if miscommunicated or misunderstood):

The study is a year and a half, involving roughly 9 visits to our clinic. During your visits, we will conduct neuropsychological assessments (memory testing, various pencil & paper tasks, remembering word lists, stories, etc.). You will also meet with physicians who will monitor your condition throughout the study. During some of your visits, you will have blood drawn, have an MRI, and PET-scanning. Visits may last from one to four hours at the beginning and end of the study, with shorter visits of one to two hours in the middle of the study. For the entirety of the study, you will be randomized (i.e. assigned by chance) to a daily dose of either valacyclovir or a placebo (i.e. inactive/sugar pill). Study staff will always be available to work with you and answer any questions you may have.

We will leave mention of the LP for the in-person conversation with the study MD. If the patient/caretaker asks about it specifically, mention that he/she will be able to discuss this with the physician at the screening appointment. Know what you don't know and leave specific conversations for the appropriate study team member.

Completing the call
Ask the patient/caretaker if they have any remaining questions, comments, or concerns. Remind them again of their appointment date and time/next steps for scheduling the screen.

What to bring to the visit:
The patient should bring a list of his/her current medications, his/her medical records (though not a limiting factor in scheduling a screen), a government issued photo ID and someone close to him/her, like a family member or friend, who will be able to answer questions about the patient's memory and frequency of contact with the patient.

a. **Possible types of IDs:** US passport or passport card, US Military ID (active duty or retired military and their dependents), Permanent Resident Card, Driver's License or other state photo identity card issued by a Department of Motor Vehicles, a foreign government passport, Canadian provincial driver's license or Indian and Northern Affairs Canada (INAC) card and US Government Employee ID with photo. Hospital-issued identification is also acceptable and is generally obtained at the hospital registration desk. The ID must contain DOB and a photo.
b. **HSV Labs:** If a patient is coming from out of state, or farther away in NY, they are free to go to an independent Quest Lab to have HSV labs drawn, to be ordered by their Primary Care Doctor. We will reimburse for this afterwards. Results should be faxed to us at 646-774-6398 and reviewed prior to the screening appointment.
c. **Routine Labs:** We can accept routine labs completed externally, within 30 days of screening.
d. **Informant Proclivity:** If the patient doesn't have an informant or refuses one (and seems like a viable pre-screen) we should schedule them for an in-person visit to begin discussing the protocol and describe participation; though actual screening measures will not be carried out. This may slightly delay proceedings, but bringing the patient in to be introduced with staff and space is a step in the right direction to get a patient comfortable with the process and knowing there are qualified staff on site who are here to address their concerns.

<u>Another important point about informants:</u>
Our biggest concern is that informants provide quality reports; how frequently informants see patients isn't as paramount. The informant can be family, a friend, a neighbor, home health aide, etc., really anyone who can

comment on the patient's memory. RC should discuss anything that seems like an ethical violation or major issue in what they observe of the Patient-Informant relationship, but aside from that, the actual nature of the relationship we don't query. We also do not inquire about the mental or physical status of the informant.

- **Memory Disorders Center (MDC) (primary contact Arlene Meija;** am4717@cumc.columbia.edu**)**

For patients co-enrolled in the ADRC protocol, and one of our protocols at MDC.

- **Center for Excellence in Alzheimer's Disease (CEAD) (primary contact Priscilla Liriano:** 212-305-2473**;** pl2654@cumc.columbia.edu**)**

Patients seen here are followed by Wendy Gonzalez, NP and Dr. Honig.

- **Cross Referral between Dr. Luchsinger/Dr. Devanand (NYSPI Specific) (Primary Contact: Charleny Escalante;** cie2104@ cumc.columbia.edu)

We will work with Charleny Escalante for the TOPAD study.

- **NIA Email Blast (NYSPI and NYU) Primary Contact: Carolyn Hirschman;**

email: chirschman@jbsinternational.com; adear@mail.nih.gov

The VALAD protocol is featured on the NIA's monthly clinical trials recruitment email blast under the 'Drugs" section (every protocol included in this blast has a header under which the link to the protocol's corresponding NIA website is featured). This initiative is managed by the program manager.

- **Registries (NYSPI and NYU) Primary Contact: For registry contacts, see program manager or visit corresponding registry website under "Contact Us" tab.**

  We work with various registries including Antidote Bridge, PatientsLikeMe, Alzheimer's Prevention Registry, Alzheimer's Association Trial Match and other communities alike. These initiatives will be managed by the program manager.

- **BAI Primary Referral Sources:** BAI will refer from investigator and co-investigator clinical patients.

- **NYU's Primary Referral Sources:** NYU will recruit from their ADRC and the Barlow Center.

Protocol Participation:

Consent Procedures

At all sites, participants referred to the study will undergo a screening process (MMSE and initial check for inclusion/exclusion criteria). If the patient appears eligible based on screening, an investigator at the site will confirm by patient interview that all inclusion/exclusion criteria are met and will go over the details of the study with the patient and the informant, as described in the informed consent form. Participants will also be informed that they need to have an informant available in person or by phone to be interviewed in order to be in the study. Patients will be given ample time to review the consent form and will be given the opportunity to ask questions of investigational staff prior to signing.

NYU subjects and caregivers will sign both NYU and NYSPI consent forms. Dr. Devanand will sign all NYSPI consents with NYU subjects after meeting with NYU subjects briefly and discussing the protocol with them. This is required**.**

Throughout the study, the study physicians at each site will cross-cover one another for patient assessments and management in the study. All study physicians are board certified psychiatrists or neurologists and their clinical role is to serve as the study physicians.

Patients with mild AD with Folstein MMSE score 18-28 at screen will sign consent to participate in the protocol; all patients will be required to have the capacity to consent to the protocol, with IRB-approved PCS forms being completed. If the Folstein MMSE declines to below 18 out of 30 at any time-point during the trial, an independent assessment of capacity will be conducted. If the independent assessor determines that the patient retains the capacity to participate in the study, the patient will continue in the study. If the patient no longer retains the capacity to consent in the study, then the patient will be asked to assent to continued participation and to also agree that the surrogate designated by the patient will continue to act in this capacity. If both these criteria are met, the patient will continue in the study. If both these criteria are not met, the patient will be withdrawn from the protocol.

Documenting Consent

Voluntary written informed consent will be obtained from all patients. All patients will be assessed for capacity to consent and this will be documented in the chart. The consent form describes the nature of the procedures and time requirements, potential risks, the confidentiality of information, and the rights of research subjects, including their right to withdraw from the research at any time without loss of benefits to which they are otherwise entitled. It is made explicit that this protocol involves randomized double blinded treatment with valacyclovir or placebo with return visits at specified time points, and a description of the research assessments. The consent process also includes documentation of permission to obtain previous medical records.

The informant must also provide written consent, via the caregiver consent form, indicating their understanding of the study, willingness to provide information about the patient, and complete questionnaires and interviews with the research staff.

The IRB-approved forms for informed consent and for assessment of capacity are made part of the patient's permanent medical record, with a copy being filed in the research chart.

Patients and informants will sign every new version of consent form following the IRB approved amendment.

Screening Eligibility (Inclusion/Exclusion Criteria: pages 4 to 5)

The study sample will be composed of outpatient participants who have been diagnosed with probable AD by NIA clinical diagnostic criteria and test positive for serum antibodies to HSV1 or HSV2. RC and MD will

complete the inclusion/exclusion criteria form. Patients who do not meet all inclusion/exclusion criteria will not enter the study and will be considered a screen fail and noted as such on the corresponding log.

Recruitment Logs: Logs to be kept at both study sites unless otherwise noted in description.
The following logs will be used to track recruitment:

1) **Patient Tracker:** This log includes the tracking of active study patients, patients who have been scheduled for a screening visit, patients who are pending screening evaluation (but not yet scheduled), and patients who are pending/we are unable to contact. The last seen/contacted column should be updated every time the patient or caregiver is contacted.

NAME/ MRN	Referral Source	Study MD/ RC	Referral Date	Contact info	Comments	Final Status

2) **DPO Referral Tracker (This log is NYSPI specific):** This log tracks DPO subjects who were elucidated to be interested or eligible in their EPIC chart (and whose names were sent to Dr. Devanand and Betina for pursuit by DPO providers) and their status in the referral process. This log also provides context as to why there was no referral (i.e. not interested or eligible after-all?) Context for this log comes from Betina as well as the patient's last DPO provider note.

Name	DPO	MRN	DOB	Age	Dx	Next Apt Date	Pertinent Hx	MMSE	MMSE Date	Eligible ?

3) **Screen Fails/Archived Subjects:** This log tracks subjects who have come in for a screening visit but did not meet criteria to be enrolled in protocol.

NAME/ MRN	Referral Source	Study MD/ RC	Referral Date	Contact info	Comments	Final Status

4) **Phone Screening Log**: This log is primarily for the tracking of advertising respondents.

NAME/ MRN	Referral Source	Study MD/ RC	Referral Date	Contact info	Comments	Final Status

Study Visits

Prior to Screening Visit
The screening visit encompasses completion of the screening packet to determine eligibility as well as all consent procedures. Research staff at NYSPI must schedule 4-6 screening visits per week, distributed amongst study physicians as follows:

In any case where Dr. Deliyannides/Dr. Pelton are doubtful of a screening case (diagnosis), or have to make an initial diagnosis, they should call Dr. Devanand to consult prior to the patient departing from the clinic. If the physicians don't reach out to Dr. Devanand themselves, one of the RCs will reach out to Dr. Devanand on their behalf.

Ideally, screening visits are carried out on Mondays or Tuesdays as there is ample clinic availability. Screening visits are permitted on Wednesdays and Fridays despite limits on available clinic space. Scheduling research appointments is permitted on Monday, Tuesday, and Friday each week.

Additional conference rooms can be booked for these days. The screening visit, including consent procedures, is estimated to take 1-1.5 hours on average. In developing the schedule, allow up to 45 min for the study physician to obtain consent.

Medical Records
Prior to the visit, if the patient is an outside referral and/or called in from an advertisement, RCs should ensure that medical records are obtained from the subject's primary care physician and/or neurologist. If medical records are not obtained this will not serve as a limiting factor on scheduling the screen; the patient should be brought in for screen anyway. Subjects may also bring their own records in person at screen but are encouraged to send records to the clinic prior to the visit to move the review process along faster.
Subjects must come to the screening visit with the individual who will serve as their study informant. All patients and informants should be made aware of New York State law, which stipulates that the request and delivery of medical records to patient by provider must follow official, written and signed request. The physician must comply within a 24-hour turnaround time and provide records to the patient accordingly.

If the patient is an internal (DPO-CUMC) referral, all available records should be printed from EPIC for reference at the visit. This includes labs, radiology/scan reports, and notes from the DPO provider. A coordinator should never exclude a patient for any reason based on the EPIC records, with the exception of MMSE (18-29 is acceptable for screening criteria; questionable if MMSE of 17). The only information that you do not need to print out: address and personal information, insurance information, other non-clinical and non-research information.

It is a strict expectation that 24 hours prior to a VALAD screening visit the RC will review all records available in the EPIC chart, MDC chart, independent medical records sent in from external provider, etc. This is key to understanding who your patient is medically and personally.

<u>RC Responsibilities during Study Visits:</u>
From Screening until week 78, it is the expectation that the respective RC (ideally, the RC who conducted the phone screen with the patient) will be present in the exam room during all study visits, with patient and study MD, to preside over all activity and provide any relevant information, including self-reported measures such as the UPSIT. This will ensure that there are no gaps in knowledge or information shared throughout the duration of the patient's protocol participation.

The RC will always check all forms, both RC and MD, prior to the patient leaving the clinic, to ensure that all necessary measures were completed accurately. If another RC is present, they should cross check the forms. This should be done on the same date as the visit itself, no matter how late it gets.

Patients should take their regular medications prior to coming in for study visits. If they have medications that they take at lunchtime, they should bring them and take them at their regular dosing time when they are here. It is a good idea to take the patient's chart, and particularly their list of medications, along with the patient when there are procedures outside our clinic (such as MRI, PET, LP). Nurses or technicians at these other sites often wish to see the list of meds the patient is on and patients tend to lack reliability in reporting current medication administration.

Screening Visit: Procedures

NYU Capacity to Consent:
Per PI agreement: NYU subjects will sign all consent forms even if deemed as "not having capacity" (per NYU's standard, which is different from NYSPI's standard and includes MMSE and subjective consent quiz). There will not be notes in the NYU subject chart about lacking capacity. NYU will continue to abide by NYU's rules and standards NYU subjects lacking capacity will not undergo the LP.

At screening, the patient meets with the study physician (or delegated staff at NYU and BAI) to be consented. The coordinator should be in the room to ensure their own understanding of the protocol and consent procedures and can supply physicians with necessary information. The physician will obtain signatures and sign the Patient and Caregiver Consent Forms, the PCS Cover Sheet and Form II, and the Consent Procedure Note with the patient and caregiver and review the inclusion/exclusion criteria. NYU and BAI will utilize their equivalent PCS Forms at the Screening visit. BAI patients only sign BAI consents.
NYU subjects and caregivers will sign both NYU and NYSPI Patient and Caregiver consent forms to cover procedures performed at both NYU and NYSPI/CUMC facilities.

The RC then completes a "Patient Tracking Form," which outlines key information about subjects and caregivers. The RC then takes vitals (BP, pulse) and completes the MMSE with the patient. If blood pressure is high or out of range, the RC should repeat BP twice, 10 minutes apart each time. Any pressure above either 160 systolic or below 100 diastolic needs to be reported to an MD on site, for further instruction.

For MMSE, use the three words in the second or third array since patients who have been undergoing regular neurological follow up for memory disorders tend to be familiar with "apple, table, penny." This is necessary to ensure MMSE inclusion, barring circumstances where an MMSE has been documented in the previous month. The RC also completes the Informant FAQ if applicable per clinical standards, Metal Screening Questionnaire, and the Medical Records Release form with the patient and/or their caregiver.

It is recommended that measures used for determining eligibility be completed earlier within a visit; should a subject screen fail on key criteria early in the visit, there is no need to complete other study measures because this patient has already been found to be ineligible.

The patient then meets with the study physician again (or delegated staff at NYU and BAI) to discuss eligibility and review the inclusion/exclusion criteria again.

For patients who sign consent, an RC will draw blood for SMAC, CBC, and HSV. If patients are "difficult draws" at NYSPI, the NYSPI phlebotomist (Manny de la Nuez; X8048) will be contacted.

As patient and caregiver depart, let them know that the final blood results and follow up will be communicated to them by the coordinator in 3-4 business days.

The RC will contact Quest Diagnostics to arrange pickup of the HSV sample. The RC will fill out the Quest requisition as described in the blood draw policy section of this manual. The requisition form and tube will be checked by the RC who filled them out and the back-up RC. Those who check will be looking to make sure the patient name, IRB number, correct collection time and date, language about research use only, and the

110014F HSV Box are checked on the form. They will then compare these to the tube to make sure all details are accurate and matching. The security guards on the first floor of NYSPI have the key to the Quest lockbox, which is located on the floor immediately in front of the mailboxes on the first floor.

The RC centrifuges the red top (SMAC) tubes on centrifuge pre-setting 3 (3200 rpm, 20 minutes) after allowing the blood to clot in an upright position for 30 minutes. The RC does not centrifuge the purple top tube. The RC will fill out the NKI requisition (NYSPI) as described in the blood draw policy section of this manual. Staff at NYU will fill out the requisition for their local lab, which will be used to process both red and purple top tubes, as will BAI.

The requisition form and tubes will be checked by the RC who filled them out and the back-up RC. Those who check will be looking to make sure the patient's name, X number (NYSPI specific medical record number), sex, ward unit, facility name, date and time of draw, and proper tests requested are checked on the form and match the information on the tubes. The red top and purple top tubes are then left in the refrigerator in the lab on the 4th floor (Pardes Building at NYSPI) for processing by NKI. The NKI form should be time stamped by the machine located in the lab. The NKI form has 3 sheets: the first page (white) should be placed in the front sleeve of the specimen transport bag containing the tubes and put in the fridge, the second page (yellow) should be placed face-down in the tray in the lab, and the third page (pink) should be kept in the patient's chart. NYU requisition forms will contain data to be collected and checked per participant as will BAI forms.

