Protocol Synopsis for Research Project Involving Human Subjects

PROTOCOL INFORMATION

Title of Research Activity: **The Health and Aging Brain Study: Health Disparities TAU PROJECT**

Name of Principal Investigator: Sid O'Bryant, PhD

Names of each Co-Investigators: Leigh Johnson (Co-PI), PhD.

David Mason, DO (Co-I and study doctor)

Sponsoring Agency / Company (if applicable): National Institute of Aging

Sponsor's Protocol Number (if applicable): R56AG058533

A. Specific Aims –

Despite a primary goal of the National Alzheimer's Project Act (NAPA)[1] being to "improve outcomes for ethnic and racial minority populations that are at higher risk for Alzheimer's disease(AD)", very little research has been conducted among the U.S. Hispanic population[2,3]. By the year 2050, the percentage of Hispanics in America age 65 and above will nearly ***triple,*** while *declining* or remaining flat among other ethnic groups[4]. With 65% of the U.S. Hispanic population being Mexican American[5], this ethnic group reflects a rapidly growing segment of the aging population that is at increased risk for MCI and AD[6,7] at younger ages[2,8,9]. Additionally, Hispanic/Latinos will experience the largest growth in AD and AD related dementias (ADRDs) between now and 2060[10]. With the generation of the 2018 AT/N Framework[11], there is an increased focus on amyloid (A), tau (T) and neurodegenerative (N) markers to understand AD as a biological construct. However, as pointed out in the framework, there is a need to understand these biological markers among diverse and community-based populations. Despite the tremendous focus on amyloid, tau and neurodegenerative markers, ***no prior work*** has examined PET tau burden among Mexican Americans despite the fact that tau burden has been found to fluctuate as a function of race/ethnicity at autopsy and CSF studies[12-15]. Here we propose to conduct the first-ever pilot study of tau burden among Mexican Americans.

There is now a tremendous push to move tau PET tracers to Regulatory approval in order to advance novel intervention trials and to guide clinical care. Flortaucipir(^{18}F), laboratory name **^{18}F-AV-1451,**is the single most investigated PET tracer for the study of cerebral tau burden. In fact, a PubMed search (7/23/19) using the search term "AV1451" identified n>100 publications; however, when the term "Hispanic" was added, no results were identified. With novel clinical trials (intervention and prevention)

targeting both amyloid and tau, there is a huge need to understand tau burden among Mexican Americans. Prior work by our team, and others, has shown that when compared to non-Hispanic whites, Mexican Americans (1) are at increased risk for MCI and AD[6], (2) are diagnosed at a more advanced stages of disease progression[3,8] (3) develop MCI and AD at younger ages[2,8,12], (4) have a lower frequency of the ApoEε4 allele[2,3,16], (5) suffer from a disproportionate burden of modifiable risk factors for MCI and AD (e.g. diabetes, depression)[2,3,17] and (6) demonstrate an AD proteomic profile that is metabolic in nature[18]. In our HABLE-Amyloid pilot project, we now have data showing that amyloid burden among Mexican Americans that have been clinically diagnosed as MCI or AD (1) have significantly lower amyloid burden as compared to non-Hispanic whites; however, they also (2) have comparable levels of neurodegeneration as measured by plasma NfL levels. Therefore, our data demonstrates medical, genetic, proteomic and amyloid differences among Mexican Americans diagnosed with MCI and AD as compared to non-Hispanic whites. In fact, we have identified cognitive loss at younger ages that is associated with neurodegeneration in the absence of amyloid among Mexican Americans. Given that tau is associated with global neurodegeneration, it is possible that Mexican Americans are suffering altered levels of tau burden when compared to non-Hispanic whites. This also suggests that the "accepted" sequence of pathological burden could be fundamentally different among this population. However to date no studies are examining Tau burden via PET scan in Mexican Americans. Moreover, questions remain regarding the feasibility of recruiting this population into Tau research studies.

This study seeks to address this gap through the achievement of the following specific aims: 1) Conduct a pilot study regarding the feasibility of recruiting Mexican Americans with known amyloid status into a PET tau scan study, 2) Examine the prevalence of tau burden among community-dwelling Mexican Americans suffering with known amyloid burden.

The current study is **highly significant** for several reasons: (1) this is the first-ever study of the tau hypothesis among Mexican Americans; (2) this study will examine how tau is potentially differentially present among Mexican Americans; (3) this study will demonstrate, for the first time, the feasibility of recruiting Mexican Americans into a PET tau scan study.

B. Background and Significance -

The long-term goal of this research is the generation and validation of biomarkers of Alzheimer's disease (AD) among Mexican Americans. Despite the rapidly growing Mexican American elderly population, little research has been conducted on AD among this ethnic minority group. Research that has been conducted suggests that a significant health disparity exists with Mexican Americans (1) being at increased risk for AD, (2) being diagnosed with AD at younger ages and more advanced stages, (3) experiencing significantly longer disease duration as well as delays in diagnosis and treatment, and (4) being misdiagnosed due to invalid/inaccurate measures. The 2018 AT/N Framework has now provided a biologically-based system for examining the emergence and progression of AD; however, all of the data in support of this framework is based on non-Hispanic whites. This means that our fundamental understanding of the pathological processes underlying AD is not reflective of our diverse U.S. population. Additionally, the research underlying our conceptualization is based on clinic-based samples, which are substantially biased. Therefore, here we will conduct a pilot study of cerebral tau burden among Mexican Americans with known amyloid status to set the stage for a large-scale community-based study of the 2018 AT/N Framework among a diverse cohort.

