Study Protocol and Statistical Analysis Plan

Cognitive Decline and Alzheimer's Disease in the Dallas Lifespan Brain Study

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Document approval date: November 18, 2021

6. PROTOCOL

PROTOCOL Version 6

PROTOCOL TITLE

Cause or effect? Untangling the relationship with amyloid and tau deposits to cognitive decline and Alzheimer's disease in the Dallas Lifespan Brain Study

Phase II, Investigational Drug, Alzheimer's Disease

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IND/IDE Holder Name:	Neil M. Rofsky, M.D.
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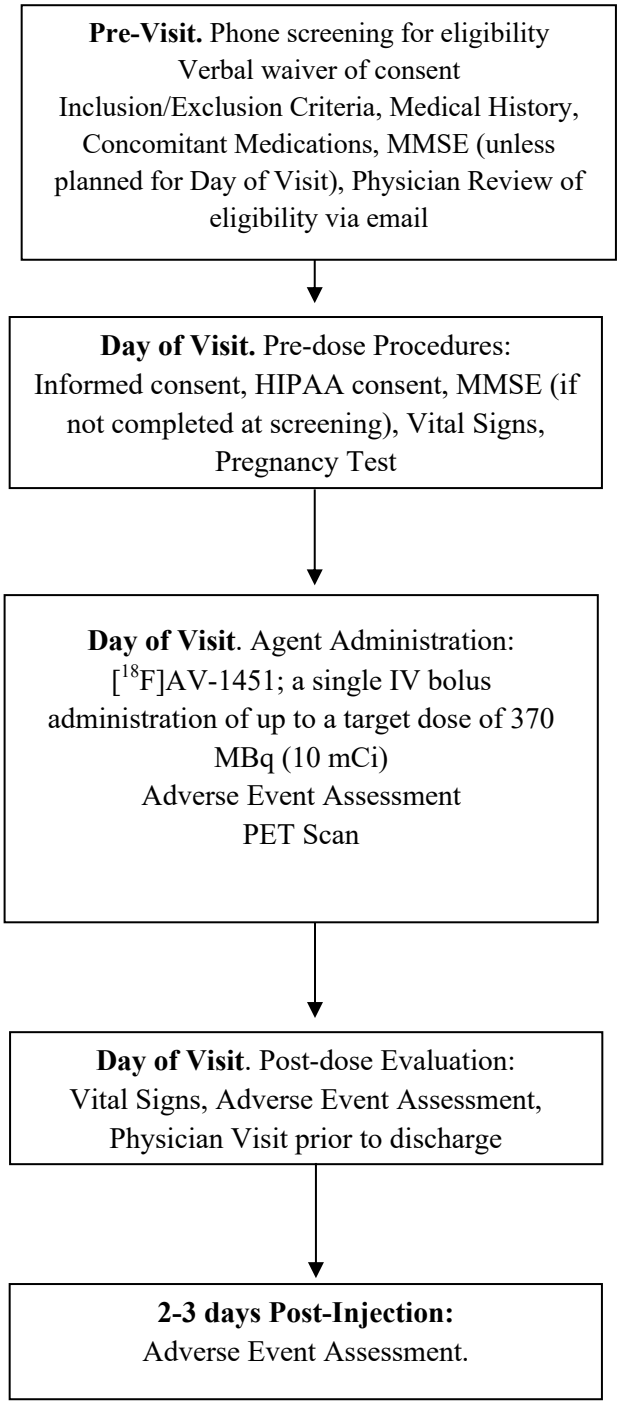
6.1. LIST OF ABBREVIATIONS

AD	Alzheimer's Disease
AE	Adverse Event
AVID	Advancement Via Individual Determination
BOLD	Blood Oxygen-Level Dependent
CFR	Code of Federal Regulations
COI	Conflict of Interest
CSF	Cerebrospinal Fluid
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLBS	The Dallas Lifespan Brain Study
DSMB	Data and Safety Monitoring Board
FDA	The Food and Drug Administration
GCP	Good Clinical Practice
hERG	Human ether-a-go-go related gene
HHS	Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
HRPP	Human Research Protection Program
ICH	International Conference of Harmonization
IND	Investigational New Drug
IRB	The Institutional Review Board
IV or iv	Intravenously
MHD	Maximum Human Mass Dose
MMSE	Mini-Mental State Examination
MPRage	Magnetization-prepared radio-frequency pulses and rapid gradient-echo
MRI	Magnetic Resonance Image
NCI	National Cancer Institute
NOAEL	No-Observed-Adverse-Effect-Level

OHRP	Office of Human Research Protections
PET	Positron Emission Tomography
PHF	Paired Helical Filaments
PI	Principal Investigator
SCCC	Simmons Comprehensive Cancer Center
SUVr	Standardized Uptake Value Ratio
TBI	Traumatic Brain Injury
TdP	Torsades de Pointes
UPIRSO	Unanticipated Problems Involving Risks to Subjects or Others
UTD	University of Texas at Dallas
UTSW	University of Texas Southwestern Medical Center

6.2. STUDY SCHEMA FOR WAVE 3 MODIFICATION



6.3. STUDY SUMMARY

Title	Cause or effect? Untangling the relationship with amyloid and tau deposits to cognitive decline and Alzheimer's disease in the Dallas Lifespan Brain Study
Protocol Number	Version 6
Phase	Phase II
Methodology	Open label
Study Duration	5/1/2019 - 6/30/2022
Study Center(s)	Single-center
Objectives	We will conduct tau PET scans on up to 125 adults using the radiopharmaceutical AV-1451. This will allow us to determine tau deposition across adults of different ages and assess the relationship of current tau burden to cognitive function and amyloid deposition collected over the previous 10-year interval.
Number of Subjects	Up to 125
Diagnosis and Main Inclusion Criteria	Eight- to ten-year follow-up Dallas Lifespan Brain Study participants who were cognitively normal at the time of enrollment from 2008 to 2014.
Study Product(s), Dose, Route, Regimen	[^{18}F]AV-1451 (7-(6-[F-18]fluoropyridin-3-yl)-5H-pyrido[4,3-b]indole) for Injection, a single intravenous (IV) bolus administration of up to a target dose of 370 MBq (10 mCi)
Duration of administration	Single dose
Reference therapy	Not applicable
Statistical Methodology	Tau deposition will be examined via estimating the mean standardized uptake value ratio (SUVr) of [^{18}F]AV-1451 in six temporal brain regions of interest in both the left and right hemispheres. Linear mixed-model analysis will use the Tau SUVr values to examine relationships with changes in other Alzheimer's Disease pathology and changes in decline of cognitive function in brain changes associated with typical aging.

6.4. BACKGROUND AND RATIONALE

6.4.1. Disease Background

Alzheimer's disease (AD) is a highly prevalent disorder of dementia in older adults. AD neuropathology is marked by the presence of amyloid plaques and tau neurofibrillary tangles (Khachaturian, 1985). Autopsy studies (Trojanowski et al., 1997), as well as magnetic resonance imaging (MRI) studies (Jack et al., 1997; Convit et al., 1993; Killiany et al., 1993) in living persons, have established that the neurodegenerative changes in AD begin in medial temporal lobe structures and later progress to adjacent temporal, parietal and frontal neocortical regions (Braak & Braak, 1991; Price et al., 2001). Magnetic resonance image studies of AD consistently reveal volumetric loss in the hippocampus using both cross-sectional and longitudinal approaches (Jack et al., 1997; Convit et al., 1993; Killiany et al., 1993). The primary symptom of early-stage AD is memory impairment (Mohs et al., 1998; Storandt et al., 2002) possibly accompanied by deficits in attentional control (Balota & Faust, 2001). Normal aging, however, is also marked by cognitive decline (Park et al., 2009; Park et al., 2014), as well as structural brain changes (Raz & Rodrigue, 2006). Autopsy data had shown in the past that about 30% of older adults with no obvious cognitive impairment show some degree of the neuropathology typically associated with dementia at autopsy (Bennett et al., 2006; Kemper, 1994).

Importantly, the recent ability to image β-amyloid and tau deposits *in vivo* using positron emission tomography (PET) scanning has revolutionized our understanding of early stages of AD. Evidence suggests that amyloid deposits may be detected 10 - 15 years before memory symptoms appear. These findings are leading to the ability to diagnose AD years before symptoms begin (see Jack et al., 2013 for a review). Much less is known about the impact and developmental course of tau deposition because the ligand to image tau was only recently invented. There is increasing evidence that tau is particularly toxic to the brain and is a later precursor of AD than amyloid deposits. Additional research on β-amyloid and tau deposition in aging is crucial, as much work suggests that treatment of AD may be most effective when implemented early in the time course of the disease (Sperling et al., 2011). Understanding the impact of tau deposits and its interactions with amyloid deposition allows us to see the development of early markers of AD, which are important in understanding the trajectory of the disease. An important approach to understand the amyloid/tau puzzle and its relationship to AD is a large-scale longitudinal study of normal aging that integrates extensive neuroimaging and cognitive assessments along with tau imaging. A key aspect in separating normal from pathological aging is the inclusion of adults across the lifespan, establishing baselines from a sufficiently early stage to detect the very beginnings of pathological decline.