A subject will not be considered eligible unless all inclusion/exclusion criteria are met. Inclusion/ exclusion criteria checklist will be signed at screen or baseline by both research coordinator and study physician.

For BAI, NYU, and NYSPI subjects, HSV antibody results take 2-4 days to be posted online in the e- portal, Quanum/Care 360; so results are not immediately known. Once the initial results are published, the RC will print them for the subject's chart and get signed by the study physician. Note: If the IgM results are "pending" from the results, the RC will continually monitor until the final results are published in Quanum/Care 360 to be printed and signed by the study physician.

To access results in Quanum/Care 360: https://portal.care360.com/care360/care360.login
Username: jpollina **Password:** Devy1600!

Information concerning eligibility should be promptly communicated to the patient by the RC; for subjects who screen HSV negative, a study physician will have to reach out and inform of not only ineligibility but appropriate follow up.

Documentation of communication (via progress note filled out by study physician) of screen failed subjects must be kept in each screen failure chart at all study sites. All of this information needs to be presented in the team Wednesday morning meeting for all active patients, and any questions should be raised with the team, e.g., referral for specific ineligible patients.

Scheduling Baseline Measures: Procedures for NYSPI and NYU (BAI will follow this protocol with modification made per their site standard)

All baseline measures (PET scans, optional LP, MRI) should be scheduled once HSV positivity has been confirmed for those patients with qualifying MMSEs. It is important that all key measures get on the books as soon as possible to avoid unnecessary back and forth with patients or caregivers and to simply move the protocol along in an expeditious manner. Note, we must confirm at screen that patients and caregivers are available to come in on either a Monday or Friday for their Tau PET (18F-MK-6240 tau ligand exclusively available M/F). If the caregiver is not available, study staff will offer to arrange dropping off and picking up the patient (from tau PET) and do what we can to make it work. This is applicable to NYSPI/CU and NYU, BAI will schedule per their site standard.

Priority must be given to scheduling the MRI. Once the MRI has been confirmed, the PET scans and LP can be officially scheduled to accommodate the MRI.

If the patient would like to complete multiple procedures on the same day, schedule the MRI followed by amyloid PET on baseline day 1. An alternative is MRI followed by LP on baseline day 1. LP should be the last procedure for day 1. Theoretically, MRI followed by amyloid PET; followed by LP could be scheduled on the same day but this should be reserved for a highly cooperative and cognitively intact patient, with a sufficient gap of at least 2 hours between procedures to account for unanticipated delays for each procedure. The patient would still need to return a second day to complete the tau PET, which must be separated by at least 24 hours from the amyloid PET scan. When scheduling a PET scan and the LP on the same day: a gap of at least 4 hours if LP is done first, a gap of 1 hour if PET is done first.

Ideally, all patients will complete all baseline measures as dictated per protocol, however, if a patient cannot complete one of the measures, for example, tau PET (due to failure on the part of the Kreitchman PET Center, failure to successfully produce the ligand, an unforeseen scheduling conflict on the patient's part, etc.) we will not discontinue that patient from the protocol; instead, we will try to complete the procedure on another day. If that is not possible, write an exception or deviation, report to the IRB if needed, and continue the patient in the protocol.

PET, MRI and LP will take place at CUMC/NYSPI. It will be the responsibility of the NYU RC to obtain patient availability for MRI, both PETs, and LP (if applicable) at the end of the patient's screening visit and report to NYSPI staff within 24 hours. The NYU coordinator will email this availability (along with any forms such as PET Center Forms) to the NYPSI coordinator using patient ID, not name. Staff at NYSPI will schedule the patient for each respective procedure and will need the patient's availability as soon as possible in order to schedule each procedure as per the patient's request. The NYSPI coordinator will then communicate booked dates/times to the NYU team so they can communicate this information to their patient in timely manner. The MRI, PET scans, and LP should be scheduled by the NYSPI coordinator within one week of the NYU coordinators initial request.

Research Pharmacy
Ordering Study Drug/Randomization: Procedures for All Sites

The New York State Psychiatric Institute pharmacy is the research pharmacy for the study. The randomization code was generated by the study statistician when the study began and this code is maintained by the research pharmacy with Dr. Howard Andrews who leads the Data Coordinating Center for the study. The research pharmacy updates the randomization table as participants enroll in the study and are dispensed study medication (valacyclovir or placebo) and sends the updated table to Dr. Howard Andrews on a monthly basis. Any discrepancies are resolved by the research pharmacy with Dr. Andrews.
For all Columbia/NYSPI, NYU and BAI patients: The NYSPI research pharmacy will manage study drug kit generation and send these out for the entire duration of each patient's protocol participation.

NYSPI pharmacy dispenses kits for NYSPI subjects on-site at clinic visits and when needed through shipping the kits to the home of the patient or caregiver. Each subject's first study drug kit will be dispensed by the NYSPI pharmacy to the study physician/research coordinator to be distributed at the baseline study visit. The pharmacy will send NYU/BAI kits to NYU/BAI RC's for later distribution to subjects by staff on site. NYSPI Pharmacy must include a receipt in every study drug shipment sent to sub sites, indicating what is included in each study drug shipment. These receipts are necessary for accession, filing and compliance purposes.

At least two weeks before the patient's scheduled Baseline visit, the Study Drug Order Form will be submitted to the NYSPI pharmacy by the NYSPI RC specifying kits for weeks 1-8 and 9-16. NYU and BAI coordinators will scan and send the study drug order form to NYSPI coordinators at least two weeks in advance, specifying

weeks 1-8 and 9-16. As a reminder, the study drug order form should not be submitted until a study physician confirms eligibility, the patient is contacted, and the baseline MRI/PET scans are scheduled.

Coordinators assign subject identification numbers for the protocol, ascending sequentially from 101 at NYSPI, from 1001 at NYU and from 2001 at BAI.

Randomization is not officially completed until the first bottle of study medication is handed to a patient at their baseline visit. Subject IDs will not be reassigned, even if a patient does not come back after baseline (once randomized, always randomized).

Study drug kits are broken down as follows:
(NYSPI) For weeks 1-12: 644 total capsules.
Week 1-2: 28 capsules x 2 bottles (2g per day, 1g morning (2 caps), 1g evening (2 caps)
Week 3-4: 42 capsules x 2 bottles (3g per day, 1.5g morning (3 caps), 1.5g evening (3 caps)
Week 5-8: 56 capsules x 4 bottles (4g per day, 2g morning (4 caps), 2g evening (4 caps)
Week 9-16: 56 capsules x 8 bottles (4g per day, 2g morning (4 caps), 2g evening (4 caps)
From then onward it's 56 capsules x 8 bottles (4g per day, 2g morning (4 caps), 2g evening (4 caps), unless clinically indicated by the study physician.

(NYU) For weeks 1-12: 644 total capsules.
Week 1-2: 28 capsules x 2 bottles (2g per day, 1g morning (2 caps), 1g evening (2 caps)
Week 3-4: 42 capsules x 2 bottles (3g per day, 1.5g morning (3 caps), 1.5g evening (3 caps)
Week 5-8: 56 capsules x 4 bottles (4g per day, 2g morning (4 caps), 2g evening (4 caps)
Week 9-12: 56 capsules x 4 bottles (4g per day, 2g morning (4 caps), 2g evening (4 caps)
Week 12-16: 56 capsules x 4 bottles (4g per day, 2g morning (4 caps), 2g evening (4 caps)
From then onward it's 56 capsules x 12 bottles (4g per day, 2g morning (4 caps), 2g evening (4 caps)), unless clinically indicated by the study physician.

It will be the responsibility of each RC to track when each replenishment is due (there is a log in each subject chart for this) and complete the study drug order form. Given that NYSPI pharmacy will be sending kits out to NYU and BAI RC's, it is the expectation that NYU and BAI coordinators scan and send a copy of the completed "Study Drug Kit Send Out Log" to coordinator(s) at NYSPI as a tracking and management tool. This will be done during the Baseline period. NYSPI, NYU and BAI kits will contain 4 months/16 weeks' worth of valacyclovir/placebo.

NYSPI, NYU and BAI RC's will complete the study drug order form at least two weeks prior to subject replenishment due date. NYU and BAI coordinators will scan and send completed study drug order form to the NYSPI coordinator for distribution to NYSPI Pharmacy team.

At all three sites, kits will be returned to coordinators at scheduled study visits so that compliance checks can be conducted in tandem with a check in with the patient regarding how they're feeling (update of AE and Con Med Logs should be completed at this time based on result of conversation with patient). Coordinators must call patients once a month to check in with the patient regarding medication compliance, and any AEs and Con Med changes.

Kits returned to NYU and BAI coordinators will be stored at respective pharmacy or other designated storage location, for later monitoring by the NYSPI team and eventual destruction at end of study.

NYSPI Pharmacy Team:
Robert Jung (Robert.Jung@nyspi.columbia.edu; Research Pharmacist)
Kirwan Walsh (Kirwan.Walsh@nyspi.columbia.edu; Research Pharmacist)
Francine Weber (Francine.Weber@nyspi.columbia,edu; Pharmacy Director)

Week 0 (Baseline) Visit: Procedures for NYSPI and NYU (BAI will follow this protocol with modification made per site facility standards)
Details on MRI, PET scans, and LP procedures can be found in the specific Policy & Procedures Manual for each respective procedure located in the next section

Participation Standards: The team will re-iterate expectations, as it pertains to participating in the study, with both subjects and caregivers. In brief, if subjects/caregivers agree to participate, the expectation is that they will remain in the protocol for the entire 78-week duration.

Baseline measures will need to be completed over a span of a few days. Informants do not have to be present during all baseline study procedures, but the informant must drop off and pick up the subject (or make arrangements for this; research team staff can assist as well).

Description of NYU staff activity at NYSPI for all procedures is included in this manual as NYU staff may need to be present at each procedure if necessary, per subject request.

Prior to baseline, the RC will find out whether or not the subject has undergone any of the neuropsych testing that will be conducted per protocol. If so, any neuropsych test administered within the CUMC, NYU or BAI system 3 months or less prior to Baseline, can be used for the purposes of the protocol but this must first be checked with investigational staff for final approval. All data from historic neuropsych testing will be copied onto study specific CRFs, and entered into the VALAD database with the current, baseline date (not the date of original testing).

The coordinator will take vital signs and administer the ADAS-COG 11 and NACC Neuropsychological Battery. The coordinator will administer the UPSIT. Finally, the coordinator will complete the initial NACC packet (the GDS and 3-page demographics form). Qualified/certified staff at NYU and BAI will complete the aforementioned NACC measures, coordinators will complete all other measures as dictated per protocol.

The patient will then see the study physician, who will write a progress note and complete the MD NACC packet, the Concomitant Medications log, the CIBIC-Plus, and the CDR. The physician will also complete the ADCS-ADL with the informant. This informant interview can be done over the phone at a later time within the Baseline period, as well.

The coordinator will then draw blood for APOE genotyping (yellow top), which is to be stored at the Human Genetics Resources Core (HGRC). Both NYU and NYSPI subjects will have APOE drawn at NYSPI during Baseline, as will BAI subjects. BAI staff will store APOE on site for later send out to the HGRC. The RC will fill out the HGRC form as described in the blood draw policy section of this manual. The form and tubes will be checked by the RC who filled them out and the back-up RC. They will sign the corresponding accuracy log.

An extra serum tube (red top) will also be drawn for all subjects, processed, and stored in the -80 freezer on Pardes floor 4 (at NYSPI, BAI will store locally). Please see the Lab manual section for greater processing description.

As described in the consent forms, all clinically applicable information collected during the trial will be disclosed to patients and their caregivers, as well as interpretation of baseline MRI, 18F-Florbetapir amyloid PET radiological read, and results from CSF analysis.

After the baseline evaluation, the results of outcome measures specified in the hypotheses will not be disclosed. Apolipoprotein E genotyping results will not be disclosed nor will results from 18F-MK-6240 tau PET scan; tau PET imaging results are still in research development and there is no standardized method to make a clinical read and provide a report to the patient.

At both sites, the medication kit is dispensed when the study physician sees the patient and reviews the medication kit.

After all procedures for the day are completed, follow-up visits are scheduled. The RC must review the Checklist for the visit and ensure that all forms listed in it are completed on the checklist page before the patient leaves the clinic. The RC will double check that the study physician has completed all necessary forms, as well. After all verifications are complete, the patient and caregiver may be sent home.

A few important notes to keep in mind at Baseline:

A. The ADCS-ADL must be done by the study physician who sees the patient (At BAI, neuropsych and rating scales are completed per site standard with trained staff and raters). It should be done at the end of the visit, i.e., after NACC and other forms are administered (specific forms will vary from visit to visit but ADCS-ADL should always be done at the end). The ADCS-ADL should be administered to the informant but when the informant is not sure about the answer to a question, it can be done with the patient as well. The study physician must fill it out completely based on the best information available, even if it seems to be spotty based on unclear patient and informant responses.
B. We will use our own discretion in deciding whether subjects and caregivers should be compensated with Petty Cash, or through filling out a reimbursement form, which would result in a check being sent to the subject or caregiver's place of residence. Reimbursement forms require collection of social security number and W9 completion from the payee.
C. The RC must do the maximum, not the minimum, and know every detail about their patient(s) to truly make this a successful study. There needs to be an ongoing conversation about patient concerns, not just facts of the study. The single most important thing will be establishing a decent rapport with the study patient and making sure they (as well as their caregivers) know that we're here to address their concerns and make participation in the study convenient for them. This will keep them coming back.

Weeks 2 & 4 Phone Call/Visit

- In-office or telephone call by study physician to assess subject study drug compliance and any patient history changes. This telephone call or in office visit should last approximately 10 minutes.
- Physician will write note and RC will complete medication compliance form.

Medication Compliance Calls: The RC will call the patients or caregivers **once a month** and medication compliance will be documented on a log upon query. These calls will occur throughout the subject's 78 weeks of protocol participation. During phone contacts, patients should be reminded that they will be followed by a physician here. Patients should know exactly what they'll be getting through participating in research.

The following compliance script will be used when placing these calls:

Hi Mr./Mrs. _____. This is _____ calling from Columbia about the "Antiviral therapy in Alzheimer's disease" study that you/your family member is enrolled in. Do you have a few minutes to talk with me? I am just reaching out to check-in and see how you (and the patient) are doing. (If now is not a good time to speak, schedule a specific time when they know they will be available via phone. It is good to note in your personal tracking if there are certain days or times that are best for phone contact in the future) -person on the phone (patient or caregiver) should be where they have the study medication available

(To complete over phone before the patient starts a new Study Drug Kit)

The last kit you received had 8 study drug bottles. Can you tell me how many bottles have been finished? Can you count how many pills are left in the unfinished bottles?
_____finished bottles
_____pills remaining

Now, let's go over the kit you just received and will be starting on _____. Can you read me the labels on the bottles of the new kit?

Thank you. As I mentioned, you will be starting the new box on _____. The pharmacy will ship you a new box by Fedex before this kit finishes. Please do not discard the old bottles. You can bring them with you in your next appointment. Feel free to reach out to me if you encounter any problems.

The patient will be encouraged to come in if and when they believe it is necessary to be seen by study staff/medical team on protocol. AE and Con Med Logs to be updated based on information obtained at these calls.

Week 12 Visit

This visit should be completed in 2-4 hours.