A tremendous amount of progress in neuroimaging biomarkers of AD has been accomplished within the last decade, which is largely due to the Alzheimer's Disease Neuroimaging Initiative (ADNI), the most

comprehensive study of AD globally to date. In fact the FDA has now approved multiple PET imaging biomarkers of amyloid for use in the diagnostic process. Flortaucipir(18F) is the single most studied radiotracer specifically for the detection of brain tau among living patients. Prior to this technology, confirmation of tau pathology was only possible with lumbar punctures or at autopsy. However, in our prior discussions with the HABLE cohort, no participants said they would undergo lumbar punctures. Additionally, no prior work has been undertaken to determine if neuroimaging biomarkers of tau and amyloid AD vary according to ethnicity or if ethnicity impacts the appropriate diagnostic cut-values.

C. Preliminary Studies

Our group has extensive experience recruiting Mexican Americans into aging research and are leaders in the field of aging, MCI and AD among this ethnic minority group. The team has recruited n>2000 Hispanics (primarily Mexican Americans) into multiple projects, including the Health & Aging Brain among Latino Elders (HABLE) recruitment protocol of the Health & Aging Brain Study, the Texas Alzheimer's Research & Care Consortium (TARCC), Project FRONTIER and the CMS-funded MIGHTY Care waiver project. Together these efforts have resulted in over 50 peer-reviewed publications with over 20 emphasizing underserved populations (see PIs CV).

Our current team currently runs one of the most comprehensive studies of Mexican American brain aging ever conducted, the Health & Aging Brain Study HD: Health Disparities (2016-128). The goal of the HABLE HD parent study is to examine health disparities in aging. This project will recruit 1000 MA and 1000 non Hispanic whites for baseline and 24 month follow up.

In 2018, we were funded to obtain PET scans on a subset of the cohort. The PET scans were separated into 2 IRB protocols (Amyloid project 2017-165 and the TAU Project). The TAU Project will leverage the ongoing Health and Aging Brain Study: Health Disparities Amyloid Project (IRB# 2017-165) project to conduct tau PET scans among n=40 Mexican Americans.

D. Investigator Experience

The PI, and his research team, has extensive experience building and maintaining community-based as well as clinic-based longitudinal research cohorts. Our team has recruited n>8,000 participants from underserved communities into funded programs from the DFW region since 2012. CV attached.

E. Experimental Design and Methods

1) Methods and Procedures -

Overview

The Health and Aging Brain Study HD: Amyloid Project (2017-165) is currently recruiting up to 1000 participants from the Health and Aging Brain Study HD: Health Disparities (2016-128) to undergo amyloid PET scans. All other research components are captured as part of the parent IRB protocol. Here, we propose to re-contact n=40 participants who self-identify as Mexican American, that have already undergone amyloid PET scans as part of IRB 2017-165, and have given permission for re-contact.

Participants will be re-contacted using the **Recruitment Script (see attachment).** *Please note that the script for this study is minimal. Our team has extensive experience recruiting older underserved individuals*

into research. We have found our participants prefer to have discussions face to face rather than over the phone. Additionally, during the amyloid study, we informed participants of the potential for another PET scan study in the future.

For those individuals who wish to participate, an appointment will be set up for him/her to come to our research offices for an in-person visit to conduct the consent and screening visit. This can take place in one visit or spread out over multiple visits. The study doctor will review the information collected in the medical exam and determine eligibility.

If the participant meets eligibility criteria, the research team will schedule an appointment for the participant to receive the brain scan at an imaging center. Participants will undergo a PET scan. Participants will be screened by the research team during the medical exam, and by the imaging center staff before they are scanned. The imaging center personnel will carry out their standard/internal procedures for verifying PET scan eligibility. If the imaging center identifies a safety concern they will notify the research team. Participants unable to undergo a scan will be withdrawn from the study by the research team. The participants may meet a member of the research team at the imaging facility on the day of the scan. Participants must complete the PET scan in order to be compensated for his/her time.

The data collected in this study will be linked with the participant's data collected in The Health and Aging Brain Study HD: Health Disparities IRB# 2016-128 and The Health and Aging Brain Study: Health Disparities Amyloid Project IRB# 2017-165.

This study will be posted on clinicaltrials.gov. This study will cross reference AVID's IND and an IND has been obtained for the UNTHSC site, FDA IND Number 145437 Any SAEs will be reported to the FDA, AVID, and the IRB.

The following may take place over multiple visits based on the participant's schedule and scanner availability.