The Dallas Lifespan Brain Study (DLBS) began in 2008 and was designed to utilize the new *in vivo* imaging techniques to address uncertainty regarding how AD pathology relates

to the developmental process of aging and cognition, fueled in part by the partial overlap of pathological markers and decline in mnemonic function observed in a substantial proportion of 'normal' aged individuals (Mohs et al., 1998; Whalley, 2002). As shown in Figure 1, a total of 296 participants were recruited for Wave 1 from 2008 to 2014 to the DLBS and they received cognitive testing, structural and functional MRI, as well as a scan for beta amyloid using the radioligand AV-45 (florbetapir F 18, also known as "[^{18}F]AV-45"). A total of 183 returning participants were tested four years later in Wave 2, and they received the same battery (shown in Figure 2) as in Wave 1. In addition, 60 of these were also scanned with Flortaucipir F 18 (also known as "[^{18}F]AV-1451"). [^{18}F]AV-1451 is a newly-developed Phase II ligand that measures tau deposit in the human brain and this drug was provided to the DLBS by Avid Radiopharmaceuticals.

The objective of the current project is to manufacture [^{18}F]AV-1451 (Flortaucipir F 18) at the University of Texas Southwestern Medical Center (UTSW) for use in Wave 3 of the DLBS. We will offer an AV-1451 PET scan to past Wave 1 and 2 participants. We will first contact those who completed Waves 1 and 2, followed by those who completed only Wave 1 until we have used the 125 doses we were allocated. Figure 3 shows the specific procedures associated with this protocol for the up to 125 participants who will receive tau imaging in Wave 3. The inclusion of tau imaging in Wave 3 will allow us to relate tau deposition in the brain to the 10-year history of amyloid deposition and cognitive decline in the DLBS participants and understand the independent and joint contributions of tau to cognitive decline and early AD at different ages.

Figure 1. Dallas Lifespan Brain Study Overview and Timeline

The DLBS is an ongoing, comprehensive study of the relationship between brain structure and function to decline in cognition across the lifespan. The focus of this protocol is noted in, "DLBS Wave 3."