- Clinical assessment: Progress note, CDR, ADCS-ADL, and CIBIC-plus will be completed (Study Physician completes at NYSPI; PI or delegated/certified Sub-I at NYU and BAI).
- Neuropsychiatric measures: ADAS-Cog11 (Research Coordinator completes at NYSPI, delegated/certified staff at NYU and BAI).
- RC will record vitals.
- RC draws blood for: SMAC blood chemistry (red top), complete blood count (lavender top) and plasma acyclovir levels (lavender top).
    - For SMAC blood chemistry and complete blood count, the RC will fill out the NKI requisition (NYSPI) or NYU Langone Lab req if NYU subject, and BAI specific lab req at BAI, as described in the blood draw policy section of this manual. The req and tubes will be checked by the RC who filled them out and the back-up RC. Those who check will be looking to make sure the patients name, X number (med rec number), sex, ward unit, facility name, date and time of draw and order, and proper boxes are checked on the form and match the information on the tubes.
    - Plasma acyclovir levels will be drawn, processed and stored for further analysis by the Acosta Lab at UAB. Plasma should be checked for: ID, draw time, date, date/time of most recent dose, valacyclovir/placebo, DOB, Dr. Devanand, IRB #.
- For patients consenting to the LP, CSF (and plasma) will be collected (Dr. Bell performs the LP, NYSPI RC processes and stores specimens for both NYU and NYSPI LP subjects). The NYSPI RC will fill out the LP and Plasma forms and tubes according to the LP procedure section of this manual. The form/tubes will be checked by the RC, the back-up RC and the program manager.
- Before the patient leaves, the RC will double check that the study physician completed all necessary forms. After verification is complete, the coordinator will confirm that all RC forms have been completed, as well. The RC must check the checklist for the visit, and ensure that all forms listed in it are completed and ticked off on the checklist page. Only after both of these checks have taken place can the patient and caregiver be sent home.

Week 26 Visit

The week 26 visit is estimated to take about 2-3 hours.

- Neuropsychiatric measures: MMSE and ADAS-Cog11 (RC at NYSPI, delegated/certified staff at NYU and BAI).
- Clinical assessment: Progress note, CDR, ADCS-ADL, and CIBIC-plus (study physician completes at NYSPI; PI or delegated/certified Sub-I at NYU and BAI).
- SMAC blood chemistry (red top) will be collected to assess kidney function (RC completes). The RC will fill out the NKI requisition (NYSPI) or NYU Langone Lab req if NYU subject, BAI specific lab req if BAI subject; as described in the blood draw policy section of this manual. The req and tubes will be checked by the RC who filled them out, the back-up RC and the program manager. Those who check will be looking to make sure the patients name, X number (med rec number), sex, ward unit, facility name, date and time of draw and order, and proper boxes are checked on the form and match the information on the tubes.
- Coordinator will record vital signs.

- Before the patient leaves, the RC will double check that the study physician completed all necessary forms. After verification is complete, the coordinator will confirm that all RC forms have been completed, as well. The RC must check the checklist for the visit and ensure that all forms listed in it are completed and ticked off on the checklist page. Only after both of these checks have taken place can the patient and caregiver be sent home.

Week 52 Visit

This visit will take 3-4 hours.

- Re-evaluation of diagnosis, Progress note, CDR, ADCS-ADL, CIBIC-plus, and NACC packet (study physician completes at NYSPI; PI or delegated/certified Sub-I at NYU and BAI).
- ADAS-Cog11, NACC neuropsychological battery, NACC RC questionnaire forms, vital signs. (RC completes at NYSPI, delegated/certified staff at NYU and BAI).
- No blood will be drawn.
- Before the patient leaves, the research coordinator will double check that the study physician completed all necessary forms. After verification is complete, the coordinator will confirm that all RC forms have been completed, as well. The RC must check the Checklist for the visit and ensure that all forms listed in it are completed and ticked off on the checklist page. Only after both of these checks have taken place can the patient and caregiver be sent home.

Week 78 Visit or Endpoint (dropout) visit

End of Study Procedures: We will not break the blind at Week 78. We will only break the blind after the entire clinical trial is over and the final subject enrolled completed all week 78 procedures. We will provide all test and procedure results to the referring MD, then let the referring MD decide what to do in terms of prescribing valacyclovir. The RC will need to summarize cognitive testing over protocol duration, in preparation. A full report inclusive of the subject's experience in the study will be provided in addition to the cognitive testing summary (see below).

These measures will span over 2-4 clinic visits.

- This visit follows a very similar protocol to the week 0 visit, with the addition of blood drawn for SMAC, CBC, and HSV antibodies.
- The RC will fill out the Quest forms and tubes as described in the blood draw policy section. The form and tubes will be checked by the RC who filled them out, the back-up RC and the program manager. Those who check will be looking to make sure the patient initials, IRB number, correct collection time and date, language about research use only, and the 6447 and 90849 HSV Boxes are checked on the form. They will then compare these to the tube to make sure all is accurate and matching.
- NYSPI and NYU subjects will have MRI, PETs, and LP performed at NYSPI/CUMC as previously described in this manual and as described in each respective "Procedures" section. The NYSPI RC will fill out the LP and Plasma forms and tubes according to the LP procedure section of this manual. The form and tubes will be checked by the RC who filled them out, the back-up RC and the program manager.
- The RC will draw blood for plasma (lavender top), SMAC (red top), CBC (lavender top), and HSV (marble top) antibodies.
- The RC will fill out the NKI requisition (NYSPI) or NYU Langone Lab requisition if NYU subject or BAI specific lab req if BAI subject, as described in the blood draw policy section of this manual. The requisition and tubes will be checked by the RC who filled them out, the back-up RC and the program manager. Those who check will be looking to make sure the patients name, X number (med rec number), sex, ward unit, facility name, date and time of draw and order, and proper boxes are checked on the form and match the information on the tubes.
- Re-evaluation of diagnosis, Progress note, CDR, ADCS-ADL, CIBIC-plus, NACC packet, and concomitant medications log. (Study physician completes at NYSPI; PI or delegated/certified Sub-I at NYU and BAI).
- ADAS-Cog11, NACC neuropsychological battery, UPSIT, and vital signs. (RC completes at NYSPI, delegated/certified staff at NYU and BAI).

- Plasma acyclovir specimens, collected from all subjects, should be checked for: ID, draw time, date, date/time of most recent dose, valacyclovir/placebo, DOB, Dr. Devanand, IRB #.
- Patients will have a final MRI and PET Scans, following the protocol of the baseline visit.
- Patients who agreed to the LP will have a third and final LP, providing plasma and CSF specimens.
- Adverse Events will be recorded on the Adverse Events Log (RC completes).
- Medications will be recorded on the Concomitant Medications Log (Study physician completes).
- A Protocol Exit form is completed (RC completes).

Whenever a patient ends the protocol, regardless of time-point, the protocol exit form needs to be completed. If a patient terminates the protocol early for any reason, the patient needs to be brought back to complete all planned study visits and procedures under the intent-to-treat principle. Any intervening treatments or other changes will be documented but will not affect the assessments. During this time, the patient should be instructed not to participate in any other treatment research protocol. Before the patient is free to go the RC should double check that the study physician has completed all necessary forms. After this is checked the coordinator should confirm that all RC forms have been completed. Only after both of these checks have taken place can the patient and caregiver be sent home.

Study records (scan reports, lab results) for patients referred to VALAD by DPO Providers, will be dropped off in a manila folder, with Renata on NI3. These records will be dispersed to respective DPO provider. RC should compose a brief narrative of what exactly each manila folder contains, and which study visits have been completed to date.

Biological Specimens and Scans:

We will be collaborating with the following laboratories:

1. **Edward P. Acosta, Pharm.D.** University of Alabama at Birmingham
   CSF Specimens and Plasma Specimens
2. **Dr. Leslie Shaw, Ph.D U**niversity of Pennsylvania
   CSF Specimens
3. **Marielba Zerlin-Esteves,** Human Genetics Research Core (HGRC) CUMC
   CSF Specimens, APOE/DNA Specimens, Plasma Specimens
4. **Quest Diagnostics (HSV ½ IgG)/ARUP Lab (HSV ½ IgM)**
   HSV1/HSV2 Testing
5. **Nathan Kline Institute (NKI)**
   Routine Laboratory Testing
6. **NYU Langone Local Hospital Lab**
   Routine Labs for NYU subjects
7. **Banner Health Hospital Laboratory (BAI)**
   Routine Labs for BAI subjects

Lab Results

All lab results need to be reviewed and signed by the study physician promptly after they are received. The physician should initial and date all results and indicate any clinically significant findings.

Blood Draw Policy & Procedures

Test	Tube	Visit	Process
SMAC Folate B12	2 Red tops,	Screen, Week 12, Week 26, Week 78	1. Check off Chem 1, TSH, Folate, Vitamin B12 on NKI requisition form/ NYU Langone Lab Req or BAI Lab Req. 2. Invert 5 times.

	8 mL Serum Sep clot activator Ref # 455071P		3. Stand up right for 30 minutes before centrifuge. 4. Centrifuge for 20 minutes 5. Fill entire label on tube (Ward 890, get X number from KIS-EMR or equivalent medical record number from NYU and BAI medical records interface) and make sure it matches requisition form. If the blood was drawn at baseline, check off "New Admission" under "Reason for Test". If the blood was drawn at a follow up visit, check off "Other" and specify the study week. 6. Submit to refrigerator with requisition form to room 4200 (NYSPI). NYU will submit these specimens to their lab or lab drop off site, as will BAI. 7. RC's and PM will check tubes and forms and confirm their accuracy.
CBC	1 Lavender top, 4mL K3EDTA Ref # 454021	Screen, Week 12, Week 78	1. Check off CBC on NKI requisition form or NYU Langone Lab Req or BAI Lab Req. 2. Invert 10 times. 3. Fill entire label on tube and make sure it matches requisition form. 4. Submit to refrigerator with requisition form to room 4200. NYU will submit these specimens to their lab or lab drop off site, as will BAI. 5. RC's and PM will check tubes and forms and confirm their accuracy.
			<u>Dr. Bell's Directions</u> • The CBC needs to include platelet count. • Patients on anticoagulants are not eligible for LP. • Patients on aspirin or NSAIDs need to stop 7 days before LP as long as they have their PCPs permission. • PT/INR not necessary since we are not taking people on anticoagulants.
Extra Serum Specimen	1 Red top, 8 mL	Week 0 Only	1. Invert 5 times. 2. Stand up right for 30 minutes before centrifuge. 3. Centrifuge for 20 minutes. 4. Aliquot 1 mL of specimen into 2, 2 mL cryovials. 5. Label cryovials with Subject ID, Date, PI, IRB Protocol Number, and time drawn. 6. Store specimens in a Biohazard Bag, in the -80 freezer.
ApoE	1 Yellow top, 8.5mL ACD solution A Ref # 364606	Week 0	1. Put 1st of the 3 copies of the HGRC barcode stickers on the tube. 2. 2nd sticker in ApoE binder log. 3. 3rd sticker on ApoE completed HGRC form (make a copy). 4. Give Marielba's lab on PH19 a copy of HGRC form and have her sign the other to file in ApoE binder. 5. RC's and PM will check tubes and forms and confirm their accuracy.

HSV 1 & 2 quantitative IgG	1 red/grey speckled top, 7.5mL serum separated Ref # 367987 (Order from Quest)	Screen & 78	1. Invert sample 10 times after collection. 2. Put sample into a biohazard bag. 3. Put patient's initials on tube label with date and IRB #. 4. Fill out Quest req form for account T46194 from office 1500A; BAI will complete this section with their BAI specific Quest account number. 5. Only put the patient's initials in the patient name section and indicate their sex, time/date of draw, and "non-fasting". 6. Put IRB #7537 (NYSPI) or NYU IRB# in Patient ID/MRN, or BAI IRB# in Patient ID/MRN. 7. Put "For Research Only – Not Legal" in the Comments (to Print on Report) section in Specimen information. 8. Check off test 6447 HSV1/2 IGG, Type AB Specific. 9. Fill in 90849 HSV (IGM) W/RF at the bottom of the form and check it off. 10. Place sticker with patient initials from the Req form onto tube. 11. Get key for Quest drop-off box from security guard in the lobby of Pardes building 1st floor. 12. Call Quest to pick up sample at 1051 Riverside Drive (866-697-8378) (they will ask for the account number T46194, need to call before 4PM for pick up; NYU will call Quest to their respective location as will BAI. 13. Sample can stay at room temperature for 4 days. 14. RC's and PM will check tubes and forms and confirm their accuracy. Results take about 2-4 days and will be retrieved by RC online via Care 360.
HSV-1&2 quantitative IgM	1 Red Top (8 mL Serum Sep clot activator) (Ref # 455071P) 1 ARUP LAB 4ml Plastic Transport tube	Screen & Week 78	When using a serum separator tube, follow these instructions: Note: Collect the specimen in a plain red-top tube containing no anticoagulants or preservatives. Transfer the serum with a pipette to an ARUP LAB 4ml plastic tube and place transport tube into a blue ARUP LAB frozen temperature specimen bag to be placed in our -80 freezer. Serum should be clear and free from all red cells. Perform venipuncture as with any other blood collection device. 1. Invert the tube gently no more than eight times. Further inversion may cause alterations in sample integrity. 2. Place patient's initials on tube label with date and IRB # 8089. 3. Do not remove the stopper at any time. Do not centrifuge immediately after drawing blood. Allow the blood to clot in an upright position for at least 30 minutes but not longer than 1 hour before centrifugation. 4. Centrifuge for at least 15 minutes at 2200-2500 RPM within one hour of collection. Ambient centrifuge will be used. 5. Transfer at least 1 mL of serum to an 4ml ARUP LAB plastic transport tube 6. Label tube with PT ID#, Date collected, Time collected. Time point: (Screen / Wk 52) and HSV 1&2 IgM 7. Place labeled ARUP Transport tube into Blue ARUP LAB frozen temperature specimen bag. Write account # on bag: VALAD: 496059. VALMCI: 496060 8. Place Blue ARUP lab bag in -80 freezer. Samples will be shipped 5 at a time.

			9. Add specimens' information to biospecimen tracker as: ARUP HSV IgM
Plasma	3 Lavender top, 4mL K3EDTA Ref # 454021	Weeks 12 & 78 If LP, specimen will be drawn at CRR	1. Invert 10 times. Centrifuge the three 4mL lavender tops at 1000 x g for 10 minutes to obtain plasma. 2. Once samples have been centrifuged. Pipette 1-2 mL of plasma (at minimum, 1 mL) into four 2mL cryovials (to have a duplicate for UAB in case of shipping issues). 4mL tube should produce about 2.5 mL of plasma. 3. Label two of the cryovials for UAB and fill out duplicate collection logs with ID, draw time, date, date/time of most recent dose, valacyclovir/placebo, DOB, Dr. Devanand, IRB # 4. The two UAB samples should freeze in two separate boxes in an upright position immediately and be maintained in the 4930 freezer at -80°C until shipment. 5. Another 2mL cryovial will be submitted to the HGRC same day of collection (3 copies of HGRC stickers, 1st: sample, 2nd: Plasma form for Marielba to sign, 3rd: Plasma binder log). BAI staff will store specimen on site for later send out to the HGRC. 6. The 4th cryovial should be filled with the remaining specimen to be stored in the NYSPI freezer (or BAI freezer if BAI subject). 7. RC's and PM will check tubes and forms and confirm their accuracy via signature in the appropriate log 8. Plasma for NYU patients who do not undergo LP will be drawn at NYU with NYSPI supervision. Specimens will be frozen and stored at NYU and then shipped to HGRC and UAB.

Shipping Plasma to UAB:

1. Batch ship (every 5 subjects) samples via FedEx, UPS or other overnight service with sufficient dry ice to keep samples frozen and adhere to IATA guidelines.
2. Do not ship on Thursday or Friday or day before holiday.
3. **Notify UAB Antiviral pharmacology lab (205-975-2461, kedria@uab.edu) when shipment** leaves with FedEx/UPS air bill number.
4. **Ship all samples with the collection log to:**

Edward P. Acosta, Pharm.D., Antiviral Laboratory Director
Lab Contact: Kedria Walker, B.S. and
Kevin Ryan J kjryan@uab.edu (Lab tech)

University of Alabama at Birmingham
Division of Clinical Pharmacology
1670 University Blvd., VH 270
Birmingham, AL 35294

Note: All specimens collected and processed for delivery to collaborating labs are to go through three checkpoints: 1.) the RC who drew and processed the specimen, 2.) the secondary RC 3.) the program manager. Each individual checking specimens will ensure accuracy of labeling (subject ID, DOB or initials, Visit, IRB#, Date) and that all specimens being shipped correspond to (and match with 100% accuracy) the logs they are being sent with.