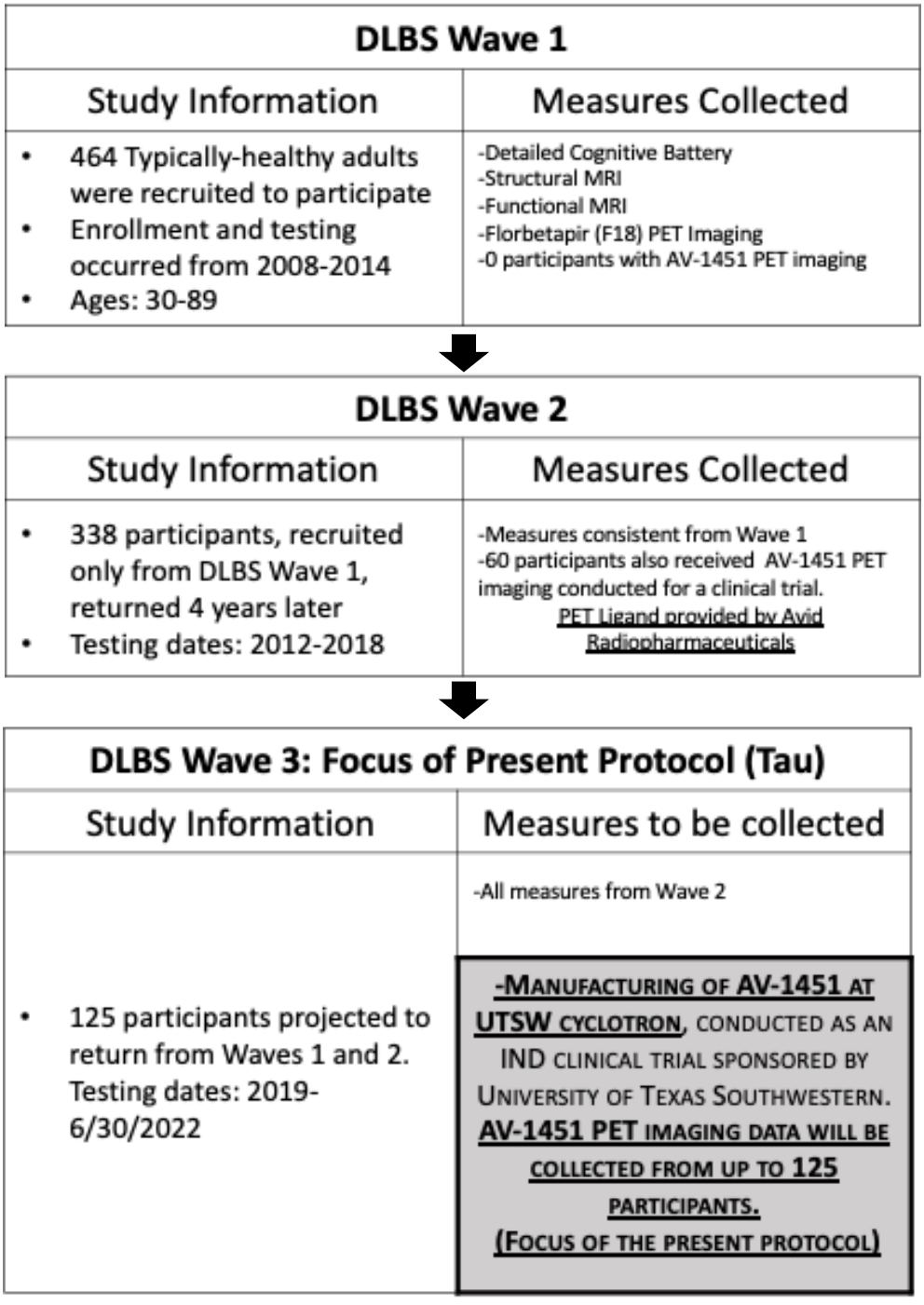


Figure 2. Sequence of Wave 3 Assessments

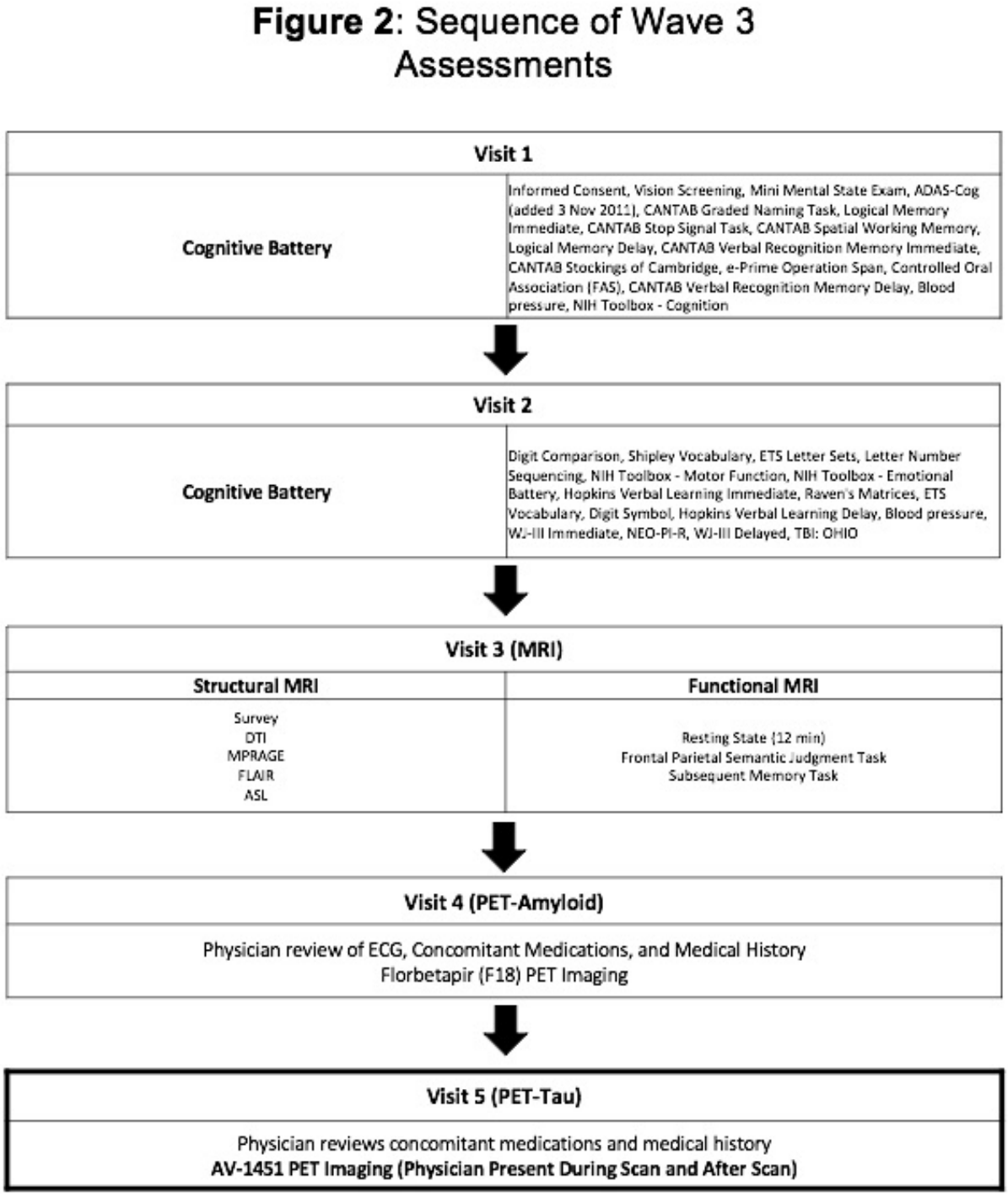
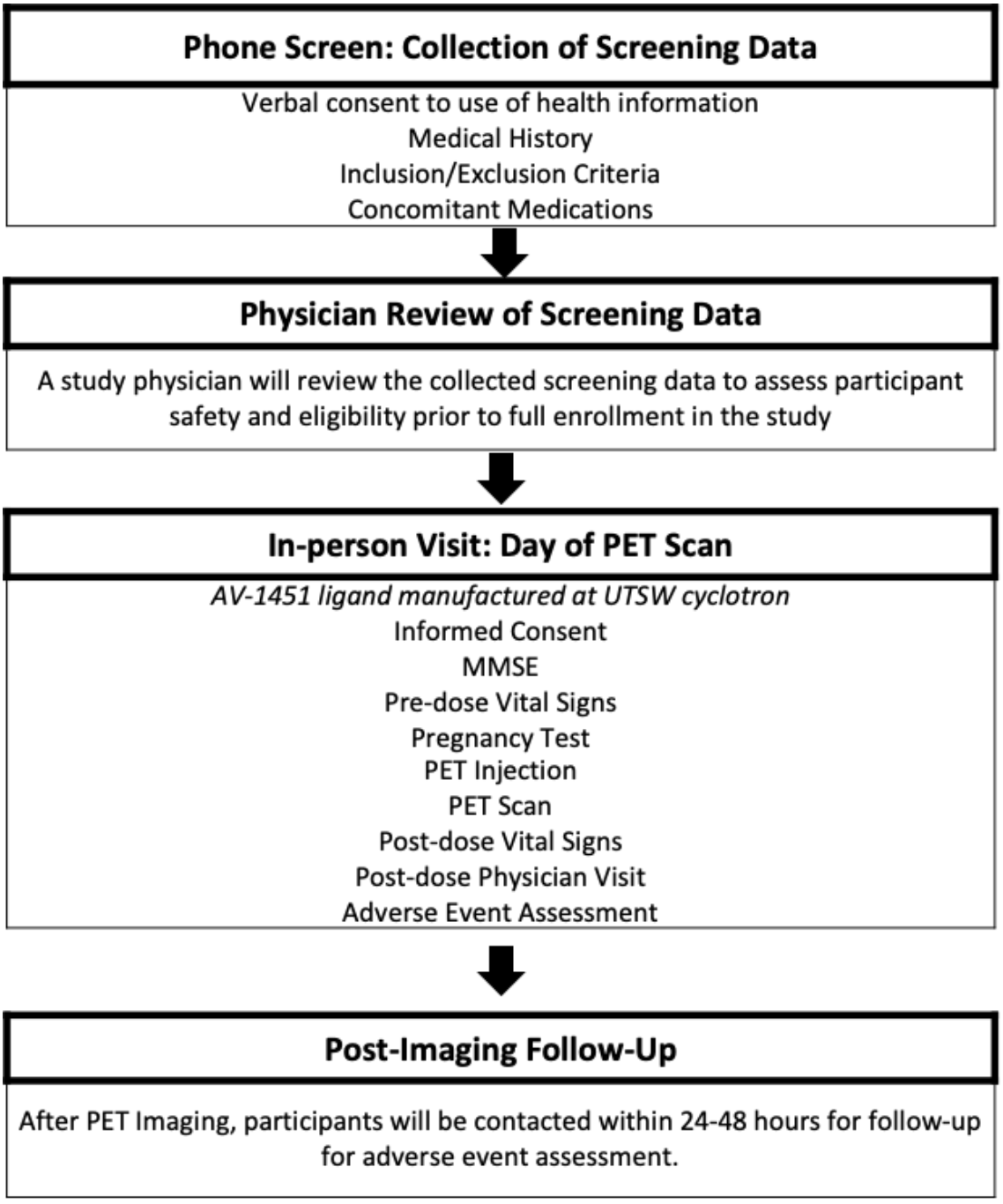


Figure 3. PET-Tau Imaging Procedures



6.4.2. Study Agent Background and Associated Known Toxicities

A PET/CT tau imaging agent, [18F]AV-1451, was developed by Avid Radiopharmaceuticals, a wholly owned subsidiary of Eli Lilly and Company. For this study, Avid and UT Southwestern have signed a clinical agreement that allows UTSW to produce this imaging agent, [18F]AV-1451, which is in Phase II clinical trials, and a focus of the present IND. It has been extensively evaluated by various *in vitro* and *in vivo* methods, including human brain sections, and human PET/CT imaging, as well as in animal models of Alzheimer's disease (Chien et al., 2013; Declercq et al., 2016; Schöll et al., 2016; Xia et al., 2013). It has been shown to have a high affinity for tau tangles. Based on studies in humans, it is estimated that the dose of radiation from [18F]AV-1451, averaged over the entire human body, is comparable to the range of other approved brain imaging agents, such as an agent [18F]FDG (1.0 rem) and [18F]florbetapir ([18F]AV-45) (1.3 rem) (see Appendix V). In completed studies with a total of 273 subjects the following adverse events were reported in at least 1% of subjects and were not thought by the investigator to be related to study procedures, or otherwise thought by the investigator to be related to flortaucipir: diarrhea, headache, muscle spam, dysgeusia, injection site pain (see Appendix V).

In vitro autoradiography results showed that [18F]AV-1451 bound with high affinity to aggregated tau protein and with preferential selectivity for aggregated tau vs. β-amyloid positive sections (Xia et al., 2013). The K_d calculated for [18F]AV-1451 binding to aggregated tau protein in human brain slices was measured to be approximately 15 nM. In that study, the dissociation constant (K_d) could not be calculated for [18F]AV-1451 binding to PHF-tau purified from the human brain samples because at lower ligand concentrations (< 200 nM) autoradiographic signals were indistinguishable from noise, and at high concentrations binding was nonspecific and random. They also compared a competitive binding assay versus a panel of 72 common central nervous system targets, observing no clinically relevant inhibition for [18F]AV-1451. [18F]AV-1451 has demonstrated rapid uptake *in vivo* in mouse, rat, and monkey brains followed by moderate clearance (Appendix V; Declercq et al., 2016; Xia et al., 2013).

Preclinical toxicity studies of [18F]AV-1451 showed a good safety profile with no observable effects at high multiples of the intended maximum human dose (Appendix V). With respect to risk for genotoxicity, positive results in the *in vitro* Ames test and chromosomal aberration studies did not manifest in the *in vivo* rat micronucleus study at doses greater than 750 times the intended human dose. [18F]AV-1451 was positive in the *in vitro* hERG assay. However, the cardiovascular assessments performed during the dog toxicology studies showed no evidence that [18F]AV-1451 prolongs the QT interval at high multiples of relevant clinical doses, and therefore risk of QT prolongation is not included in the risk profile. Out of an abundance of caution, and in consideration of previous

exclusionary criteria, this study will exclude participants with a history of risk factors for Torsades de Pointes and participants taking drugs known to increase QT intervals.

Human dosimetry has been obtained for nine participants (Appendix V). The radiotracer distribution was consistent among the participants and showed rapid hepatobiliary clearance. The organs of the gastrointestinal tract (upper large intestine, small intestine and liver) received the greatest exposure. The whole-body effective dose for a 10 mCi (370 MBq) injection of [^{18}F]AV-1451 was calculated to be 8.92 mSv. This is comparable to the effective doses of approved ^{18}F-labeled compounds such as [^{18}F]florbetapir and [^{18}F]fluorodeoxyglucose.

The distribution of the imaging agent in the brain closely matches the expected pattern of deposits. Considering the well supported specificity of [^{18}F]AV-1451 to tau tangles and its robust clinical safety record, this imaging agent should allow us to effectively meet the objectives of this research project. Avid Radiopharmaceuticals has signed a clinical agreement allowing UT Southwestern to produce up to 125 doses of this tau imaging agent ([^{18}F]AV-1451) for the current DLBS Wave 3.

6.4.3. Other Agents

6.4.3.1. Florbetapir F 18

The inclusion of florbetapir F 18 allows us to get a complete picture of the two major markers of AD pathology – tau and amyloid – in healthy adults. Florbetapir F 18 is an FDA-approved radiopharmaceutical that can be commercially obtained and is used to assess amyloid burden in the brain. It is known that amyloid accumulates long before behavioral and cognitive changes manifest. Better characterization of where and when amyloid accrues and its relationship to tau burden and cognitive changes will provide critical knowledge to help assess Alzheimer's disease, treat patients, and develop therapies. To meet this objective, all participants in the study will have undergone Florbetapir F 18 PET scans at three different times approximately 4 years apart over the last 10 years. See Figure 1. The third Florbetapir F 18 PET scan will be acquired prior to acquisition of the third Tau PET scan under a UTSW IRB approved protocol.

6.4.3.2. Florbetapir F 18 mechanism of action

Florbetapir F 18 is an FDA approved radiopharmaceutical compound containing the radionuclide fluorine-18 bound to the compound florbetapir, a molecule that binds with high affinity to beta amyloid plaque, a peptide that plays a key role in Alzheimer's Disease pathogenesis. The radionuclide fluorine-18 was chosen as it has a half-life of 110 minutes allowing it to accumulate sufficiently in the brain before undergoing positron emission decay. In *in vitro* binding studies using postmortem human brain homogenates containing

β-amyloid plaques, the K_d for florbetapir F 18 was 3.7 ± 0.3 nM. The binding of florbetapir F 18 to β-amyloid aggregates was demonstrated in postmortem human brain sections using autoradiographic methods, thioflavin S and traditional silver staining correlation studies as well as monoclonal antibody β-amyloid-specific correlation studies. Florbetapir F 18 binding to tau protein and a battery of neuroreceptors was not detected in *in vitro* studies (Eli Lily 2012).