Blood Collection

The following order-of-draw is recommended when drawing several specimens during a single venipuncture and is used to avoid possible test result error due to cross contamination from tube additives: (1) Blood culture tube (2) Serum tube with or without clot activator or
gel separator (3) Heparin tube with or without gel separator (4) EDTA and (5) Glycolytic inhibitor. Always follow your facility's protocol for order of draw.

Scheduling the Lumbar Puncture (LP): Weeks 0, 12, and 78 (NYSPI/NYU Specific; BAI will apply this protocol with modification made per facility stanadard)

The NYSPI coordinator will schedule Dr. Bell for a two-hour appointment with her scheduler, Terri Rivera (tr2454@cumc.columbia.edu). Terri should be emailed as soon as a subject confirms they will undergo the procedure. Dr. Bell's availability will be released the month prior by Terri Rivera (NYSPI coordinator must email Terri the month prior asking for Dr. Bell's LP availability for the following month). Dr. Bell should **only** be scheduled either 10:00am-11:00pm or 11:00am-12:00pm. NYU staff will communicate their subject's availability, along with any relevant forms, to NYSPI coordinator within 1 day of successful screening and LP interest confirmation. Dr. Bell can be scheduled to see two patients in one day as she often has limited availability.

When Dr. Bell is confirmed, the coordinator will email Elizabeth Guerrido (eg2414@cumc.columbia.edu) a formal CRR space request (see below), copying Ismael Castaneda (ic2444@cumc.columbia.edu) and Janelle Nunez (jn2531@cumc.columbia.edu. When emailing the CRR please attach the "CRR Outpatient Appointment Email Request Form". Comments on this form:

1. Please leave the first two questions that ask for EPIC MRN empty as we will not be enrolling our patients in EPIC.
2. For the question that asks "Are there extenuating circumstances preventing you from registering this participant in EPIC?" Please select the "Yes" checkbox.
3. "Eagle (CUIMC) MRN (7 digit number)" refers to their CROWN MRN. If the patient has never been see at Columbia and does not have a CROWN MRN please list "Needs to be assigned"
4. We will be performing a blood draw for week 12 and week 78 LPs. Please indicate "Blood draw" on the form if it is one of these visits.
5. We will not need any labels printed at the CRR for NYP Core Lab specimens.
6. Under "Special Procedures" please check off "Lumbar Puncture"

For NYU patients, the NYSPI coordinator will send a confirmation email to NYU staff as well when everything is confirmed.

Participant Demographic
Study Participant Name:
DOB:
Race/ethnicity:

Gender:
MRN: (If available from EPIC)

Study information
Study CRR: CRR#2017-041
PI: Davangere Devanand, MD, 646-774-8658, dpd3@cumc.columbia.edu
Emergency MD: Study physician, Phone number, Email
Coordinator: Coordinator, Phone number, Email
Duration: Two hours
Room /space needed for the study visit: Exam room 5
Blood draw: dependent on study week

BEFORE THE LP

10 DAYS BEFORE LP: Please ensure your patient is not on any blood thinners (aspirin included). If they are on any blood thinner, ensure this blood thinner is okay to be stopped with the study physician. If so, please note to call them 8 days before the LP to stop taking any blood thinner at least a week prior (last day taking the medication should be the day you call. Ensure that stopping the medication for a week is sufficient given the medication (confirm with NYSPI coordinators).
2 DAYS BEFORE THE LP: Create a word document with your patient's medication list on it. If there are any blood thinners list a discontinuation date. Create LP labels for all the LP vials (template can be found in the shared drive). Confirm you have all your supplies needed for the LP.

LP Protocol (2 hours)

Subject and informant will be seated in CRR outpatient waiting room. The RC will prep the room for LP, and instruct the subject to put on a gown using the procedure room bathroom. Once the LP begins, Dr. Bell and the RC will wear disposable surgical gown, gloves and surgical mask for the 20-30 minute LP procedure (disposal in CRR Biohazard bin when complete). After the subject has sufficiently recovered from LP (about 45 minutes) and dressed, the research coordinator will disinfect the Procedure Room via Clorox wipe down. Subject and informant will depart directly for home from facility. Labs will be drawn by the CRR nurse. Biospecimens collected (CSF and blood) will be processed by RC at the CRR Lab. Coordinator will follow the CRR Lab's infection control guidelines and will wear surgical mask gloves and lab coat while processing specimens, which will then be placed in a biohazard bag and cooler, to be transported to respective drop-off location.

Procedure Preparation, CSF Collection, and Patient follow-up:

1. Patient should eat breakfast and take all of their medications, as usual, prior to arrival.
2. NYSPI: An RC will arrive 15 minutes prior to the appointment to set up and check the patient in at the front desk. NYU: RC and subject will arrive 30 minutes prior to the procedure (if the NYU coordinator joins, which isn't required). NYSPI coordinators will remain present for the entire procedure duration. NYSPI staff will process, store and ultimately ship specimens.
3. RC will set up paper and pillowcase on the procedure table and lay out the patient gown.
4. RC will set out all the materials for the procedure by the window and rolling tray: LP kit, betadine (found in CRR clinic room), alcohol, tubes, extra needles, bandages, sterile gloves (size 7.5), gauze, syringes, lidocaine. An image of how materials should be set up can be found in the LP Policy and Procedures Manual.
5. RC will set up all the forms Dr. Bell needs by the desk: collection forms, progress note/continuation sheet, time out sheet. The protocol verification time out sheet and continuation forms can be found in the desk drawer. If these are running low notify Sonia to replenish.
6. The patient's chart should be present. The RC should pull out the patient's medication list and signed consent form to be reviewed by Dr. Bell.

7. During the summer, the air conditioning should be turned on in the exam room prior to Dr. Bell's arrival.
8. The other RC will walk patient and caregiver to PH10 to meet Dr. Bell 15 minutes prior to their appointment time. The caregiver should wait in the waiting room throughout the procedure.
9. During weeks 12 and 78, the patient will need to have their blood drawn and processed for plasma in the PH lab 15 minutes prior to the procedure. After the blood draw the subject can be escorted to the procedure room.
10. Patient will need to remove their shirt, unbutton their pants, and put a gown on.
11. Patient will be directed to lie on their side on the exam table and the RC help them to stay on the table. Dr. Bell may ask the patient to pull their legs closer to their chest or curl their chin towards their knees. The RC should ensure that the patient keeps their hands in front of them and does not reach towards their back.
12. Dr. Bell will feel the patient's lower back for the best spot and sterilize the skin with betadine. Dr. Bell will inject lidocaine 1% local anesthesia twice and then perform the LP with a 20-gauge sprotte spinal needle, filling 2 collection tubes once CSF is flowing.
13. 24 mL CSF will be withdrawn into 2, 12mL collection tubes, one research coordinator will take these tubes into the lab to begin processing. The other should remain with patient.
14. Once all the CSF is collected Dr. Bell will clean off the betadine and place a bandage over the needle insertion site.
15. The RC will help to roll the patient over onto their back. The patient must lie still on their back for at least 45 minutes.
16. One RC will go to the waiting room and bring in the caregiver while Dr. Bell cleans up the procedure materials.
17. Dr. Bell will explain the need for extra hydration and for the patient to remain off their feet for the next 2 days. Once she has spoken to the patient and caregiver and completed all the necessary forms, Dr. Bell will leave. The RC should remain with the patient until they are able to stand.
18. After the patient has gotten up, they should change out of their gown and begin hydrating.
19. The RC should collect all excess materials to bring back to NYSPI, throw out the paper on the exam table, and place all soiled linens in the bag in the hallway.
20. The RC should walk the patient out of the hospital and back towards the most convenient building where they parked/took the train.
21. A 24-hour follow up call will be placed to assess for any AEs. RCs will call their respective patients.
22. As described below, reports from Baseline analysis of CSF AD Biomarkers will be provided to CUMC PI then shared with Dr. Wisniewski, who will provide report to NYU subjects.

CSF Processing

1. Processing the 24 mL of CSF collected from the patient:

a. 2mL of CSF for HGRC: The RC should pipette 1mL of CSF into two, 2 mL cryogenic vials.
b. 19mL of CSF for UPenn: The RC should pipette 9.5 mL of CSF into two, 12mL polypropylene clear capped transfer tubes.
c. 1mL of CSF for UAB: the RC should pipette 1 mL of CSF into one, 2mL cryogenic vial.
d. Any additional sample should be placed into 1.8 mL cryovials, labeled, and stored in the -80 freezer on the 4th floor of NYSPI.

Location	Amount	Type of Label
HGRC	1 mL into (1) 1.8 mL cryogenic vial 1 mL into (1) 1.8 mL cryogenic vial	Small barcode sticker on both cryovials Patient ID, IRB#, Devanand, CSF, date, time collected
UPenn	9.5 mL into (1) 12 mL propylene clear capped transfer tube	Patient ID, IRB #, study visit, drug dose, last dose date, last dose time, date collected, time collected,

	9.5 mL into (1) 12 mL propylene clear capped transfer tube	method of collection, needle gauge, volume CSF and time frozen
UAB	1 mL into (1) 1.8 mL cryogenic vial	patient ID, date collected, time collected, method of collection, volume CSF and time frozen
Any additional sample	Additional into (1) 1.8 mL cryogenic vial	Patient ID, IRB#, Devanand, CSF, date, time collected

2. Labeling tubes

a. HGRC cryovials: small barcode stickers. Matching barcode numbers should be placed on both cryovials and the form submitted to HGRC. Another copy of this form should be placed in the HGRC binder.
b. CSF tubes for UPenn: RC types labels for clear capped tubes to include patient ID, IRB #, study visit, drug dose, last dose date, last dose time, date collected, time collected, method of collection, needle gauge, volume CSF and time frozen.
c. CSF for UAB: patient ID, date collected, time collected, method of collection, volume CSF and time frozen.

<u>CSF Storage & shipment: UAB and UPenn</u>

Storage of UAB and UPenn Samples

a. Freeze the UAB and UPenn samples upright for *at least* 20 minutes on dry ice. Store/freeze the CSF in the two, 12 mL polypropylene clear capped UPenn tubes and 2mL UAB cryovial in -80°C freezer in room 4930 in respective UPenn and UAB boxes and/or bags.
b. These tubes can be stored in the MDC freezer for 6 months, but we will batch ship specimens to both labs every 2-3 patients, every 5 patients max. Fill out corresponding shipment logs to match information listed on tubes/vials.

Shipment of UAB and UPenn Samples:

a. Each box log and tube should include ID, DOB, IRB #, and time/date of draw.
b. If shipping that day, again, samples for UPenn and UAB need to be upright on dry ice for at least 20 minutes before being packed. **Do not allow samples to thaw at any point after they have been frozen.** Never ship a sample that was not first frozen upright on dry ice for at least 20 minutes. All shipments are priority overnight.
c. Place small pieces of dry ice in a bubble-wrap bag.
d. Quickly transfer sample tube from dry ice to the bubble wrap bag.
e. Seal the bag with the self-adhesive flap.
f. Quickly place bubble bag with content into the zip lock bag.
g. Place directly on dry ice in Styrofoam shipping box.
h. Fill the box with dry ice and cover. Place container into cardboard box.
i. Affix Federal Express shipping label and call for pick up.

Address to ship to UPenn. Notify Dr. Shaw's lab when shipment leaves; contact Magda (Magda.Brylska@uphs.upenn.edu) with FedEx air bill number. 215 662 6266
Dr. Leslie Shaw, MD
7 Maloney South, University of Pennsylvania Medical Center
3400 Spruce Street, Philadelphia, PA 19104

Notify UAB Antiviral pharmacology lab (205-975-2461, kedria@uab.edu) when shipment leaves with FedEx air bill number. 205-410-6358 (Kedria cell phone). Date and time. direct sig
Ship all samples with this form to:
Edward P. Acosta, Pharm.D., Antiviral Laboratory Director
Lab Contact: Kedria Walker, B.S.

University of Alabama at Birmingham
Division of Clinical Pharmacology
1670 University Blvd., VH 270 Birmingham, AL 35294

CSF Storage & shipment: HGRC

1. HGRC vials will not be stored on site, they will be dropped off at the HGRC on the day of the LP. The CSF for the HGRC will NOT be frozen, the specimens are dropped off at the HGRC same day of the LP, so freezing isn't necessary.
2. There should be four copies of each barcode number on separate stickers. A small sticker should be placed on each of the two cryovials, another (larger sticker) should be placed on the bio sample form, and the last (larger sticker) should be placed on the CSF biological storage log in the bio samples binder. Subject ID, PI, Collection date, and IRB protocol number will also be included in the cryovials brought to the HGRC.
3. The RC should fill out the CSF Bio Sample form from the HGRC with the information specified, including the matching barcode sticker.
4. The RC should make a copy of this form and bring it to the HGRC. HGRC will keep the copy and sign the original. The signed original should then be copied. One copy of the form should be kept in the patient's chart, and the other should be kept in the bio samples binder.

CSF Analysis and Reports: UAB and UPenn

a. UPenn: On a quarterly basis, tau, ptau, and AB42 will be analyzed and reported for all subjects. Neurofilament Light (NL) will be analyzed and reported on as well. The site will receive report of NL results, but these results will not be shared with subjects. Only baseline CSF analyses of tau, ptau and AB42 will be shared with subjects.
b. UAB: At Weeks 12 and 78, plasma acyclovir levels will be drawn and analyzed for all subjects. On a quarterly basis, week 12 and 78 plasma acyclovir levels will be reported to the site, but not shared with subjects. This test isn't clinically relevant but is of relevance to the research team as a check on randomization and subject drug compliance.

18F-Florbetapir Amyloid PET Imaging Procedures (NYSPI/NYU specific, BAI will follow this protocol with modification made per facility standard) – Week 0 & Week 78

Scheduling:

a. NYSPI Coordinator uses iLab to fill out the time request form. Each participant will need a separate request (if there are 3 participants, 3 separate requests will need to be initiated). NYU staff will communicate subject availability and relevant forms to NYSPI coordinator within 1 day of successful screen being confirmed.
b. Confirm if the available dates work with the subject's schedule. If not, follow up with potential dates.
c. Coordinator officially requests a slot. Please note slots are first-come-first-serve. It is best to try to schedule as far in advance as you can per protocol.
d. Coordinators will need to attach all the necessary forms including a scanned copy of the signed consent form, the scan requisition form, and the pregnancy attestation form.
e. NYSPI coordinator will also need to create an order in EPIC for the PET scan, in tandem with iLab. Both the order in EPIC and the request in iLab are required to make an appointment.
f. Amyloid PET scans are offered the following times on Thursdays: 14:00, 14:15, 14:30, 15:00, 15:15, and 15:30.

1) RPOs: The scan requisition form can be downloaded directly in iLab or from the server. Note that there are separate forms for amyloid and tau scans.
a. The date needs to be filled out in 01-Jan-2018 format. The scan requisition section needs to be digitally signed with a PDF editor.

b. Use military time when filling out the time request form. Military time will be calculated in 24 hours. 12.00 am would be 0000 hours 12 pm would be 1200 hours and 11 pm would be 23 hours.

2) Pregnancy: All female patients need to be sign documentation prior to scheduling their appointment. The patient will also need to indicate the year of their last menstrual period.

a. You may want to contact Kim Goldner (kg2614@cumc.columbia.edu) regarding this process, she can also answer questions regarding the cancellation policy.

PET PRE-SCAN PROCEDURES:

1. During study screening:
   a. check for inability to cooperate/claustrophobia (sedation is not offered for this protocol), inability to lie on scanner bed for 20 minutes, inability to achieve venous access sufficient for tracer administration, and past radiation exposure.
   b. Have the patient sign the pregnancy attestation form if applicable.
2. Schedule scan 2-3 weeks in advance on iLab (NYSPI). Scans need to be cancelled 48 hours in advance, otherwise we will be charged for the scan time.
3. Create an order for the PET scan in EPIC, in tandem with iLab.
4. Need to confirm appointment with patient and caregiver at least 3 times before 2-day cancellation window. The NYU team will have to communicate a cancelation to NYSPI as the team at NYSPI will then have to cancel both tracer and scan in iLab.
5. Call patient and caregiver 10 days and 5 days before scan to confirm appointment. NYU staff must place these reminder calls to their subjects.
   a. If they do not pick up, leave voicemail for them to call back to confirm.
   b. If patient and caregiver do not confirm/do not pick up the phone, cancel PET scan.
6. Call patient and caregiver 3 days and 1 day before scan to remind them of the appointment.
7. NYSPI staff will contact Kim (kg2614@cumc.columbia.edu) to create an MRN for the patient if they do not already have one.
8. Scanning can happen no earlier than 11:00am and no later than 4:00pm.

Ordering Amyvid Dose from PETNET:

As of 1/1/19, it is the responsibility of the study team to order Amyvid doses through PETNET Direct.
Website: https://apps.mipetsource.com/home/#/login Acct#: 147944

1. At the far left-hand corner of the homepage, there is a link called "e-ordering." Please click the e-ordering link.
2. Once on the dose calendar, click the link on the far left-hand side called "Add Reserved Dose."
3. When placing your orders for 18F-Florbetapir, reserve 12 mCi. We inject 10 mCi +/- 10% Also: Calibration time is the injection time, place patient ID (not name) in respective field, and name Dr. Devanand as the Referring Provider.
4. Confirmation emails will be sent to the program manager, who will then forward the emails to RCs.
5. Doses can be canceled up until 8am on the day the calibration is due. To cancel a dose, one must call PETNET Direct **(1-877-473-8638).** Cancelations will not be accepted electronically.

ON THE DAY OF THE SCAN:

1. Patient should eat breakfast and take all of their medications, as usual, prior to arrival at PET Center (RC will inform them at 24-hour confirmation). a patient has a long schedule for that day, the patient should bring all medications that they need to take during that time, e.g., medications typically taken during lunchtime if scans are scheduled before and after lunchtime.
2. RC will schedule patient (or patient and coordinator if NYU patient and NYU coordinator joins for the scan) to meet her/him at the Memory Disorders Clinic 30-45 minutes before scan. NYSPI RC must remain present for all scanning procedures if running an NYU patient. Typically, the PET scan will not be the first thing a patient does at baseline or week 78, for these longer visits RC's should keep their eye on the time to

ensure that they arrive at the PET center at least 15 minutes before their scan time to check them in at the front desk.

3. NYSPI RC needs to bring the Pregnancy Attestation Form, a copy of the PET Requisition, and a copy of the signed consent or consents (NYU and NYSPI) if NYU subject. The PET center will keep all forms. All of these forms can be uploaded to iLab which eliminates the need for a hard copy. If the consent form has been changed between the patient's week 0 visit and week 78 visit the patient must sign the updated consent and the NYU or NYSPI RC should bring this updated consent to week 78 PET scan. Always bring the entire subject chart with you if you feel this will be helpful in answering any question staff might pose. The subject will be asked to state his/her name and DOB, which should match the orders/scan request placed by the PI/coordinator.
4. RC needs to bring her/his dosimetry badge.
5. When checking in the person at reception will only need the IRB protocol number from the RC. Once the patient is checked in the RC will wait in the PET center with the patient and caregiver until they are called in.
6. NYSPI RC will have all forms ready for review however the PET center will likely have the forms printed from the prior iLab submission.
7. RC will make sure the patient has removed all metals from head – pins, clips, earrings.
8. The PET technician will set up the patient on a bed with a blanket for them to relax during the uptake period.
9. Once the patient is set up the RC will go to the waiting room to wait for the patient. If the patient does not have a caregiver with them the RC needs to remain in the room with the patient but sit at least 6 feet away. If the caregiver is present, they will remain with the patient until it is time for them to enter the scanner, then come out to the waiting room with the RC.
10. Patient will be at the PET center for about 1.5 hours (scan acquisition time is 20 minutes and the uptake time is 50 minutes). The RC will go back to the scanner 5 minutes before the scan time is up to retrieve the patient and sign a copy of the PET checklist.
11. Once the scan is done the RC will take the patient and caregiver back to the clinic to complete any other necessary measures or to the most convenient location to exit and head to their train or car, if NYU subject, they may leave at this time.

POST SCAN PROCEDURES:

1. Instruct patient that he/she can continue normal activities after PET scan.
2. Patient is advised to drink several glasses of water and contact study physician if there is any persisting pain in his/her hand or arm (slight soreness and bruising is expected since a small tube was inserted into vein of arm).

Obtaining Amyloid Scan Reads
(completed through the PET Department's Safety Read System in RedCap) :

Amyloid reads will be completed by Dr. Akiva Mintz, MD (am4754@cumc.columbia.edu) and/or Dr. Mikhail Dobrouvin, MD (md2367@cumc.columbia.edu) Amyloid read reports are available in RedCap 1-10 days following amyloid PET scan.

To access an Amyloid read:

1. Website: https://radiosftp.cpmc.columbia.edu /redcap/redcap_v8.11.7/DataEntry/record_status_dashboard.php?pid=31&pagenum=2

1. Navigate to **"Record Status Dashboard" (on the left-hand side of the home-page)** and all VALAD subjects are on the list of study subjects receiving reads that will automatically populate when one navigates to the Record Status Dashboard.
2. Subjects are identified on this list by "NYSPI #7537" followed by respective Study ID.
3. RCs must download a PDF the report with "saved data," print, file in subject chart and obtain signature and date on the amyloid read by the patient's study MD.

4. SUVR: Once the analysis and decisions about how to interpret SUVR are confirmed by Hengda He, we will decide how to communicate results to subjects and caregivers, with Drs. Mintz and Kreisl. Dr. Mintz would like to be informed of discrepant cases (between amyloid pos/neg status and SUVR AD Dx interpretation).

Study physicians will review the amyloid read and SUVR results with the patient and caregiver when they come in for their next visit. If the patient wants the results sooner the physician may call to discuss but in-person discussion is strongly preferred. Some reads may require immediate follow up.

1. Prior to filing, PI or study physician will need to sign and date at the bottom of the report.
2. Reports for NYU subjects will be sent to NYU from NYSPI coordinator via secure email after review by Dr. Devanand. Dr. Wisniewski will call NYU subjects with findings.

18F-MK-6240 Tau PET Imaging Procedures (NYSPI/NYU specific, BAI will follow this protocol with modification made per facility standard) – Week 0 & Week 78

General Note:

a) For patients who have confirmed radiation exposure from the past year, contact Dr. Mintz via email for review of patient medical records/self-report of scanning as soon as you've been made aware of the issue. This information is captured on the Metal Screening Questionnaire and the Medical Screening Form. Prior research scans will count toward actual, calculated radiation exposure by Dr. Mintz but SOC scans will not. Dr. Mintz is to evaluate research scan radiation exposure prior to running PET scans. We should go ahead and book scans under the assumption that there will not be a significant delay in scanning, even for those patients who have had previous research scans; we will cancel/rebook if need be per Dr. Mintz.

b) For the sake of IRB Compliance, the VALAD team will always email Dr. Mintz in regard to patients who have been exposed to radiation in the past year (SOC or research). Dr. Mintz will compose either a stock reply that piggy backs off of Dr. Weintraub's decision that SOC scans will not count toward radiation exposure in this protocol, or a more pointed reply with pointed scan scheduling directions if a patient had a research scan(s) in the past year. IRB needs assurance that patients will not exceed 5 REM yearly allowable limit FDA guidelines.

Scheduling:

1. NYSPI Coordinator uses their own iLab account to fill out time request form. Each participant will need a separate request (if there are 3 participants, 3 separate requests will need to be initiated). NYU staff will communicate subject availability and relevant forms to NYSPI coordinator within 1 day of successful screen being confirmed.
2. NYSPI Coordinator will create an order for the PET scan in EPIC, in tandem with iLab.
3. Confirm if available dates work with subject's schedule/follow-up with potential dates.
4. Coordinator officially requests slot. Please note slots are first-come-first-serve. It is best to try to schedule as far in advance as you can per protocol.
5. Coordinators will need to attach all the necessary forms including a scanned copy of the signed consent form, the scan requisition form, and the pregnancy attestation form.

Please Note the following tau PET Scheduling Proclivities:

Scheduling for MK-6240 will utilize the following time slots. We allow two tau dose synthesis failures before proceeding with randomization.

1. MK-6240 injection times will be concentrated on Monday's and Friday's.
2. MK-6240 will not be available on Tuesdays, Wednesdays, and Thursdays.
3. The following injection times are available Monday's and Friday's: 14:00, 14:15, 14:30, 15:30, 15:45, and 16:00
4. The PET scan requisition form can be downloaded directly in iLab or from the server. Note that there are separate forms for amyloid and tau scans.
    a. The date needs to the filled out in 01-Jan-2020 format. The scan requisition section needs to be digitally signed with a PDF editor.

b. Use military time when filling out the time request form. Military time will be calculated in 24 hours. 12.00 am would be 0000 hours 12 pm would be 1200 hours and 11 pm would be 23 hours.

5. Pregnancy: All female patients need to be sign prior to scheduling their appointment. The patient will also need to indicate the year of their last menstrual period.
    a. You may want to contact Kim Goldner (kg2614@cumc.columbia.edu) regarding this process, she can also answer questions regarding the cancellation policy.

PET PRE-SCAN PROCEDURES:

1. During study screening:
    a. check for inability to cooperate/claustrophobia (sedation is not offered for this protocol), inability to lie on scanner bed for 40 minutes, inability to achieve venous access sufficient for tracer administration, and past radiation exposure.
    b. Complete pregnancy form if appicable
2. Schedule scan 2-3 weeks in advance in iLab. Scans need to be cancelled 48 hours in advance, otherwise we will be charged for the scan time. Call patient and caregiver 10 days and 5 days before scan to confirm appointment. NYU staff must place these reminder calls to their subjects.
    a. If they do not pick up, leave voicemail for them to call back to confirm.
    b. If patient and caregiver do not confirm/do not pick up the phone cancel PET scan.
3. Call patient and caregiver 3 days and 1 day before scan to remind them of appointment.

ON THE DAY OF THE SCAN:

1. Patient should eat breakfast and take all of their medications, as usual, prior to arrival at PET Center (RC will inform them at 24-hour confirmation). If a patient has a long schedule for that day, the patient should bring all medications that they need to take e.g., medications typically taken during lunchtime if scans are scheduled before and after lunchtime.
2. NYSPI RC will schedule patient (or patient and coordinator if NYU patient) to meet her/him at the Memory Disorders Clinic 30 minutes before scan. NYSPI RC must be present for all scanning procedures if running an NYU patient. NYU RC's presence is optional. Typically, the PET scan will not be the first procedure a patient completes at baseline or week 78, for these longer visits RC's should keep their eye on the time to ensure that they arrive at the PET Center at least 15 minutes before their scan time to check in at the front desk.
3. NYSPI RC needs to bring the Pregnancy Attestation Form, a copy of the PET Center Checklist, and a copy of the signed consent or consents (NYU and NYSPI) if NYU subject. The PET center will keep all forms. If the consent form has been changed between the patient's week 0 visit and week 78 visit, the patient must sign the updated consent and the RC should bring this updated consent to week 78 PET scan. Always bring the entire chart with you. This will be helpful in answering any question staff might pose.
4. RC needs to bring her/his dosimetry badge.
5. When checking in at reception, the RC will need the IRB protocol number. Once the patient is checked in the RC will wait at the PET center with the patient and caregiver until they are called in.
6. NYSPI RC will give the consent form, and pregnancy attestation, subject ID, and RPO forms to the PET tech.
7. RC will make sure the patient has removed all metals from head – pins, clips, earrings.
8. Pre-injection vital signs (BP, heart rate, temperature, respirations) must be collected by the PET tech and recorded on the PET Center Checklist. The RC must check to ensure this has been done.
9. RC(s) will remain with patient and caregiver during the injection process. RC and caregiver must sit or stand at least 6 feet away from the patient at all times to reduce exposure to radiation. The PET technician will set the patient up on a wheeling bed with a blanket during the uptake period. At this time, the caregiver should go and wait in the PET center waiting room unless the subject is anxious and needs the caregiver in room with them.
10. The RC should remain with the patient and use this time to organize the patient's chart and if the patient is in condition for measure administration, administer measures as required per protocol. Best use should be

made of the lengthy wait time for radioligand uptake. The RC should always be 6 feet away from the patient.

11. Patient will be at the PET Center for 2 hours (scan acquisition time is 40 minutes and the uptake time is 80; 120 minutes in total). The RC (s) will go back to the scanner 5 minutes before the scan time is up to retrieve the patient and review/sign a copy of the PET checklist.
12. Post scan vital signs (BP, heart rate, temperature, respirations) must be collected on the PET center checklist, this will have to be checked by an RC every time an 18F-MK-6240 scan is completed.
13. Room # and Scanner Type (ID) will need to be recorded on the PET center checklist and tracked per patient from baseline to 78 weeks to ensure consistency of scanner used.
14. Once the scan is complete the RC will take the patient and caregiver back to the clinic to complete any other necessary measures. NYU subjects and coordinators may leave at this time.

POST SCAN PROCEDURES:

1. Instruct patient that he/she can continue normal activities after PET scan.
2. Patient is advised to drink several glasses of water and contact study physician if there is any persisting pain in his/her hand or arm (slight soreness and bruising is expected since a small tube was inserted into vein of arm).
3. 24 hours after the scan, the RC will place a follow up safety call to the patient or caregiver to assess for adverse events and/or pain. RCs will call respective subjects.
4. Clinical reads will never be performed on tau scans. Performing clinical reads with non-FDA approved tracers is against federal regulations.

Important Reminder for RCs:

Dr. Devanand has advised of the following policy: if tau imaging procedures get canceled due to technical issues, the main goal is to keep the patient in the protocol. Therefore, the patient may not complete an imaging procedure, but continue in the protocol.

If a patient is unwilling to do the tau PET scan, the patient will still be enrolled in the protocol and will be followed to 78 weeks. This will be a protocol deviation. Of course, this is only a final resort, and all decisions must be reviewed with the patient's study physician and Dr. Devanand, if needed.

Important Contact info for PET:

Kim Goldner (Director of PET Center Technical Services): kg2614@cumc.columbia.edu; 212.342.2999
Rodolfo Arevalo (Project Coordinator); ra2874@cumc.columbia.edu**; 212.342.2999**
Akiva Mintz, MD (PET Center Director/Attending Radiologist): (am4754@cumc.columbia.edu)
Mikhail Dubrouvin, MD (Attending Radiologist): (md2367@cumc.columbia.edu)

MRI Protocol: NYSPI MRI Suite (BAI will follow this protocol with modification made per site standard)

MRI PRE SCAN PROCEDURES: – Week 0 & Week 78

1. After Recruitment and screening – complete the Metal Screening Questionnaire. All implants NEED TO BE CONFIRMED and reviewed with the MRI suite in tandem with the Metal Screening Questionnaire.