6.4.3.3. Florbetapir F 18 safety issues

In clinical studies, 555 patients were exposed to Florbetapir F 18. Florbetapir F 18 caused no serious adverse reactions in the studies and the reported adverse reactions were predominantly mild to moderate in severity. The most common reported adverse reaction was headache, occurring in 2% of patients, followed by musculoskeletal pain, blood pressure increased, fatigue, nausea, and injection site reaction, all occurring in < 1% of patients (Eli Lily 2012).

6.4.4. Rationale

Tau pathology is a primary feature of Alzheimer's disease, and can now be measured *in vivo* using the recently developed PET radiotracer [18F]AV-1451. Autopsy studies have long established that many older adults who exhibited no signs of cognitive impairment in life are found at autopsy to possess the neuropathological hallmarks of Alzheimer's disease: amyloid plaques and neurofibrillary tau tangles. In the previous decade, PET imaging tracers made it possible to image amyloid plaques but not tau tangles in the living brain, providing substantial insight into the cascade of events leading from a healthy to a diseased brain. However, these studies have also indicated that amyloid has a limited direct effect on the neurodegeneration and cognitive decline indicative of incipient dementia. One prevailing theory, supported by *in vivo* measures of amyloid and tau, is that amyloid induces tau tangle pathology, and it is tau that directly connects to neurodegeneration and cognitive decline. The recent development of tau imaging ligands, including [18F]AV-1451, provides an opportunity to better understand the joint influence of tau and amyloid on neurodegeneration and cognition, as well as insight into the neurological cascade from health to dementia of the Alzheimer's type. An understanding of this cascade is critical for therapeutic and intervention trials.

The main objective of the present project is to assess evidence for neurofibrillary tau pathology in the brains of adults who are participants in Wave 3 in a larger project — the DLBS. This is a longitudinal observational study and tau imaging will be open-label. The DLBS protocol includes structural MRI, diffusion tensor, functional MRI, and a comprehensive cognitive and psychosocial battery as well as amyloid PET imaging. The DLBS participants (current age range: 38 - 96) allows us to address directly the role of tau deposition in declining cognition in a sample that was cognitively normal at the start of the

study eight years earlier. This population of subjects is critical to study because pathology for Alzheimer's disease starts long before clinically observable effects develop. The timing of tau development relative to amyloid is not well understood. The Wave 3 data will provide us the ability to relate tau aggregation in Wave 3 to magnitude of amyloid deposition both during Wave 3 and across the previous 8 - 10 years. We can also connect tau deposition in Wave 3 to present cognitive function and magnitude of decline over 8 - 10 years.

While [^{18}F]AV-1451 was not available and no tau scanning was done for Wave 1 in the DLBS, we were able to conduct 60 [^{18}F]AV-1451 PET scans in DLBS on 60 Wave 2 participants as part of a clinical trial by Avid Radiopharmaceuticals. During Wave 3 (the focus of the present protocol), we propose to manufacture [^{18}F]AV-1451 via the UTSW Cyclotron and Radiochemistry Program. We will administer one dose to up to 125 participants in Wave 3. This portion of the study is important because it will allow us to assess longitudinal changes in [^{18}F]AV-1451 in the 60 previously tested Wave 2 participants, and its relationship to growth in amyloid and decline in cognition. Secondly, we can see whether it increases more rapidly as a function of age. Finally, it will allow us to add to the information on [^{18}F]AV-1451's safety profile. These data, in combination with DLBS behavioral data and MRI scanning and amyloid imaging, will provide a comprehensive picture of the aging mind over a period of years, allowing us a window into maintenance of cognitive health and, for some subjects, transition towards dementia.

Key neurological endpoints for this study include estimation of amyloid and tau deposition in participants at Wave 3. Tau deposition will be examined via estimating the standardized uptake value ratio (SUVr) of [^{18}F]AV-1451 in temporal regions (both left and right) of interest: (1) inferior temporal gyrus, (2) middle temporal gyrus, (3) superior temporal gyrus, (4) entorhinal cortex, (5) parahippocampal gyrus, and (6) fusiform gyrus. SUVr of [^{18}F]AV-1451 in these regions is elevated in those with mild cognitive impairment or Alzheimer's disease (Johnson et al., 2016; Scholl et al., 2016). There are sometimes hemispheric-specific effects, so left and right hemispheres will be analyzed separately. We also note that Wave 3 amyloid deposition will be measured across eight cortical regions: dorsal lateral prefrontal cortex, orbitofrontal cortex, lateral parietal cortex, posterior cingulate cortex, anterior cingulate cortex, precuneus, lateral temporal cortex, and occipital lobe and then averaged.

Key cognitive endpoints for this study include measures of processing speed, episodic memory, working memory, and executive function. Processing speed tasks measure participants' ability to quickly do simple mental tasks, such as comparing two strings of numbers. Episodic memory tasks measure their ability to remember contextual information, such as remembering the details of a story. Working memory tasks measure their ability to store and manipulate long strings of information in memory; a common task has participants repeating a list of numbers back to the experimenter in reverse order (n-

back task). Executive function tasks measure participants' ability to solve simple problems. A wide range of research has shown that these cognitive functions typically decline in healthy aging and often decline more sharply in those with AD pathology, particularly memory (Amieva et al., 2005; Epelbaum et al., 2017; Mortamais et al., 2017). The current study is one of the first to be able to examine how *in vivo* measures of tau deposition relate with declines in these cognitive functions.

6.5. STUDY OBJECTIVES

6.5.1. Primary Objectives

6.5.1.1. To determine the time course of tau deposition with age and assess its relationship to changes in cognitive function over a 10-year interval by conducting tau PET scans on up to 125 adults from previous waves of the DLBS using the tau tracer [18F]AV-1451.

6.5.2. Secondary Objectives

6.5.2.1. To assess the relationship of tau burden to hippocampal volume and cortical thickness and their contributions to predicting decline in memory and other cognitive functions.

6.5.2.2. To determine whether rate of amyloid accumulation over the past 8 - 10-year interval predicts tau deposition.

6.5.2.3. To examine the detrimental effect of tau deposits, as well as the joint effect of tau and amyloid, on changes in brain activity and cognitive function.

6.5.2.4. To examine differences in cognitive, structural, and functional decline between those with and without amyloid and tau pathology.

6.5.3. Exploratory Objectives

6.5.3.1. As findings are made while pursuing these secondary objectives, we will sometimes conduct additional follow-up analyses to better understand these findings. For example, a sufficient number of subjects vary in their socioeconomic status (SES), we will likely examine if SES is related to the time course of tau deposition.

6.5.4. Primary Endpoints

6.5.4.1. The primary objective will involve completion of up to 125 [^{18}F]AV-1451 PET scans on returning Wave 1 and 2 DLBS participants. Once these data are collected, data collection will stop.

6.5.5. Secondary Endpoints

Tau deposition will be examined via estimating the SUVr of [^{18}F]AV-1451 in temporal regions (both left and right) of interest: (1) inferior temporal gyrus, (2) middle temporal gyrus, (3) superior temporal gyrus, (4) entorhinal cortex, (5) parahippocampal gyrus, and (6) fusiform gyrus. Amyloid accumulation will be measured continuously as the SUVr value averaged across eight cortical regions: dorsal lateral prefrontal cortex, orbitofrontal cortex, lateral parietal cortex, posterior cingulate cortex, anterior cingulate cortex, precuneus, lateral temporal cortex, and occipital lobe.

6.5.5.1. Hippocampal volume and regional cortical thickness will be estimated using FreeSurfer (ver. 5.3), with surface parcellation manually edited, when necessary, by our team of experts.

6.5.5.2. Longitudinal declines in brain structures will be measured using linear mixed models with estimated cortical thickness and white matter volumes from waves 1, 2, and 3 as our primary structural measures, BOLD signal from a subsequent memory task, a semantic judgment task, and resting state as our functional measures, and time of scanning entered as an interaction term.

6.5.5.3. Joint effects of tau and amyloid will be examined by including them as an interaction term in a linear mixed-model analysis.

6.5.5.4. Cognitive decline will be assessed using the following constructs: processing speed, episodic memory, working memory, and executive function. Scores on these constructs will be averaged across relevant DLBS tasks and standardized based on performance at the beginning of this longitudinal study (Wave 1).

6.6. SUBJECT ELIGIBILITY

Participants will be eligible to volunteer for this scan if they participated in Waves 1 or 2 of the DLBS. To determine medical eligibility for the scan by the study physician, those who volunteer when contacted will be asked for verbal consent to provide medical information needed for the physician review. At the subsequent PET scanning visit, all participants must sign the consent form to be eligible for the PET study.

6.6.1. Inclusion Criteria

6.6.1.1. Participated in Waves 1 or 2 of the DLBS

6.6.1.2. Adults aged 38 to 96 years old.

6.6.1.3. Subjects must indicate that they are not currently pregnant if they are women of child-bearing potential. Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for 90 days following completion of therapy. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

6.6.1.3.1. A female of child-bearing potential is any woman (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:

- Has not undergone a hysterectomy or bilateral oophorectomy; or
- Has not been naturally post-menopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

6.6.1.4. Volumetric Brain MRI Image (T-1 Weighted MPRage) collected as part of DLBS Wave 1, 2, or 3 protocol.

6.6.1.5. Completed at least 9 years of formal education, or the equivalent of freshman year of high school.

6.6.1.6. Fluent English speakers.

6.6.1.7. Tolerate laying 20 minutes on a flat table for the PET scan.

6.6.1.8. Ability to understand and the willingness to sign a written informed consent.

6.6.2. Exclusion Criteria

6.6.2.1. MMSE score lower than 22; all DLBS participants at the time of initial Wave 1 enrollment between 2008 - 2014 had an MMSE score of 26 or above, indicating normal cognitive function. However, in the time interval between

Waves, it is possible that mental capacity may have deteriorated. We will exclude all participants in Wave 3 testing who have an MMSE lower than 22.

6.6.2.2. Taking some types of sedatives, benzodiazepines, or anti-psychotics.

6.6.2.3. Currently undergoing chemotherapy or radiation for cancer.

6.6.2.4. New history of substance abuse.

6.6.2.5. Has a history of drug or alcohol dependence within the last year, or prior prolonged history of dependence.

6.6.2.6. Recreational drug use in past six months.

6.6.2.7. Central nervous systems disease or brain injury that would preclude participation in the study.

6.6.2.8. Psychiatric or neurological disorder that would preclude participation in this study.

6.6.2.9. Has clinically significant hepatic, renal, pulmonary, metabolic or endocrine disturbances which pose safety risk.

6.6.2.10. Has a current clinically significant cardiovascular disease that poses a safety risk.

6.6.2.11. Has a current clinically significant infectious disease or a medical comorbidity which poses a safety risk.

6.6.2.12. Has received or will receive investigational medication within the 30 days of PET/CT scan.

6.6.2.13. Has received or will receive a radiopharmaceutical for imaging or therapy within 24 hours of PET/CT scan.

6.6.2.14. Is a participant who, in the opinion of the investigator(s), is otherwise unsuitable for a study of this type.

6.7. STUDY PROCEDURES

6.7.1. Screening/Baseline Procedures

In the past, participants who participated in this component of the study received an ECG and a separate physician visit where their medical history was reviewed to determine eligibility. In 2019, flortaucepir was approved by the FDA for medical use and there was no requirement for a physician in-person visit or the ECG prior to the scan. Thus, we have incorporated this practice, and in Wave 3 participants will not receive the ECG. In addition, we have eliminated the physician visit to determine eligibility for this study, and instead it will be collected via a phone screening. We can reduce the participant burden for this research scan by eliminating these two events and instead obtaining a verbal waiver of written consent. This will eliminate one visit for every subject by having both the physician review medical information electronically and the subject provide a verbal waiver of consent over the phone to determine eligibility.

Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before written informed consent was obtained.

All screening procedures will be performed within 30 days prior to registration unless otherwise stated. For participants who will complete their scan over 30 days since their screening date—most often, this is due to having to reschedule their initial appointment—we will confirm whether their medications, medical history (e.g., surgeries), and allergies have changed since their initial screening. Any such changes will be documented, and changes that may affect their eligibility to participate in this study will be submitted to the physician to confirm whether they are still eligible to participate.

The screening procedures include:

6.7.2. Screening Procedures

The verbal consent obtained over the phone will be used to obtain relevant medical information for screening prior to full informed consent at the time of the visit. The specific components of the screen are below. All of this information will be reviewed by a study physician to ensure participant safety before enrollment in the PET study.

6.7.2.1. Medical history

Complete medical and surgical history, history of infections and concurrent disease, and neurological disease history

6.7.2.2. Review subject eligibility criteria

6.7.2.3. Review concomitant medications

6.7.2.4. Mini-Mental State Examination (when considered necessary)

6.7.2.5. Physician Review of subject's medical history, eligibility criteria and concomitant medications prior to enrollment

6.7.3. Procedures On Day of Treatment

Participants will complete the in-person visit at UTSW PET Imaging Center. Assessments will be conducted by a study RA, with the PET Injection and PET scan being conducted by a UTSW PET Technologist. An Attending physician will assess the participant's post-scan vital signs and review any evidence for possible adverse events prior to discharge.

6.7.3.1. Informed Consent

Informed consent and HIPAA consent will be completed on the day of the scan before any other procedures are done.

6.7.3.2. MMSE

Participants who have not completed the MMSE questionnaire in the last 30 days will be asked to complete the questionnaire for purposes of this research study.

6.7.3.3. Pregnancy Test

The day of scanning, females that are of childbearing potential will have a urine pregnancy test performed once again. Results of these tests must be negative in order to proceed with the PET scan.

6.7.3.4. Pre-dose Vital signs

Subject's weight, height, supine blood pressure, pulse rate, and respiratory rate will be collected.

6.7.3.5. Adverse event assessment

Participants will be assessed for possible adverse events that occur as a result of study procedures beginning at the time of written informed consent occurred up to the time of the follow-up phone call described in section 6.7.3. See sections 6.8.2 and 6.8.3 for Adverse Event monitoring and reporting.

6.7.3.6. PET Injection

The subject will receive up to a target dose of 370 MBq as a single IV bolus of [18F]AV-1451. Participant will be assessed for any adverse events.

6.7.3.7. PET Scan

Approximately 80 minutes after injection subjects will be placed in the UTSW PET/CT scanner for a 20-minute brain scan. In total, the imaging visit could take up to 180 minutes for the physician to clear the patient for safety. A member of UTSW staff will be nearby during the procedure. The PET/CT scanner at the PET/CT Center will be used to perform scans for this study. Participant will be assessed for any adverse events.

6.7.3.8. Post-dose Vital signs

Subject's supine blood pressure, pulse rate, and respiratory rate will be taken after PET scan is complete.

6.7.3.9. Post-dose Physician visit

A physician will see and discharge the subject. Physician will ascertain any adverse events that occurred during visit.

6.7.3.10 Participant Compensation

Screen Procedure. If participants complete the screen procedures, $25 will be deposited to their study account which operates as a cash-based bank card.

The Scanning Visit. Participants who go on to be scheduled for the AV-1451 Wave 3 PET Session will be compensated $200 additional dollars on this card, even if the session is terminated for some reason. The bank card is study-specific card all enrolled participants can use it to withdraw cash or as a credit card. The card can be used as either debit or credit, and participants will be instructed by study personnel on how to use the card.

Travel Costs. If travel exceeds 50 miles, participants will be approved to receive $0.58.5 a mile for each additional mile. If a participant prefers not to drive, they can arrange transport with an outside source (eg Uber, Lyft, Cab service) and get reimbursed from their receipts, or we can arrange travel with a university approved carrier and charge it directly to our accounts. We will also make flight arrangements if they are necessary.

Serving As A Stand-By Participant. The scanning agent we use is quite expensive and can only be used the day of the scan. For this reason, it is problematic for us if someone does not show up. Just in case this happens, we are paying an extra participant $100 to be ready to participate in a scan if someone does not show up. Each stand-by participant would sit in the waiting room for 2-3 hours.

6.7.4. Follow-up Procedures

Study personnel will make a follow-up phone call to the participant within 2 to 3 business days after the scan, but no less than 48 hours post injection. The purpose of this

phone call will be to check if participants have experienced any new adverse events since injection on the imaging day.

Furthermore, as the DLBS is a longitudinal study, participants may continue to be contacted every 4 years for study participation for as long as the study is funded.

6.7.5. Time and Events Table for [18F]AV-1451 Study

Evaluations	Pre-Visit Screen	Visit Pre-dose	Visit Dose	Visit PET Imaging	Visit Post-Imaging	2 – 3 days Post-Injection
Inclusion/Exclusion Criteria	X					
Medical / Disease History	X					
Concomitant Medications	X					
Physician Review of eligibility via email	X					
Informed Consent		X				
MMSE	X	X				
Vital Signs[1]		X			X	
Pregnancy Test		X				
[18F]AV-1451 Administration			X			
PET Imaging				Continuous 20-minute scan		
Physician Visit prior to discharge					X	
Follow-up Phone Call						X
Adverse Event Assessment			X	X	X	X

[1]Height and weight will be measured prior to injection on imaging day.

6.7.6. Removal of Subjects from Study

Subjects can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator(s) for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

6.7.6.1. Subject withdraws consent (termination of treatment and follow-up).

6.7.6.2. Subject is unable to comply with protocol requirements.

6.7.6.3. Treating physician determines continuation on the study would not be in the subject's best interest.

6.7.6.4. Subject (female) tests positive for pregnancy at any point in the study.

6.8. ADVERSE EVENTS

6.8.1. Experimental Drug

6.8.1.1. Contraindications

There are no known contraindications to the usage of flortaucipir F 18 ([^{18}F]AV-1451). Pregnant or lactating females have been excluded from all [^{18}F]AV-1451studies due to the potential risks of radiation to the fetus. Non-radioactive flortaucipir was positive in the *in vitro* hERG assay with an IC_{50} of 0.610 μM. If the flortaucipir hERG channel IC_{50} is converted to a ng/mL concentration (161 ng/mL), and compared to the maximum theoretical flortaucipir peak plasma concentration in a subject given a 20 μg dose (3.8 ng/mL), the safety margin is at least 42-fold. The safety margin increases to over 900-fold when accounting for plasma protein binding in the calculation (plasma protein unbound fraction, fu-human = 0.047). Additionally, *in vitro* cardiovascular assessments in dogs showed no evidence of QT prolongation. Nonetheless, until sufficient human cardiovascular safety data are available, clinical studies will exclude subjects with a history of risk factors for torsade de pointes and subjects taking drugs known to prolong the QT interval.