   ** **Obtaining MRI Clearance**** If the patient checks 'YES' for any item on this questionnaire (examples include metal stents, wire mesh), clearance must be obtained prior to the MRI scan or the scan will not take place. It is acceptable to schedule the scan prior to obtaining clearance. The coordinator must obtain the name of the patient's implanting surgeon from the patient/caregiver as soon as possible. It is the coordinator's responsibility to follow-up with the patient and/or surgeon to determine the presence or absence of a contraindication. The coordinator will then fax/email the surgeon's office the MRI suite's Request for Proof of MR-Safe Implants, including a signed Release of Information and a fax cover sheet with the patient's name, DOB, and any other available information

about their surgery. This form must be completed and signed by the surgeon. The coordinator will email the completed form to Dr. Lawrence Kegeles (Larry.Kegeles@nyspi.columbia.edu) for clearance. The coordinator should print a hard copy of the Metal Screening Form, Request for Proof of MR-Safe Implants, and Dr. Kegeles' clearance email to bring to the scan. If requested by Dr. Kegeles, the subject should be advised that there is a possibility of movement and overheating of the implant as a result of the scan.

2. Ask about claustrophobia.
3. Schedule an appointment in the Calpendo for 30 minutes (the actual scan takes 30-40 minutes + time for removing metal, wanding and paperwork, etc.)
   a. Schedule scans at least 24 hours in advance.
   b. NYU staff will communicate subject availability and relevant forms to NYSPI coordinator within 5 days of successful screen being confirmed.
   c. Request the patient to be at least 30 minutes early. If NYU subject, both RC and subject will arrive 30 minutes in advance of scan.
   d. Scan cancellation needs to be 95 hours (4 days) before scheduled scan. NYU staff will communicate cancelations to NYSPI staff so that the official cancelation can be made in Calpendo.

ON THE DAY OF THE SCAN for Research Coordinator:

1. Bring the subject in to the MRI suite along with caregiver if needed. The caregiver can wait in the waiting area.
2. NYSPI RC will give the consent form and metal questionnaire (and clearance if needed) to the tech first.
3. NYSPI RC will get billing form from Joe, check box to indicate we want a neuro read. Fill out the rest of the form and return to Joe.
4. Make sure subjects remove all metals – pins, clips, credit cards etc.
5. NYSPI RC will wand the patient to make sure there are no other metals.
6. The tech will check and then take the subject into the scanner room.
7. RC must go in to help place the subject in a comfortable position.
8. RC should wait with the technician outside the scanning room and keep an eye on the patient throughout the duration of the scan. If the RC notices excessive movement, they should notify the tech about the possibility of re-running that scan section.
9. The tech can instruct the subject over the intercom.

AFTER THE SCAN:

- The RC should enter the scan room and make sure that the subject gets out of the scanner carefully.
- Let them collect their belongings and take them out of the MRI suite.
- The study will be uploaded to XNAT (NYSPI).
- Go to XNAT.nyspi.org and check in your projects and download when ready (NYSPI RC).
- You can then download the scan to a PC or MAC and then send it over NYSPI - file transfer or burn on CDs and send them to the respective sites.
- RC will print the MRI report for PI or study physician to review and sign it. PI or study physician will sign and date at bottom of page. Make sure this is completed in clear handwriting.
- Pay attention to reading each report carefully, ensuring that the narrative structure of unremarkable reports are not identical.
- Reports for NYU subjects will be sent to NYU from NYSPI coordinator via secure email after review by Dr. Devanand. Dr. Wisniewski will call NYU subjects with findings.

Important MRI Contact info:

Mathew Riddle MRI Unit Coordinator
New York State Psychiatric Institute1051 Riverside Drive, Room SB315 New York, NY 10032
Mathew.Riddle@nyspi.columbia.edu

Dr. Lawrence S. Kegeles Professor of Clinical Psychiatry (in Radiology), Psych Translational Imaging
(Contact for MRI Implant Clearance)
Larry.Kegeles@nyspi.columbia.edu

MRI without contrast: Scan sequences:

1. **3 Plane Localizer**
2. **Accelerated Sagittal MPRAGE – IR-SPGR**
3. **Sagittal 3D FLAIR**
4. **Axial T2 STAR**

Note: As a general rule, we cannot accept data from outside MRI or PET scans for research purposes.

MRI Protocol: Mind Brain Behavior Institute (BAI will follow this protocol with modification made per site standard)

Informants will not be permitted to attend the actual MBBI MRI scan, and will wait in the facility waiting room, unless there is an emergency. RC will remain at MBBI MRI suite through completion of scan and will escort subjects/informants to exit and go home.

MRI scans will be conducted in the Mind Brain Behaviour Institute (MBBI) scanner "Eve" when they are not cleared to complete a scan on the NYSPI scanner. Subjects scanned at MBBI for Baseline will need to be rescanned at MBBI for Week 78 (on the same scanner) as is the case for subjects scanned in the NYSPI scanner.

Administrative points to keep in mind:

1. Scanner to be used for this protocol:
   a. "Eve" Eve is fMRI machine; "June" is non-fMRI machine.
      Siemens Prisma
      3T, 60cm bore
      80 mT/m @ 200 T/m/s whole body gradients
      128 RF receiver channels
      2 RF transmit channels
      Multinuclear spectroscopy capable
      13 tons, 213 cm long
      Closed helium cryocooled (zero helium boil off) magnet
      Head, neck, body and spine coils come with system
2. Certified MBBI Tech will run our scans. Availability during COVID-19 is only on Tuesdays and Wednesdays, and she will only assist up to 2 scans per day.
3. Clinical Reads
   a. If there is an incidental finding on the clinical read, it is MBBI policy that a MD from Columbia Neurology do the incidental finding follow-up call with the patient. Our MDs will be notified of the findings via letter and perform follow up with subjects over the phone as well.
   b. RC's need to complete the request for a clinical read in RedCap prior to the patient's scan
4. Medical Coverage
   a. If medical coverage is deemed necessary for a patient by Dr. Devanand (i.e. the patient is very impaired, on Lorazepam, or deemed "difficult"), the patient must be scheduled to be scanned on a Monday or Tuesday, as Dr. Devanand and Dr. Kerner indicated that those are the only days both are available for MBBI medical coverage (on site). In this case, Dr. Devanand and Dr. Kerner will be present at MBBI and sit in a counseling room adjacent to the MRI room, in case of a medical emergency.
   b. If no medical coverage is deemed necessary, Dr. Devanand and Dr. Kerner must be made aware of the date/time of a patient scan, so that he/she is available by phone/beeper.
   c. In the case of what staff deem to be "any major medical emergency," MBBI calls 911 immediately.

d. To gain independent access to the building, MDs providing medical coverage must have M2 level training, else will have to be swiped in by their staff, which could pose an inconvenience. To sit in with patients (in the actual MRI scanning room), MDs must have M3 level access.

5. Data Transfer
   a. All data is uploaded to FlyWheel, which is a cloud application accessible to those with a UNI.
   b. We will be able to do fMRI QC using FlyWheel.
   c. PM will be able to download the scan onto CDs, as she has been doing from XNAT. Dania can do this as well.
6. Week 78 Scans
   a. Dr. Devanand confirmed that the patients scanned at MBBI at baseline must be scanned again at MBBI at Week 78.

Procedures:

1. All scans will be booked using iLAB (Devanand NYSPI Group) for 45 minutes.
   a. Kathleen confirmed that we already have an account set-up.
   b. There is a tau Chartstring which will be used for the billing of **VALAD** scans only.
   c. Use the tau Chartstring each time when booking a scan in iLAB.
   d. The scan must be booked by the PI research staff who will be accompanying the patient to the scan
   e. When booking the scan, ensure that MBBI Tech is available to run the scan.
   f. A RedCap record will be set up the day you schedule the scan so that the patient's clinical read can be recorded in a timely manner.
2. At the initial screening visit, the designated RC will complete MBBI's Metal Screening Questionnaire.
   a. If needed, staff will obtain medical records pertaining to the patient's implant and send to Dr. David Gultiken (dg3155@columbia.edu)
3. On the day of scan:
   a. Designated RC will ensure that the patient's chart is brought to MBBI.
   b. Designated RC will meet patient and MBBI Tech at MBBI (3227 Broadway) 30 minutes before the scheduled start-time of the scan. If NYU patient, NYSPI RC will meet outside MBBI 30 minutes prior to scan. NYU RC presence is optional.
   c. Designated RC will assist the patient in changing into scrubs provided by MBBI.
   d. Designated RC will complete wanding and all metal screening procedures with the participant.
   e. Designated RC will escort patient to MRI bed.
   f. Designated RC will provide ear plugs to the participant, per MBBI policy.
   g. Once scan is complete, RC will escort the patient out of the MRI scanner bed and bring him/her back to the dressing room.
   h. Dispose of scrubs in soiled linen basket.
   i. Complete subject payment form with the participant and schedule remaining baseline measures.
4. After Scan/FlyWheel Procedures
   a. Lauren and MBBI Tech will be able to queue the MRI/fMRI QC post-scan using FlyWheel.
   b. Lauren will download scan onto three CDS (copy for: CU, DU, QC)
   c. Research staff will obtain clinical read (RedCap) and review it with Study MD.
      i. If not listed, RC will include patient's name, study ID, and date of birth on the document. RC is then required to initial and date the upper right-hand corner.
      ii. Study MD is required to initial and date the lower right-hand corner.
   d. Dr. Devanand or study MD will then sign IRB MRI Findings Letter. Letters will be sent to NYU RCs for report to NYU subjects by respective NYU study MD.
   e. RC to give the findings letter and clinical read document to patient at his/her next visit, or within a month of the scan date.
5. Scan Cancellation Procedure/Policy
   a. Cancellations must be made 48-hours in advance in iLAB.
   b. If the cancellation must be made less than 48 hours prior to the scan, you must email Kathleen Durkin (kd2649@columbia.edu) directly.
   c. To cancel:

i. Login to iLAB.
ii. Go to Zuckerman Mind Brain Behavior Institute (MBBI): MR Core along the left side, Core Facilities, Click Schedule Equipment.
iii. Click view schedule for the scanner which you booked your scan on.
iv. Find the reserved block, click on "details," that appear to the left.
v. On the screen that appears, there will be a "delete reservation" button in the lower-right corner.

Additional Protocol Points:

New Staff Communication:
For emails regarding scheduling and procedures for an individual patient, communicate amongst coordinators for confirmation of correct language, phrasing, etc.
For broader issues pertaining to the protocol or communication with people outside our core team, your draft email should be sent to both program managers specifically for review. In this draft email, you need to explain the context and include the sequence/chain of emails that led you to generate your draft email. For emails with broader implications, e.g., IRB protocol changes of significance, Dr. Devanand and the entire study team should be copied.
Program Managers are to be CC'd on all key communication; when in doubt, CC a program manager as this will ensure that the proper material is always sent to the proper party covering questions within the email narrative such as Who, What, Where, When, and Why?

Standing Communication Review Protocol:
All communications to outside entities, e.g., DSMB, NIA should be presented for review in our Wednesday meeting and sent out only after that. The exception is if Dr. Devanand has instructed you to do something immediately (in between our Wed meetings).

For clinical and other emergencies, let Dr. Devanand know immediately. Otherwise, bring all pending issues and materials, including those that need signature, to the weekly meetings on Wednesday at 3:00pm in Room 2001.

Adverse Events and Serious Adverse Events:
Adverse events (AE) and serious adverse events (SAE) will be carefully monitored, recorded, and reported in this study. An AE is an unexpected medical occurrence or worsening of symptoms, which does not necessarily have a causal relationship with study treatment. A SAE is a medically serious event, any event requiring hospitalization, and death.

Each patient that has an AE or SAE reported will have an AE log filed in their research chart. Both AE and SAE are to be recorded on the AE log. AE logs are data forms for this study. Hardcopy AE forms are rewritten each time new information about the event is made available, with all revisions kept in paper research charts. However, the database AE form will only contain information reflecting the final resolved event or last recorded information once the patient has left the protocol. Information regarding the treatment provided, outcome, and presumed relationship to study drug will be updated as new information becomes available. Site PIs will sign the bottom of the AE logs for their own site once the patient has exited the protocol.

SAEs are also logged on the AE form for data purposes in this study. For any SAE occurring at NYU or BAI, the SAE will first be reported to local IRB, then to NYSPI for local follow up reporting when applicable, as well as for follow up reporting to additional oversight bodies as described above (DSMB, IRB).

All information obtained between visits by the study coordinator that may be an AE or SAE needs to be communicated to the study physician who will then decide if it is an AE or SAE, consulting with Dr. Devanand if necessary. Based on the decision, the study coordinator needs to ensure that the AE and SAE

forms and completed and submitted to the relevant agencies. Individual AEs need not be reported outside of the core research group and database team. SAEs need to be reported to the IRB and DSMB and NIA.

Protocol Deviations:
If unavoidable deviations from the study protocol occur, they will be recorded on a protocol deviation form filed in the patient's research chart. A protocol deviation log of all deviations throughout the protocol for every patient will be filed in the site's regulatory binder. Site coordinators will keep a log of protocol deviations in an excel document for continual reference and recording.

Protocol Exceptions:
Requests for protocol exceptions are submitted to local IRB on a case by case basis.

Caregiver Communications:
Coordinators will log all clinically relevant communications with patients and their caregivers in the VALAD charts. The only communications that should not be recorded are those initiated by the coordinator, and those regarding scheduling.

Study coordinators will call caregivers to confirm their appointments one day before the scheduled date. When calling to confirm an appointment, take the opportunity to remind caregivers to bring study medication bottles to the clinic and confirm that they have been administering the correct dosage to the patient. For screening or scanning visits remind the patient to bring a valid form of ID.

Reimbursement/Payments:
Patients will be paid $100 for each PET scan and $50 for each MRI scan; each patient will receive 4 PET and 2 MRI scans. The patient will receive $100 for each lumbar puncture procedure. Therefore, over 18 months subjects who complete LP will be compensated $800.00; and those who do not complete LP will be compensated $500.00. In addition, informants will receive $10 per hour or $200 for the entire study that requires approximately 20 hours of informant time during the one-year study. We will also cover transportation costs that we estimate at $80 per patient on average during the study. Petty cash will be used at NYSPI and payment cards at NYU.

Monitoring Visits:
NYSPI /CUMC will conduct Site Initiation, Interim Monitoring, and Close Out visits for any sub site completing work on this protocol. Monitoring visits will include review of sub site regulatory binders(s), source documents, subject charts, database data entry, pharmacy/pharmacy logs, lab space and equipment, any space where study visits are conducted, as well as scheduled time to meet with the site PI to discuss monitoring visit findings and protocol implementation. A detailed monitoring report inclusive of all findings and action items for the site will be generated 1-2 weeks after the visit.

Research Charts:
Study site coordinators are responsible for assembling and updating each patient's research chart. Coordinators review each subject chart at the end of each subject's visit for accuracy and completion of each form. A second coordinator will double check all forms. This instant checking and cross checking is designed to ensure protocol compliance and subject safety. Staff will follow local regulations for paper research charts, with special attention paid to regulations for proper storage of consent forms.

It is recommended that the sections of a research chart be ordered as follows:
1. Patient Tracker/Table of Study Procedures/AE log/Pill Log
2. Consent
3. Labs/Medical Records
4. MRI
5. PET (tau and amyloid)
6. LP

7. Screen
8. Week 0
9. Week 2
10. Week 4
11. Week 12
12. Week 26
13. Week 52
14. Week 78

Forms and measures will be placed in the chart's specific sections and visit weeks as specified in the "**Study Visits: Measures to be Completed per Visit"** section of this manual.

Early Discontinuation and Alternate Scenarios:
The reasons for early discontinuation of a patient from the study include the following:

1. Intervening severe medical illness that either the PI or the Medical Monitor determines that it requires study discontinuation.
2. Discontinuation of treatment with valacyclovir or placebo for more than 6 weeks. After an interruption of treatment for any reason, e.g., medical illness, the patient can resume the protocol if the interruption is less than 6 weeks.
3. Based on the result of a blood draw at the week 26 visit, if the serum creatinine level increases to more than 1.5 or eGFR declines to less than 44 mL/min, we will lower the study medication to the minimum dose of 2g valacyclovir or placebo per day. Patients will then have blood collected and labs repeated at an additional visit at week 30. If, at week 30, kidney function is still abnormal based on the above criteria, study medication will be discontinued for this patient. The reduction in kidney function will be communicated to the patient's primary care physician. This is an intent-to treat protocol. Therefore, a patient who is discontinued early in the study due to the above reasons will be followed and evaluated (whenever feasible) until the Week 78 visit or until the patient withdraws his/her consent to participate.
4. Patient moves their residence to a distant location.
5. Side effects leading the subject to discontinue medication.
6. Insufficient Clinical Response.
7. Non-Compliance with study protocol and/or procedures.
8. Withdrawal of consent.
9. Death.