6.8.1.2. Special Warnings and Precautions for Use

To ensure study integrity and to reduce any risk to participants, study personnel will closely monitor: (1) the participant's study experience, (2) the actual vs. target study accrual rates, (3) participant attrition (e.g. withdrawals, dropouts), (4) patterns of adverse events (AEs) and unanticipated events, (5) patterns of protocol deviations/violations, (6) study stopping points and (7) changes in risk/benefit. Findings from the tau scan and all other research results will not be shared with the participants as explicitly noted in the consent form. Participants will be screened by a physician remotely before scheduling the scan and screened by a physician in person before leaving the scanning area. Researchers

call participants about 48 hours after the PET/CT imaging session to see if participants experienced any side-effects that may have occurred within 24 hours post-injection.

Potential risks and discomforts will be prevented and/or minimized to the greatest extent possible by using procedures such as appropriate training of personnel, monitoring, withdrawal of the subject upon evidence of difficulty or adverse event; referral for treatment, counseling, or other necessary follow-up. The study records will be treated as private to the extent permitted by law. Reassurance will be provided as needed and participants will be reminded that their continued participation in the study is completely voluntary.

6.8.1.3. Interaction with other medications

Comprehensive drug-drug interaction studies have not been performed in subjects to delineate the effect that other medications may have on the distribution of [^{18}F]AV-1451.

Please refer to the investigator brochure, Appendix V, for detail on the preclinical *in vitro* results of non-radiolabeled AV-1451 to human liver microsomes and MDCK-MDR1 cells. This testing did not yield evidence for inhibition of CYP enzymes or P-glycoprotein transport at concentrations greatly exceeding expected plasma concentrations at recommended human dosing for imaging (maximum 20 µg [^{18}F]AV-1451).

Because of the positive in-vitro hERG assay, albeit correlating to concentrations of [^{18}F]AV-1451 expected to far exceed that encountered at imaging doses (~42-900 fold safety margin), subjects with prolonged QTc interval, risk factors for prolonged QTc, or taking drugs known to prolong QT interval will be excluded.

6.8.1.4. Adverse Reactions

6.8.1.4.1. All reported events were mild or moderate in severity, and all subjects recovered.

6.8.1.4.2. Risks of adverse reactions associated with [**^{18}F**]**AV-1451** administration: In completed studies with a total of 273 subjects the following adverse events were reported in at least 1% of subjects and were not thought by the investigator(s) to be related to study procedures, or otherwise thought by the investigator(s) to be related to [^{18}F]AV-1451: diarrhea, headache, muscle spasm, dysgeusia, injection site pain

6.8.1.4.2.1. Risks and discomforts associated with the PET/CT scan procedures:

- Subjects will be required to lie still in the scanner during PET/CT scan acquisition;
- Being in the PET/CT scanner may cause discomfort including musculoskeletal (neck or back) pain, or claustrophobia.

6.8.1.4.2.2. Risks of radiation exposure (including [^{18}F]AV-1451 and low dose CT scan): [^{18}F]AV- 1451 administration and the accompanying CT scan for attenuation correction contribute to a subject's long-term cumulative radiation exposure, which is associated with an increased risk of developing cancer. Additionally, higher levels of radiation can cause damage to the developing fetus.

- The amount of radiation exposure is similar to other ^{18}F radiopharmaceuticals.
- Females of childbearing potential will usually be excluded from [^{18}F]AV-1451 studies unless they are surgically sterile, agree to use reliable contraception, or refrain from sexual activity.
- Females of childbearing potential who do participate must not be pregnant or breastfeeding at screening (negative serum β-HCG at screening and a negative urine β-HCG within 24 hours prior to injection), and must agree to avoid becoming pregnant.
- Female and male study subjects must agree to refrain from sexual activity or to use reliable contraceptive methods for 90 days following administration of [^{18}F]AV-1451 injection.

6.8.1.4.2.3. The risk of harm to the subjects from radiation for this study can be compared to risks from everyday activities. For example, the risk of developing fatal cancer during one's lifetime from this radiation exposure is comparative to the risk of suffering a fatal car crash while driving 918 miles in an automobile.

PET/CT Scan - Placement of the IV catheter for isotope injection may result in pain, infection, or bruising at the site. Placement of an IV catheter may cause anxiety.

Psychological Stress – Participants could experience uneasiness from questions being asked or knowing that personnel have their personal information.

Loss of Confidentiality – There is a risk for loss of confidentiality. Every effort will be made to keep information confidential; however, this can never be guaranteed.

Other Risks - There is a very low risk of developing fatal cancer during the participant's lifetime from this radiation. There may possibly be other side effects that are unknown at this time.

6.8.2. Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of subject safety and care.

All subjects experiencing an adverse event, regardless of its relationship to study therapy, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline or is stable in the opinion of the investigator(s);
- there is a satisfactory explanation other than the study therapy for the changes observed;
- or death.

6.8.2.1. Definitions

An adverse event is defined as any untoward or unfavorable medical occurrence in a human research study participant, including any abnormal sign (for example, abnormal physical exam, imaging finding or clinically significant laboratory finding), symptom, clinical event, or disease, temporarily associated with the subject's participation in the research, whether or not it is considered related to the subject's participation in the research.

Adverse events encompass clinical, physical and psychological harms. Adverse events occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research. Adverse events may be expected or unexpected.

Acute Adverse Events

Adverse events occurring in the time period from the signing of the informed consent, through 2 days post treatment will be considered acute adverse events.

Severity

Adverse events will be graded by a numerical score according to the defined NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0. Adverse

events not specifically defined in the NCI CTCAE will be scored on the Adverse Event log according to the general guidelines provided by the NCI CTCAE and as outlined below.

Grade 1: Mild

Grade 2: Moderate

Grade 3: Severe or medically significant but not immediately life threatening

Grade 4: Life threatening consequences

Grade 5: Death related to the adverse event

Serious Adverse Events

ICH Guideline E2A and the UTSW IRB define serious adverse events as those events, occurring at any dose, which meets any of the following criteria:

- Results in death
- Immediately life-threatening
- Results in inpatient hospitalization[1,2] or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Results in a congenital anomaly/birth defect
- Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Note: A "Serious adverse event" is by definition an event that meets ***any*** of the above criteria. Serious adverse events may or may not be related to the research project. A serious adverse event determination does not require the event to be related to the research. That is, both events completely unrelated to the condition under study and events that are expected in the context of the condition under study may be serious adverse events, independent of relatedness to the study itself. As examples, a car accident requiring $\geq$ 24 hour inpatient admission to the hospital would be a serious adverse event for any research participant; likewise, in a study investigating end-stage cancer care, any hospitalization or death which occurs during the protocol-specified period of monitoring for adverse and serious adverse events would be a serious adverse event, even if the event observed is a primary clinical endpoint of the study.

[1]Pre-planned hospitalizations or elective surgeries are not considered SAEs. Note: If events occur during a pre-planned hospitalization or surgery, that prolong the existing hospitalization, those events should be evaluated and/or reported as SAEs.

[2]NCI defines hospitalization for expedited AE reporting purposes as an inpatient hospital stay equal to or greater than 24 hours. Hospitalization is used as an indicator of

the seriousness of the adverse event and should only be used for situations where the AE truly fits this definition and NOT for hospitalizations associated with less serious events. For example: a hospital visit where a patient is admitted for observation or minor treatment (e.g. hydration) and released in less than 24 hours. Furthermore, hospitalization for pharmacokinetic sampling is not an AE and therefore is not to be reported either as a routine AE or in an expedited report.

6.8.2.2. Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs):

The phrase "unanticipated problems involving risks to subjects or others" is found, but not defined in the HHS regulations at 45 CFR 46, and the FDA regulations at 21 CFR 56.108(b)(1) and 21 CFR 312.66. For device studies, part 812 uses the term unanticipated adverse device effect, which is defined in 21 CFR 812.3(s). Guidance from the regulatory agencies considers unanticipated problems to include any incident, experience, or outcome that meets ALL three (3) of the following criteria:

- Unexpected in terms of nature, severity or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

AND

- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research);

AND

- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. Note: According to OHRP, if the adverse event is serious, it would always suggest a greater risk of harm.

Follow-up

All adverse events will be followed up according to good medical practices.

6.8.3. Steps to Determine If a Serious Adverse Event Requires Expedited Reporting to the HRPP

Step 1: Identify the type of adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE v5).

Step 2: Grade the adverse event using the NCI CTCAE v5.

Step 3: Determine whether the adverse event is related to the protocol therapy.

Attribution categories are as follows:

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE *may NOT be related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

Note: This includes all events that occur to the end of the acute adverse events reporting period as defined in section 6.8.2

Step 4: Determine the prior experience of the adverse event. Expected events are those that have been previously identified as resulting from administration of the treatment. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current known adverse events listed in the Agent Information Section of this protocol (if applicable)
- the drug package insert (if applicable)
- the current Investigator's Brochure (if applicable)
- the Study Agent(s)/Therapy(ies) Background and Associated Known Toxicities section of this protocol

6.8.3.1. Reporting Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) and SAEs to the UTSW and UTD HRPP/IRB, AVID Radiopharmaceutical, and FDA

UTSW reportable event guidance applies to all research conducted by or on behalf of UT Southwestern, its affiliates, and investigators, sites, or institutions relying on the UT Southwestern IRB. Additional reporting requirements apply for research relying on a non-UT Southwestern IRB.

According to UTSW HRPP/IRB policy, UPIRSOs are incidents, experiences, outcomes, etc. that meet **ALL three (3)** of the following criteria:

1. Unexpected in nature, frequency, or severity (i.e., generally not expected in a subject's underlying condition or not expected as a risk of the study; therefore, not included in the investigator's brochure, protocol, or informed consent document), AND

2. Probably or definitely related to participation in the research, AND
3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. Note: According to OHRP, if the adverse event is serious, it would always suggest a greater risk of harm.

UPIRSO and SAEs must be promptly reported to:

- Avid Radiopharmaceuticals within 24 hours of principal investigator (PI) awareness; For reporting, please contact MAILINDATA_GSMTINDY@LILLY. COM;
- UTSW and UTD Human Research Protection Program/Institutional Review Board within 5 working days of PI awareness.
- FDA no later than 15 calendar days after the sponsor determines that the suspected adverse reaction or other information qualifies for reporting (21 CFR 312.32(c)(1)).

Events NOT meeting UPIRSO or SAE criteria:

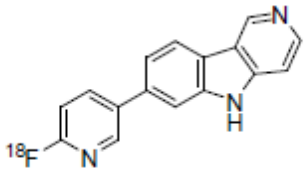
Events that do NOT meet UPIRSO or SAE criteria should be tracked, evaluated, summarized, and submitted to the UTSW HRPP/IRB at continuing review.

For more information on UTSW HRPP/IRB reportable event policy, see https://www.utsouthwestern.edu/research/research-administration/irb/assets/policies-combined.pdf.

6.9. DRUG INFORMATION

6.9.1. [^{18}F]AV-1451 for Injection

7-(6-[F-18]fluoropyridin-3-yl)-5H-pyrido[4,3-b]indole



MW = 262.27 amu

6.9.1.1. Descriptive name: Flortaucipir F 18; [18F]AV-1451

6.9.1.2. Classification: Positron Emitting Radiopharmaceutical

6.9.1.3. Mode of Action: Flortaucipir F 18 is under investigation as a diagnostic PET radiopharmaceutical for in vitro imaging of tau pathology in patients with AD and related neurodegenerative diseases characterized by the presence of tau pathology. The primary pharmacodynamic data obtained on flortaucipir F 18 show a high selectivity for binding to tau protein aggregates vs. β-amyloid in human brain tissue and rapid uptake in the brain with clearance from normal tissue in mice, rats and non-human primates. These data indicate that flortaucipir F 18 is potentially an important new tool for the in vitro assessment of tau protein aggregates (e.g. neurofibrillary tangles (NFTs)), thus providing a possible biomarker of the progressive pathology underlying neurodegeneration in AD. Such an agent may prove useful in the diagnosis, follow-up and therapeutic monitoring of AD and other dementias.

6.9.1.4. Storage and Stability: [18F]AV-1451 for Injection is stored at room temperature. [18F]AV-1451 for Injection should be stored within the original container or equivalent radiation shielding.

6.9.1.5. Protocol Dose: [18F]AV-1451 for Injection will be administered IV up to a radioactive target dose of 370 MBq with a maximum human mass dose (MHD) limited to 20 µg of compound by weight. This dose is 150 fold lower than the NOAEL observed in the rat single dose toxicity study and is 50 fold lower than the NOAEL observed in the rat and dog repeat dose toxicity studies.

Human dosimetry has been obtained in nine subjects. The results estimated an Effective Dose of 8.92 mSv for an anticipated 370 MBq (10 mCi) injection and is comparable to the effective dose of approved 18F-labeled compounds such as [18F]FDG and florbetapir F 18 injection.

The proposed dose has been shown to be well tolerated and to have acceptable image quality in preliminary human studies.

6.9.1.6. Preparation: [18F]AV-1451 for Injection is a clear solution containing [18F]AV-1451 (drug substance) formulated for intravenous bolus administration. [18F]AV-1451 for Injection will be formulated in a solution containing 10% (v/v) ethanol, USP in 0.9% sodium chloride injection, USP.

Drug product is manufactured to meet Avid Radiopharmaceutical's set of specifications.

The expiration time and date of [18F]AV-1451 for Injection are provided on the outer label of each dose based on specific activity or strength. Expiration time is 10 hours post End of Synthesis or when the strength self-life specification is reached (≥ 37 MBq/mL), whichever is soonest. [18F]AV-1451 for Injection is be stored at room temperature.

6.9.1.7. Route of administration for this study: The route of administration will be a single, intravenous bolus.

6.9.1.8. Incompatibilities: There are no known absolute contraindications to [18F]AV-1451. The effects of [18F]AV-1451 have not been studied in pregnant or lactating females and subjects that are either pregnant or lactating will be excluded from the study.

Severe drug allergies may pose a potential safety risk. Subjects will be screened by a physician for relevant drug allergy history and will excluded at the discretion of the screening physician.

Preclinical *in vitro* testing of non-radiolabeled AV-1451 showed a positive potassium ion channel assay as detailed in the investigator brochure. The theoretical peak plasma concentration of [18F]AV-1451 following the maximum recommended dose of 20 μg [18F]AV-1451 suggest a 42 fold safety margin when compared to the IC_{50} resulting in the positive test. This safety margin is likely vastly underestimated when plasma protein binding is also accounted for ~900 fold safety margin. However, given the relatively limited safety data available to date in humans, subjects with documented prolonged QTc interval on screening EKG, those with historical risk factors for QT prolongation, and subjects taking medications known to cause QT prolongation (determined at physician screening) will be excluded.

6.9.1.9. Availability: Provided by UTSW Department of Radiology Cyclotron and Radiochemistry

Xiankai Sun, PhD, Director
Associate Professor, Radiology
Director, Cyclotron and Radiochemistry Program
UT Southwestern Medical Center
2201 Inwood Rd, NE3.240
Dallas, Texas 75390

(Phone): 214-645-5978
Email: Xiankai.Sun@utsouthwestern.edu

6.9.1.10. Side effects:

6.9.1.10.1. A review of the safety information for [18F]AV-1451 showed that the product is generally well tolerated with a low incidence of mild and transient adverse events. Investigator(s) should be aware of the following risk information related to [18F]AV-1451 and the PET/CT procedures:

6.9.1.10.2. Risks of adverse reactions associated with [18F]AV-1451 administration: In completed studies with a total of 59 subjects the following adverse events were reported in at least 1% of subjects and were not thought by the investigator(s) to be related to study procedures: diarrhea, headache, dysgeusia.

6.9.1.11. Return and Retention of Study Drug

[18F]AV-1451 (drug substance) is formulated in a clear solution containing 10% (v/v) ethanol, USP in 0.9% sodium chloride injection, USP. This solution will be kept one-year post-injection as required by FDA regulations.

Contact for drug destruction policy:

Marianna Dakanali, PhD
Assistant Professor, Radiology
Regulatory Affairs Officer, Cyclotron and Radiochemistry Program
UT Southwestern Medical Center
5323 Harry Hines Blvd, Dallas, TX, 75390-8542
(Phone): 214-645-7611
(Fax): 214-645-0857
Email: Marianna.Dakanali@utsouthwestern.edu

6.10. STATISTICAL CONSIDERATIONS

6.10.1. Study Design/Study Endpoints

This is a single-center study that uses two types of designs. First, the Wave 3 data will be analyzed separately and utilizes a cross-sectional design with age as a primary continuous variable, as well as multiple aspects of brain structure, brain function, cognitive performance, and amyloid deposition used as additional predictors of different types of

cognitive function (memory, speed of processing, executive function). Then, in a second series of analyses that integrate data from Wave 1, Wave 2, and Wave 3, a retrospective-longitudinal design will be used to assess the relationship of present tau deposition to change in multiple aspects of brain structure, brain function, cognitive performance, and amyloid across time. Tau imaging agent administration is open-label, and imaging of participants will end when all eligible participants are scanned, all remaining participants have been contacted but are unable to be reached or unwilling to participate, or in the event that new safety data becomes available that indicates the study should be terminated. Study endpoints described in sections 6.5.4 and 6.5.5 are repeated below.

6.10.1.1. Primary Endpoints

The primary objective will involve completion of up to 125 [^{18}F]AV-1451 PET scans on Wave 1 and 2 DLBS participants. Measures of cognition, MRI, and amyloid PET will have been collected in previous visits. Once the tau scan data are collected, data collection will stop.

6.10.1.2. Secondary Endpoints

Tau deposition will be estimated from Wave 3 data by the SUVr of [^{18}F]AV-1451 in temporal regions (both left and right) of interest: (1) inferior temporal gyrus, (2) middle temporal gyrus, (3) superior temporal gyrus, (4) entorhinal cortex, (5) parahippocampal gyrus, and (6) fusiform gyrus. Amyloid accumulation will be measured as the SUVr value averaged across eight cortical regions: dorsal lateral prefrontal cortex, orbitofrontal cortex, lateral parietal cortex, posterior cingulate cortex, anterior cingulate cortex, precuneus, lateral temporal cortex, and occipital lobe. Both measures of tau and amyloid will be used as continuous measures rather than positive and negative dichotomy. In addition, there were 60 participants in Wave 2 who received tau imaging four years earlier. Change in tau deposition will be estimated for all returning participants who were among those that received tau imaging in both Waves 2 and 3. We also note that for all endpoints described below, we will analyze the data exclusively from Wave 3 in cross-sectional analyses, and then will also calculate change in all of these endpoints from Wave 1 to 3, and then retrospectively relate tau levels to changes in these endpoints.