Intent to Treat/ Dropouts and Missing Data:
Dropout is estimated at 15%. In patients who discontinue study medication, reason for early exit will be documented and study visits will continue at scheduled time-points per the intent-to-treat (ITT) principle.

The primary analyses will be on the ITT sample, i.e., all randomized subjects according to the treatment that they were assigned. Missing data on outcome variables will be dealt with by using (longitudinal) generalized linear mixed effects models that do not require complete measurements under the "missing at random" assumption. For MRI scan, 18F-Florbetapir PET scan, and 18F-MK-6240 tau PET scan, outcomes with just one pre and post measure, inverse probability weighting of cases with complete data will be used where weights are calculated based on the probability of a subject being a completer versus being a dropout. Sensitivity analysis will be performed to provide a range of plausible effect estimates that could arise due to non-ignorable missing data.

Treatment interruption for up to 6 weeks will be allowed for medical/surgical intervening conditions.

When a patient is at risk of dropping out:
When a patient is at risk of dropping out, study staff should assess the concern and take action accordingly, and the study doctor for that patient needs to be informed about intervening to keep the patient in the study if

possible. Staff should keep all relevant blank paper work for the week 78 or Endpoint (dropout) visit in the subject's chart at all times. While the goal is ITT assessments up to 78 weeks, in some cases this may not be possible, e.g., patient does not wish to return, patient moves to a distant location and clinic visits are no longer possible. In these instances, a final study visit should be completed whenever possible. This should be done even if not all procedures can be completed, e.g., patient is willing to come back for a final visit but does not wish to repeat the MRI or PET scan or LP. In this instance, complete all available forms and record them in the database after consultation with Dr. Howard Andrews as to which time-point the data should be entered in the database.

Assessment Instruments:
For a full reference of all forms, measures, requisitions, and notes kept for subjects participating in this protocol, please refer to the Mock Chart, which is kept in room 1600A at NYSPI. Testing materials for the ADAS-Cog11 and other procedures are stored in room 1600A.

Alzheimer's Disease Assessment Scale-Cognition (ADAS-Cog11, modified version): Includes tests of attention, category fluency, episodic verbal memory, non-verbal memory, and naming. ADAS-cog has been used in virtually all FDA registration trials in AD, and we can compare our results with the literature. ADAS-cog has three different/equivalent word list versions that will be given sequentially to reduce practice effects.

ADCS-ADL: A research measure of daily functioning in AD that has been used in several major AD trials. It includes a large section on Instrumental Activities of Daily Living that are affected in mild AD.

Clinical Dementia Rating (CDR): The formal CDR interview will be used to score 6 domains (boxes); sum of boxes. Overall score: 0=none, 0.5=questionable, 1=mild, 2=moderate, 3=severe dementia

National Alzheimer's Coordinating Centers (NACC) Forms: The physician will complete the NACC that takes 35-40 minutes and includes history, neurological exam with assessment of Parkinsonian signs, psychiatric assessment that includes the short version of the Geriatric Depression Scale and the Neuropsychiatric Inventory, Functional Activities Questionnaire (FAQ), vascular risk factors and the modified Hachinski ischemic scale.

NACC-UDS Neuropsychological Test Battery (2015 version): Montreal Cognitive Assessment (MOCA), Number Span Test Forward and Backward, Category Fluency for animals and vegetables, Craft Story21 recall (and delayed), Benson Complex Figure Recall and delayed, Multilingual Naming Test, Verbal Fluency, Phonemic Test. These tests are given for diagnostic purposes only at baseline and 52 and 78 weeks. Drs. Devanand and Stern will make consensus diagnoses at baseline (done with ADRC), and at 52 and 78 weeks, based on clinical assessment and these cognitive tests. We considered the ADCS-PACC (composite score from 4 tests) and the CogState C3 composite used in the A4 trial (PET amyloid-positive, cognitively intact subjects), but these scores were derived by examining the transition from cognitively normal to MCI; they have not yet been validated in AD clinical trials and hence we will not use them.

Apolipoprotein E (ApoE): Apolipoprotein E will be genotyped (ε2, ε3, and ε4 alleles) by LCG genomics using SNPs rs429358 and rs7412. A portion of the blood will be sent out to Prevention Genetics for identification of APOE genotype. Using a standard protocol, DNA is amplified by the polymerase chase reaction (PCR). The genotypes are determined blind to subject status (patient or control) by the sizes of DNA fragments present.

Olfaction Assessment/ The UPSIT (scratch-and-sniff odor identification test): Has been administered to several hundred thousand subjects around the world and its use is not associated with any known side effects. The UPSIT comprises synthetic odors and there is no risk of an allergic reaction with this procedure. If there is an acute upper respiratory infection, testing will be delayed until the participant has recovered.

References

1. Birks J, Grimley Evans J, Iakovidou V, et al. Rivastigmine for Alzheimer's disease. Cochrane Database Syst Rev. 2009(2):CD001191.

2. Podhorna J, Krahnke T, Shear M, et al. Alzheimer's Disease Assessment Scale-Cognitive subscale variants in mild cognitive impairment and mild Alzheimer's disease: change over time and the effect of enrichment strategies. Alzheimers Res Ther. 2016;8:8.

3. Whitehead J. Stopping clinical trials by design. Nat Rev Drug Discov. 2004;3(11):973-977.

4. Valtrex®. Research Triangle Park, NC. GlaxoSmithKline. 2011.

5. Stegert M, Kasenda B, von Elm E, et al. An analysis of protocols and publications suggested that most discontinuations of clinical trials were not based on preplanned interim analyses or stopping rules. J Clin Epidemiol. 2016;69:152-160.

6. Itzhaki RF. Herpes simplex virus type 1 and Alzheimer's disease: increasing evidence for a major role of the virus. Front Aging Neurosci. 2014;6:202.

7. Plentz A, Jilg W, Kochanowski B, et al. Detection of herpesvirus DNA in cerebrospinal fluid and correlation with clinical symptoms. Infection. 2008;36(2):158-162.

8. MacDougall C, Guglielmo BJ. Pharmacokinetics of valaciclovir. J Antimicrob Chemother. 2004;53(6):899-901.

9. Siemers E, Holdridge KC, Sundell KL, et al. Function and clinical meaningfulness of treatments for mild Alzheimer's disease. Alzheimers Dement (Amst). 2016;2:105-112.

10. Dickerson BC, Wolk DA, Alzheimer's Disease Neuroimaging I. Biomarker-based prediction of progression in MCI: Comparison of AD signature and hippocampal volume with spinal fluid amyloid- beta and tau. Front Aging Neurosci. 2013;5:55.

11. Ball MJ. "Limbic predilection in Alzheimer dementia: is reactivated herpesvirus involved?". Can J Neurol Sci. 1982;9(3):303-306.

12. Piacentini R, De Chiara G, Li Puma DD, et al. HSV-1 and Alzheimer's disease: more than a hypothesis. Front Pharmacol. 2014;5:97.

13. Wozniak MA, Frost AL, Itzhaki RF. Alzheimer's disease-specific tau phosphorylation is induced by herpes simplex virus type 1. J Alzheimers Dis. 2009;16(2):341-350.

14. Ball MJ, Lukiw WJ, Kammerman EM, et al. Intracerebral propagation of Alzheimer's disease: strengthening evidence of a herpes simplex virus etiology. Alzheimers Dement. 2013;9(2):169-175.

15. Mori I, Nishiyama Y, Yokochi T, et al. Olfactory transmission of neurotropic viruses. J Neurovirol. 2005;11(2):129-137.

16. Gillet L, Frederico B, Stevenson PG. Host entry by gamma-herpesviruses--lessons from animal viruses? Curr Opin Virol. 2015;15:34-40.

17. Wozniak MA, Frost AL, Preston CM, et al. Antivirals reduce the formation of key Alzheimer's disease molecules in cell cultures acutely infected with herpes simplex virus type 1. PLoS One. 2011;6(10):e25152.

18. Gilbert SC. Suppressive therapy versus episodic therapy with oral valacyclovir for recurrent herpes labialis: efficacy and tolerability in an open-label, crossover study. J Drugs Dermatol. 2007;6(4):400- 405.

19. Klein A, Miller KB, Sprague K, et al. A randomized, double-blind, placebo-controlled trial of valacyclovir prophylaxis to prevent zoster recurrence from months 4 to 24 after BMT. Bone Marrow Transplant. 2011;46(2):294-299.

20. Prasad KM, Eack SM, Keshavan MS, et al. Antiherpes virus-specific treatment and cognition in schizophrenia: a test-of-concept randomized double-blind placebo-controlled trial. Schizophr Bull. 2013;39(4):857-866.

21. Bech E, Lycke J, Gadeberg P, et al. A randomized, double-blind, placebo-controlled MRI study of anti- herpes virus therapy in MS. Neurology. 2002;58(1):31-36.

22. Friedman JE, Zabriskie JB, Plank C, et al. A randomized clinical trial of valacyclovir in multiple sclerosis. Mult Scler. 2005;11(3):286-295.

23. Cummings JL, Zhong K. Repackaging FDA-approved drugs for degenerative diseases: promises and challenges. Expert Rev Clin Pharmacol. 2014;7(2):161-165.

24. Lycke J, Malmestrom C, Stahle L. Acyclovir levels in serum and cerebrospinal fluid after oral administration of valacyclovir. Antimicrob Agents Chemother. 2003;47(8):2438-2441.

25. Pouplin T, Pouplin JN, Van Toi P, et al. Valacyclovir for herpes simplex encephalitis. Antimicrob Agents Chemother. 2011;55(7):3624-3626.

26. Smith JP, Weller S, Johnson B, et al. Pharmacokinetics of acyclovir and its metabolites in cerebrospinal fluid and systemic circulation after administration of high-dose valacyclovir in subjects with normal and impaired renal function. Antimicrob Agents Chemother. 2010;54(3):1146-1151.

27. Itzhaki RF, Lathe R, Balin BJ, et al. Microbes and Alzheimer's Disease. J Alzheimers Dis. 2016;51(4):979- 984.

28. Gannicliffe A, Sutton RN, Itzhaki RF. Viruses, brain and immunosuppression. Psychol Med. 1986;16(2):247-249.

29. Bradshaw MJ, Venkatesan A. Herpes Simplex Virus-1 Encephalitis in Adults: Pathophysiology, Diagnosis, and Management. Neurotherapeutics. 2016;13(3):493-508.

30. Wozniak MA, Mee AP, Itzhaki RF. Herpes simplex virus type 1 DNA is located within Alzheimer's disease amyloid plaques. J Pathol. 2009;217(1):131-138.

31. Baker HF, Ridley RM, Duchen LW, et al. Induction of beta (A4)-amyloid in primates by injection of Alzheimer's disease brain homogenate. Comparison with transmission of spongiform encephalopathy. Mol Neurobiol. 1994;8(1):25-39.

32. Kane MD, Lipinski WJ, Callahan MJ, et al. Evidence for seeding of beta -amyloid by intracerebral infusion of Alzheimer brain extracts in beta -amyloid precursor protein-transgenic mice. J Neurosci. 2000;20(10):3606-3611.

33. Burgos JS, Ramirez C, Sastre I, et al. Involvement of apolipoprotein E in the hematogenous route of herpes simplex virus type 1 to the central nervous system. J Virol. 2002;76(23):12394-12398.

34. Hill JM, Ball MJ, Neumann DM, et al. The high prevalence of herpes simplex virus type 1 DNA in human trigeminal ganglia is not a function of age or gender. J Virol. 2008;82(16):8230-8234.

35. Steiner I, Kennedy PG, Pachner AR. The neurotropic herpes viruses: herpes simplex and varicella- zoster. Lancet Neurol. 2007;6(11):1015-1028.

36. Arendt T, Bruckner MK, Morawski M, et al. Early neurone loss in Alzheimer's disease: cortical or subcortical? Acta Neuropathol Commun. 2015;3:10.

37. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol. 1991;82(4):239-259.

38. Liedtke W, Opalka B, Zimmermann CW, et al. Age distribution of latent herpes simplex virus 1 and varicella-zoster virus genome in human nervous tissue. J Neurol Sci. 1993;116(1):6-11.

39. D'Aiuto L, Prasad KM, Upton CH, et al. Persistent infection by HSV-1 is associated with changes in functional architecture of iPSC-derived neurons and brain activation patterns underlying working memory performance. Schizophr Bull. 2015;41(1):123-132.

40. Xu F, Sternberg MR, Kottiri BJ, et al. Trends in herpes simplex virus type 1 and type 2 seroprevalence in the United States. JAMA. 2006;296(8):964-973.

41. Letenneur L, Peres K, Fleury H, et al. Seropositivity to herpes simplex virus antibodies and risk of Alzheimer's disease: a population-based cohort study. PLoS One. 2008;3(11):e3637.

42. Kobayashi N, Nagata T, Shinagawa S, et al. Increase in the IgG avidity index due to herpes simplex virus type 1 reactivation and its relationship with cognitive function in amnestic mild cognitive impairment and Alzheimer's disease. Biochem Biophys Res Commun. 2013;430(3):907-911.

43. Mancuso R, Baglio F, Agostini S, et al. Relationship between herpes simplex virus-1-specific antibody titers and cortical brain damage in Alzheimer's disease and amnestic mild cognitive impairment. Front Aging Neurosci. 2014;6:285.

44. Barnes LL, Capuano AW, Aiello AE, et al. Cytomegalovirus infection and risk of Alzheimer disease in older black and white individuals. J Infect Dis. 2015;211(2):230-237.

45. Koskiniemi M, Vaheri A, Taskinen E. Cerebrospinal fluid alterations in herpes simplex virus encephalitis. Rev Infect Dis. 1984;6(5):608-618.

46. Lovheim H, Gilthorpe J, Johansson A, et al. Herpes simplex infection and the risk of Alzheimer's disease: A nested case-control study. Alzheimers Dement. 2015;11(6):587-592.

47. Lovheim H, Gilthorpe J, Adolfsson R, et al. Reactivated herpes simplex infection increases the risk of Alzheimer's disease. Alzheimers Dement. 2015;11(6):593-599.

48. Dickerson F, Stallings C, Origoni A, et al. Additive effects of elevated C-reactive protein and exposure to Herpes Simplex Virus type 1 on cognitive impairment in individuals with schizophrenia. Schizophr Res. 2012;134(1):83-88.

49. Dickerson F, Stallings C, Sullens A, et al. Association between cognitive functioning, exposure to Herpes Simplex Virus type 1, and the COMT Val158Met genetic polymorphism in adults without a psychiatric disorder. Brain Behav Immun. 2008;22(7):1103-1107.

50. Strandberg TE, Pitkala KH, Linnavuori KH, et al. Impact of viral and bacterial burden on cognitive impairment in elderly persons with cardiovascular diseases. Stroke. 2003;34(9):2126-2131.

51. Watson AM, Prasad KM, Klei L, et al. Persistent infection with neurotropic herpes viruses and cognitive impairment. Psychol Med. 2013;43(5):1023-1031.

52. Dickerson FB, Boronow JJ, Stallings C, et al. Association of serum antibodies to herpes simplex virus 1 with cognitive deficits in individuals with schizophrenia. Arch Gen Psychiatry. 2003;60(5):466-472.

53. Yolken RH, Torrey EF. Are some cases of psychosis caused by microbial agents? A review of the evidence. Mol Psychiatry. 2008;13(5):470-479.

54. Dickerson FB, Boronow JJ, Stallings C, et al. Infection with herpes simplex virus type 1 is associated with cognitive deficits in bipolar disorder. Biol Psychiatry. 2004;55(6):588-593.