6.10.1.2.1. Hippocampal volume and regional cortical thickness will be estimated using FreeSurfer (ver. 5.3), with surface parcellation manually edited, when necessary, by our team of experts.

6.10.1.2.2. Estimates of white matter integrity will be collected using diffusion tensor measures. For functional measures, BOLD signal from contrasts of interest using selected ROI's will be created using our

subsequent memory task and semantic judgment task and their relationship to tau deposition will be assessed. In addition, we will also use resting state data to look at how tau effects functional brain connectivity.

6.10.1.2.3. Joint effects of tau and amyloid will be examined by including them as an interaction term in a linear mixed-model analysis.

6.10.1.2.4. Cognitive decline will be assessed using the following constructs: processing speed, episodic memory, working memory, and executive function. Scores on these constructs will be averaged across relevant DLBS tasks and standardized based on performance at the beginning of this longitudinal study (Wave 1).

6.10.2. Sample Size and Accrual

To fulfill the primary objective of this research project, we intend to conduct tau PET imaging with up to 125 adults that were typically-aging at the start of this study. Scanning will take place over the span of the next 2 years with an anticipated accrual rate of approximately 7 subjects per month. This accrual rate was based on our experience imaging participants in the previous wave of data collection.

Statistical power was computed using G*Power (ver 3.1) assuming successful collection of tau data for the full 125 subjects and using default G*Power parameters unless otherwise specified. The secondary objectives of this study (Sections 6.5.2.1 - 6.5.2.4) are assumed to involve linear relationships between variables for the purpose of this power analysis. With this sample size, we have an estimated power of 0.93 to detect linear relationships that are medium-sized (effect size: $r = 0.30$). This robust power level will allow for strong confidence in our findings, computation of more precise 95% confidence intervals on effect sizes, and more fine-grained post hoc analysis.

6.10.3. Data Analyses

For all analyses, testing the primary and secondary objectives of this study, our measures of interest will be measured continuously and entered into linear regression or linear mixed-models analyses as appropriate. For each objective, as we have noted earlier, we will first analyze the data cross-sectionally within Wave 3 to determine whether tau SUVr is related with our dependent variables. A test-wise alpha of 0.05 will determine finding significance regarding research hypotheses, and post hoc analyses will be corrected for family-wise error using the multi-stage Holm-Bonferroni method (Holm, 1979). Then we will model changes from Waves 1 - 3 in endpoints and their relationship to tau at Wave 3.

6.10.3.1. Our primary objective, to determine the time course of tau deposition with age, will be first assessed by computing a linear regression between the AV-1451 SUVr in each of our temporal regions of interest with participant age. Next, we will determine whether this relationship is better fit by a quadratic, exponential, or growth model. We predict that tau accumulation will accelerate in old age, thus supporting a non-linear rate of deposition.

6.10.3.2. A linear mixed-model analysis will be used to relate our continuous SUVr measure of amyloid deposition with the SUVr for tau deposition in each of our temporal ROIs. An amyloid SUVr x time of testing interaction term will be used to predict changes in tau SUVr. We predict that increased amyloid burden will be associated with accelerated tau deposition.

6.10.3.3. To determine differences in cognitive, structural, and functional decline between those with and without tau and amyloid pathology, we will perform multiple linear mixed-model analyses. All variables of interest will be included as continuous measures. Tau SUVr x time and amyloid SUVr x time interaction terms will be entered in these models to predict how amyloid and tau pathology predicts longitudinal changes in our cognitive, structural, and functional measure of interest. In line with recent research, we predict tau burden in particular to be strongly associated with more rapid structural and cognitive decline.

6.10.3.4. Similar to section 6.10.3.3, relationships between estimated tau deposition (SUVr) with hippocampal volume and cortical thickness will be estimated by entering these variables as continuous measures in linear mixed-model analyses with interaction terms including time of scanning/testing. We hypothesize that elevated tau SUVr will be associated with more steep declines in hippocampal volume and cortical thickness.

6.10.3.5. To examine the joint effect of tau and amyloid, these variables will be multiplied to form an interaction term (tau SUVr x amyloid SUVr x time) that will be entered in a linear mixed-model analysis to predict longitudinal changes in cognitive, structural, and functional measures.

6.11. STUDY MANAGEMENT

6.11.1. Conflict of Interest

Any investigator(s) who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the UTSW COI Committee and IRB according to UTSW Policy on Conflicts of Interest. All investigators will follow the University conflict of interest policy.

6.11.2. Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB must approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator(s) should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the subject will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the subject and the investigator(s) is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion.

6.11.3. Registration/Randomization Procedures

Each newly consented subject will be numbered based on their assigned Dallas Lifespan Brain Study Number. This number is unique to each subject and independent of all personal identifying information.

This study does not require randomization; all participants will receive [18F]AV-1451.

6.11.4. Data Management and Monitoring/Auditing

6.11.4.1. Regulatory Documentation

The following regulatory documents will be retained.

- A copy of the official IRB approval letter for the protocol and informed consent.
- IRB Federal-wide Assurance letter.

- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study.
- Form FDA 1572 appropriately filled out and signed with appropriate documentation
- A copy of the IRB-approved consent form.

6.11.4.2. CRFs and Source data

Case report forms (CRFs) will be used for this trial. Individual patient files should include appropriate source documents, including but not limited to patient's medical records and laboratory test results. The files should include information such as visit dates, records of medical history, examinations administered, laboratory, concomitant treatment, any adverse event encountered and other notes as appropriate. These constitute "source data". All entries on the CRFs must be backed up by source data. Original electronic versions of imaging studies are also considered source data and will be kept on file by the site/imaging center.

Each patient's source file should include an original signed informed consent form. When the trial is completed, the informed consent form should be kept on file with other trial related records.

All original laboratory reports must be available for review in each patient's file. It is important that the original reports be available for review because of the possibility of inaccuracies or errors in transcribing data from original records to the CRF.

The CRFs must be kept in order and up-to-date so that they always reflect the latest observations on the subjects that are enrolled in the trial. The CRFs must be completed for each patient enrolled in the trial. This should be done as soon as possible after completion of the patient's participation in the trial. A monitor will verify the source data for all information on the CRF.

6.11.5. Monitoring

Trial monitoring will be conducted no less than annually and refers to a regular interval review of trial related activity and documentation performed by monitor. This review includes but is not limited to accuracy of case report forms, protocol compliance, and AE/SAE management and reporting. Documentation of trial monitoring will be maintained along with other protocol related documents and will be reviewed during internal audit.

6.11.6. Adherence to the Protocol

Except for an emergency situation, in which proper care for the protection, safety, and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

6.11.6.1. Exceptions (also called single-subject exceptions or single-subject waivers): include any departure from IRB-approved research that is not due to an emergency and is:

- intentional on part of the investigator(s); or
- in the investigator(s)'s control; or
- not intended as a systemic change (e.g., single-subject exceptions to eligibility [inclusion/exclusion] criteria)
    - **Reporting requirement**: Exceptions are non-emergency deviations that require ***prospective*** IRB approval before being implemented. Call the IRB if your request is urgent. If IRB approval is not obtained beforehand, this constitutes a major deviation.

6.11.6.2. Emergency Deviations: include any departure from IRB-approved research that is necessary to:

- avoid immediate apparent harm, or
- protect the life or physical well-being of subjects or others
    - **Reporting requirement**: Emergency deviations must be promptly reported to the IRB within 5 working days of occurrence.

6.11.6.3. Major Deviations (also called **violations**): include any departure from IRB-approved research that:

- Harmed or placed subject(s) or others at risk of harm (i.e., did or has the potential to negatively affect the safety, rights, or welfare of subjects or others), or
- Affect data quality (e.g., the completeness, accuracy, reliability, or validity of the data) or the science of the research (e.g., the primary outcome/endpoint of the study)
    - **Reporting requirement**: Major deviations must be promptly reported to the IRB within 5 working days of PI awareness.

6.11.6.4. Minor Deviations: include any departure from IRB-approved research that:

- Did not harm or place subject(s) or others at risk of harm (i.e., did not or did not have the potential to negatively affect the safety, rights, or welfare of subjects or others), or
- Did not affect data quality (e.g., the completeness, accuracy, reliability, or validity of the data) or the science of the research (e.g., the primary outcome/endpoint of the study)
    - **Reporting requirement**: Minor deviations should be tracked and summarized in the progress report at the next IRB continuing review.

6.11.7. Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. A summary of changes document outlining proposed changes as well as rationale for changes, when appropriate, is highly recommended. When an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

6.11.8. Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator(s) retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

6.11.9. Obligations of Investigators

The Principal Investigator and Co-Investigators are responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator and Co-Investigators are responsible for personally overseeing the treatment of all study patients. The Principal Investigator and Co-Investigators must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator and Co-Investigators will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits may be conducted and the Principal Investigator and Co-Investigators will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed and accuracy of the data verified.

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