55. Montoya JG, Kogelnik AM, Bhangoo M, et al. Randomized clinical trial to evaluate the efficacy and safety of valganciclovir in a subset of patients with chronic fatigue syndrome. J Med Virol. 2013;85(12):2101-2109.

56. Hokkanen L, Launes J. Cognitive outcome in acute sporadic encephalitis. Neuropsychol Rev. 2000;10(3):151-167.

57. Beutner KR. Valacyclovir: a review of its antiviral activity, pharmacokinetic properties, and clinical efficacy. Antiviral Res. 1995;28(4):281-290.

58. Vere Hodge RA, Field HJ. Antiviral agents for herpes simplex virus. Adv Pharmacol. 2013;67:1-38.

59. Schretlen DJ, Vannorsdall TD, Winicki JM, et al. Neuroanatomic and cognitive abnormalities related to herpes simplex virus type 1 in schizophrenia. Schizophr Res. 2010;118(1-3):224-231.

60. Devanand DP, Pradhaban G, Liu X, et al. Hippocampal and entorhinal atrophy in mild cognitive impairment: prediction of Alzheimer disease. Neurology. 2007;68(11):828-836.

61. Razlighi QR, Habeck C, Barulli D, et al. Cognitive neuroscience neuroimaging repository for the adult lifespan. Neuroimage. 2017;144(Pt B):294-298.

62. Carter CJ. Alzheimer's disease plaques and tangles: cemeteries of a pyrrhic victory of the immune defence network against herpes simplex infection at the expense of complement and inflammationmediated neuronal destruction. Neurochem Int. 2011;58(3):301-320.

63. Wozniak MA, Itzhaki RF, Shipley SJ, et al. Herpes simplex virus infection causes cellular beta-amyloid accumulation and secretase upregulation. Neurosci Lett. 2007;429(2-3):95-100.

64. Shipley SJ, Parkin ET, Itzhaki RF, et al. Herpes simplex virus interferes with

amyloid precursor protein processing. BMC Microbiol. 2005;5:48.

65. Cheng SB, Ferland P, Webster P, et al. Herpes simplex virus dances with amyloid precursor protein while exiting the cell. PLoS One. 2011;6(3):e17966.

66. De Chiara G, Marcocci ME, Civitelli L, et al. APP processing induced by herpes simplex virus type 1 (HSV-1) yields several APP fragments in human and rat neuronal cells. PLoS One. 2010;5(11):e13989.

67. Pierrot N, Santos SF, Feyt C, et al. Calcium-mediated transient phosphorylation of tau and amyloid precursor protein followed by intraneuronal amyloid-beta accumulation. J Biol Chem. 2006;281(52):39907- 39914.

68. Piacentini R, Civitelli L, Ripoli C, et al. HSV-1 promotes Ca2+ -mediated APP phosphorylation and Abeta accumulation in rat cortical neurons. Neurobiol Aging. 2011;32(12):2323 e2313-2326.

69. Doody RS, Raman R, Farlow M, et al. A phase 3 trial of semagacestat for treatment of Alzheimer's disease. N Engl J Med. 2013;369(4):341-350.

70. Kumar DK, Choi SH, Washicosky KJ, et al. Amyloid-beta peptide protects against microbial infection in mouse and worm models of Alzheimer's disease. Sci Transl Med. 2016;8(340):340ra372.

71. Krut JJ, Zetterberg H, Blennow K, et al. Cerebrospinal fluid Alzheimer's biomarker profiles in CNS infections. J Neurol. 2013;260(2):620-626.

72. Pooler AM, Polydoro M, Wegmann S, et al. Propagation of tau pathology in Alzheimer's disease: identification of novel therapeutic targets. Alzheimers Res Ther. 2013;5(5):49.

73. Liu L, Drouet V, Wu JW, et al. Trans-synaptic spread of tau pathology in vivo. PLoS One. 2012;7(2):e31302.

74. Jamieson GA, Maitland NJ, Wilcock GK, et al. Latent herpes simplex virus type 1 in normal and Alzheimer's disease brains. J Med Virol. 1991;33(4):224-227.

75. Aiello AE, Haan M, Blythe L, et al. The influence of latent viral infection on rate of cognitive decline over 4 years. J Am Geriatr Soc. 2006;54(7):1046-1054.

76. Jayasuriya AN, Itzhaki RF, Wozniak MA, et al. Apolipoprotein E-epsilon 4 and recurrent genital herpes in individuals co-infected with herpes simplex virus type 2 and HIV. Sex Transm Infect. 2008;84(7):516-523.

77. Burgos JS, Ramirez C, Sastre I, et al. Effect of apolipoprotein E on the cerebral load of latent herpes simplex virus type 1 DNA. J Virol. 2006;80(11):5383-5387.

78. Reitz C, Jun G, Naj A, et al. Variants in the ATP-binding cassette transporter (ABCA7), apolipoprotein E 4,and the risk of late-onset Alzheimer disease in African Americans. JAMA. 2013;309(14):1483- 1492.

79. Devanand DP, Liu X, Tabert MH, et al. Combining early markers strongly predicts conversion from mild cognitive impairment to Alzheimer's disease. Biol Psychiatry. 2008;64(10):871-879.

80. Devanand DP, Lee S, Manly J, et al. Olfactory deficits predict cognitive decline and Alzheimer dementia in an urban community. Neurology. 2015;84(2):182-189.

81. Devanand DP, Lee S, Manly J, et al. Olfactory identification deficits and increased mortality in the community. Ann Neurol. 2015;78(3):401-411.

82. Roberts RO, Christianson TJ, Kremers WK, et al. Association Between Olfactory Dysfunction and Amnestic Mild Cognitive Impairment and Alzheimer Disease Dementia. JAMA Neurol. 2016;73(1):93- 101.

83. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7(3):280-292.

84. Saidlitz P, Voisin T, Vellas B, et al. Amyloid imaging in Alzheimer's disease: a literature review. J Nutr Health Aging. 2014;18(7):723-740.

85. Devanand DP, Mikhno A, Pelton GH, et al. Pittsburgh compound B (11C-PIB) and fluorodeoxyglucose (18 F-FDG) PET in patients with Alzheimer disease, mild cognitive impairment, and healthy controls. J Geriatr Psychiatry Neurol. 2010;23(3):185-198.

86. Devanand DP, Schupf N, Stern Y, et al. Plasma Abeta and PET PiB binding are inversely related in mild cognitive impairment. Neurology. 2011;77(2):125-131.

87. Gu Y, Razlighi QR, Zahodne LB, et al. Brain Amyloid Deposition and Longitudinal Cognitive Decline in Nondemented Older Subjects: Results from a Multi-Ethnic Population. PLoS One. 2015;10(7):e0123743.

88. Mikhno A, Devanand D, Pelton G, et al. Voxel-based analysis of 11C-PIB scans for diagnosing Alzheimer's disease. J Nucl Med. 2008;49(8):1262-1269.

89. Leuzy A, Zimmer ER, Heurling K, et al. Use of amyloid PET across the spectrum of Alzheimer's disease: clinical utility and associated ethical issues. Amyloid. 2014;21(3):143-148.

90. Devanand DP, Bansal R, Liu J, et al. MRI hippocampal and entorhinal cortex mapping in predicting conversion to Alzheimer's disease. Neuroimage. 2012;60(3):1622-1629.

91. Razlighi QR, Oh H, Habeck C, et al. Dynamic Patterns of Brain Structure-Behavior Correlation Across the Lifespan. Cereb Cortex. 2016.

92. Habeck C, Razlighi Q, Gazes Y, et al. Cognitive Reserve and Brain Maintenance: Orthogonal Concepts in Theory and Practice. Cereb Cortex. 2016.

93. Lee S, Habeck C, Razlighi Q, et al. Selective association between cortical thickness and reference abilities in normal aging. Neuroimage. 2016;142:293-300.

94. Brickman AM, Guzman VA, Gonzalez-Castellon M, et al. Cerebral autoregulation, beta amyloid, and white matter hyperintensities are interrelated. Neurosci Lett. 2015;592:54-58.

95. Oh H, Steffener J, Razlighi QR, et al. Abeta-related hyperactivation in frontoparietal control regions in cognitively normal elderly. Neurobiol Aging. 2015;36(12):3247-3254.

96. Oh H, Steffener J, Razlighi QR, et al. beta-Amyloid Deposition Is Associated with Decreased Right Prefrontal Activation during Task Switching among Cognitively Normal Elderly. J Neurosci. 2016;36(6):1962- 1970.

97. Jacobson MA. Valaciclovir (BW256U87): the L-valyl ester of acyclovir. J Med Virol. 1993;Suppl 1:150- 153.

98. Weller S, Blum MR, Doucette M, et al. Pharmacokinetics of the acyclovir pro-drug valaciclovir after escalating single- and multiple-dose administration to normal volunteers. Clin Pharmacol Ther. 1993;54(6):595- 605.

99. Tyring SK, Baker D, Snowden W. Valacyclovir for herpes simplex virus infection: long-term safety and sustained efficacy after 20 years' experience with acyclovir. J Infect Dis. 2002;186 Suppl1:S40-46.

100. Asahi T, Tsutsui M, Wakasugi M, et al. Valacyclovir neurotoxicity: clinical experience and review of the literature. Eur J Neurol. 2009;16(4):457-460.

101. Stolp HB, Dziegielewska KM. Review: Role of developmental inflammation and blood-brain barrier dysfunction in neurodevelopmental and neurodegenerative diseases. Neuropathol Appl Neurobiol. 2009;35(2):132-146.

102. Heye AK, Culling RD, Valdes Hernandez Mdel C, et al. Assessment of blood-brain barrier disruption using dynamic contrast-enhanced MRI. A systematic

review. Neuroimage Clin. 2014;6:262-274.

103. Lycke J, Andersen O, Svennerholm B, et al. Acyclovir concentrations in serum and cerebrospinal fluid at steady state. J Antimicrob Chemother. 1989;24(6):947-954.

104. Feinberg JE, Hurwitz S, Cooper D, et al. A randomized, double-blind trial of valaciclovir prophylaxis for cytomegalovirus disease in patients with advanced human immunodeficiency virus infection. AIDS Clinical Trials Group Protocol 204/Glaxo Wellcome 123-014 International CMV Prophylaxis Study Group. J Infect Dis. 1998;177(1):48-56.

105. Birks JS, Chong LY, Grimley Evans J. Rivastigmine for Alzheimer's disease. Cochrane Database Syst Rev. 2015;9:CD001191.

106. Lam NN, Weir MA, Yao Z, et al. Risk of acute kidney injury from oral acyclovir: a population-based study. Am J Kidney Dis. 2013;61(5):723-729.

107. Wang LH, Schultz M, Weller S, et al. Pharmacokinetics and safety of multiple-dose valaciclovir in geriatric volunteers with and without concomitant diuretic therapy. Antimicrob Agents Chemother. 1996;40(1):80-85.

108. Glassock RJ, Winearls C. Ageing and the glomerular filtration rate: truths and consequences. Trans Am Clin Climatol Assoc. 2009;120:419-428.

109. Rule AD, Amer H, Cornell LD, et al. The association between age and nephrosclerosis on renal biopsy among healthy adults. Ann Intern Med. 2010;152(9):561-567.

110. Salloway S, Sperling R, Fox NC, et al. Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. N Engl J Med. 2014;370(4):322-333.

111. Bergstrom T, Trybala E. Antigenic differences between HSV-1 and HSV-2 glycoproteins and their importance for type-specific serology. Intervirology. 1996;39(3):176-184.

112. Prasad KM, Watson AM, Dickerson FB, et al. Exposure to herpes simplex virus type 1 and cognitive impairments in individuals with schizophrenia. Schizophr Bull. 2012;38(6):1137-1148.

113. Doty RL, Shaman P, Kimmelman CP, et al. University of Pennsylvania Smell Identification Test: a rapid quantitative olfactory function test for the clinic. Laryngoscope. 1984;94(2 Pt 1):176-178.

114. Fischl B, van der Kouwe A, Destrieux C, et al. Automatically parcellating the human cerebral cortex. Cereb Cortex. 2004;14(1):11-22.

115. Fischl B, Salat DH, Busa E, et al. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron. 2002;33(3):341-355.

116. Kennedy KM, Erickson KI, Rodrigue KM, et al. Age-related differences in regional brain volumes: a comparison of optimized voxel-based morphometry to manual volumetry. Neurobiol Aging. 2009;30(10):1657- 1676.

117. Fjell AM, Westlye LT, Amlien I, et al. High consistency of regional cortical thinning in aging across multiple samples. Cereb Cortex. 2009;19(9):2001-2012.

118. Ardekani BA, Guckemus S, Bachman A, et al. Quantitative comparison of algorithms for inter-subject registration of 3D volumetric brain MRI scans. J Neurosci Methods. 2005;142(1):67-76.

119. Reuter M, Schmansky NJ, Rosas HD, et al. Within-subject template estimation for unbiased longitudinal image analysis. Neuroimage. 2012;61(4):1402-1418.

120. Bakkour A, Morris JC, Dickerson BC. The cortical signature of prodromal AD: regional thinning predicts mild AD dementia. Neurology. 2009;72(12):1048-1055.

121. Dickerson BC, Bakkour A, Salat DH, et al. The cortical signature of Alzheimer's disease: regionally specific cortical thinning relates to symptom severity in very mild to mild AD dementia and is detectable in asymptomatic amyloid-positive individuals. Cereb Cortex. 2009;19(3):497-510.

122. Villemagne VL, Dore V, Bourgeat P, et al. Abeta-amyloid and Tau Imaging in Dementia. Semin Nucl Med. 2017;47(1):75-88.

123. Gibbons RD, Hedeker D, Elkin I, et al. Some conceptual and statistical issues in analysis of longitudinal psychiatric data. Application to the NIMH treatment of Depression Collaborative Research Program dataset. Arch Gen Psychiatry. 1993;50(9):739-750.

124. Laird NM. Missing data in longitudinal studies. Stat Med. 1988;7(1-2):305-315.

125. Little R, Rubin, DB. Statistical analysis with missing data. John Wiley & Sons, Inc. 2002.

126. Seaman SR, White IR. Review of inverse probability weighting for dealing with missing data. Stat Methods Med Res. 2013;22(3):278-295.

127. Diggle P, Kenward, MG. Informative drop-out in longitudinal data analysis. Journal of the Royal Statistical Society Series C (Applied Statistics). 1994(43):49-93.

128. Kenward MG. Selection models for repeated measurements with non-random dropout: an illustration of sensitivity. Stat Med. 1998;17(23):2723-2732.

129. Liu X, Waternaux, C., Petkova, E. Influence of Human Immunodeficiency Virus Infection on Neurological Impairment: An Analysis of Longitudinal Binary Data with Informative Drop-Out Journal of the Royal Statistical Society Series C (Applied Statistics). 1999(48):103-115.

130. Rotnitzky A, Robins J. Analysis of semi-parametric regression models with non-ignorable non- response. Stat Med. 1997;16(1-3):81-102.

131. Scharfstein D, Rotnitzky, A., Robins, JM. Adjusting for Nonignorable Drop-Out Semiparametric Nonresponse Models. Journal of the American Statistical Association. 1998(94):1096-1120.

132. Kraemer HC, Wilson GT, Fairburn CG, et al. Mediators and moderators of treatment effects in randomized clinical trials. Arch Gen Psychiatry. 2002;59(10):877-883.

133. Roy A, Bhaumik DK, Aryal S, et al. Sample size determination for hierarchical longitudinal designs with differential attrition rates. Biometrics. 2007;63(3):699-707.

134. Selya AS, Rose JS, Dierker LC, et al. A Practical Guide to Calculating Cohen's f(2), a Measure of Local Effect Size, from PROC MIXED. Front Psychol. 2012;3:111.

135. 18F-MK-6240 Investigator Brochure Edition II. Merck Sharp & Dohme Corp., a Subsidiary of Merck & Co., Inc. 2016.