Consent

All participants will sign an informed consent before they are enrolled. A copy of the consent document can be found in the **Attachments**. The consent form covers all possible parts of the study, and explains the risks and benefits of participation. Individuals who are unable to read and understand the written consent will be provided with an oral presentation of the consent form, and then their signature will be obtained. This process must be observed and attested to on the consent form by a witness. For individuals with Alzheimer's disease who are unable to provide independent consent, informed consent will be obtained from caregivers and consent from the participant will be obtained. Consent forms will be available in English and Spanish. Spanish speaking only participants will be consented by bi-lingual research staff. **[Note: Spanish versions will be submitted once IRB approval is received].**

Screening

After consenting, participants will be asked to complete a medical exam to determine eligibility. During this

visit, medical personnel will obtain the participant's medical history, blood pressure, collect a list of medications, and conduct an ECG. The participants will undergo a fasting blood draw for standard clinical labs. For female participants who experienced a period in the last 2 years, a urine pregnancy test will be performed. The medical exam will be conducted by the study nurse practitioner and the information obtained during this screening visit will be used by study doctor to determine participant eligibility. Below is a detailed outline of screening procedures. Please note if at any time during the screening visit it is determined the participant is ineligible, the visit will be discontinued. However, a person may not complete the scan until all procedures are completed and the study doctor has deemed the subject meets criteria for inclusion. The medical exam will be conducted by a licensed Nurse Practitioner (Large) or the study doctor (Mason). Final judgement regarding eligibility will be made by the study doctor (Mason).

Screening procedures

1. Medical History and medication review
2. Urine Pregnancy test (if necessary for female participant's)
3. ECG
4. Blood draw

1. Medical history and medication review
   A comprehensive medical history will be collected from the participant. The NP/doctor will ask about the participant's medical diagnosis and history. Additionally, participant's will be asked to bring their medications or a list of medications to the visit. The NP/doctor will compare the participant's medication to the List of Excluded medications. The NP/doctor will collect blood pressure.
2. Urine Pregnancy test
   Female participants who have had a period within the last 2 years will be required to take a urine pregnancy test. Pregnant or lactating female will be excluded from the study.
3. ECG
   The NP/doctor will conduct the ECG. Clinically significant findings on ECG specifically Bazett's[19] corrected QT (QTcB) interval exceeding accepted values (458 msec in males, 474 msec in females) will result in exclusion from the study.
4. Blood work
   Participants will be asked to undergo a fasting blood draw. Blood draws will be obtained via venipuncture and up to 20ml will be obtained for this study. Standard clinical labs will be conducted in CLIA certified laboratories and will include comprehensive metabolic panel (CMP), complete blood count with differential (CBC), thyroid panel with TSH and T4, Lipid panel, and HbA1c. Blood samples will be labeled with the participants medical ID and will not be retained for biobanking.

The study doctor will review all the information from the medical exam and determine if the participant meets eligibility criteria.

If a participant is deemed ineligible to participate, data collected from the screening visit will not be maintained for research purposes. However, as this is an FDA regulated study, consents and participant files will be maintained as required by law.

**If there are clinically significant findings on the ECG or clinical labs the participants will be notified and instructed to follow up with their personal medical provider.

The screening visit may take 30 minutes -1 hour.

<u>Positron Emission Tomography (PET) scan for utilizing Flortaucipir.</u>

A positron emission tomography (PET) scan is an imaging test that reveals how an individual's tissues and organs are functioning. A small amount of radioactive material, called a radiotracer, is necessary to show this activity. The precise type of radioactive material and its delivery method depend on which organ or tissue is being studied by the PET scan. For the current study the goal is to obtain tau imaging using a PET scan, which is currently the only pre-mortem method for directly analyzing Alzheimer's disease brain pathology.

Currently, there are no Tau tracers with FDA approval. Thus, the tracer used in this study, Flortaucipir, is not FDA approved. However, it is the single most studied radiotracer specifically for the detection of brain tau among living patients (n>2,400). The information regarding safety and efficacy of the tracer can be found in the Investigator Brochure in the attachments. Preliminary efficacy is available from 8 completed human clinical studies with Flortaucipir. No expected Serious Adverse drug reactions have yet been identified for Flortaucipir.

There are no known contraindications to the usage of Flortaucipir. Pregnant or lactating females have been excluded from all Flortaucipir studies due to the potential risks of radiation to the fetus. Non-radioactive 18F-AV-1451 was positive in the in vitro hERG assay with an IC50 of 0.610 μM.

If the Flortaucipir hERG channel IC50 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 (fu-human 0.047). Additionally, in vivo cardiovascular assessments in dogs showed no evidence of QT prolongation. Nonetheless, until sufficient human cardiovascular safety data are available, the Investigators Brochure recommends clinical studies exclude subjects with a history of risk factors for torsade de pointes and subjects taking drugs known to prolong the QT interval. Participants taking medications known to prolong the QT interval will be excluded from this study. Additionally, patients at risk of torsade de pointes and with clinically significant ECG findings will be excluded from the study.

Procedure

All participants will be injected with a 370 MBq (10 mCi) bolus of Flortaucipir (^{18}F), ^{18}F-AV-1451(^{18}F-T807). Up to 90 min post injection the participants will be positioned on the imaging table of a Siemens ECAT HR PET scanner. Soft Velcro straps and foam wedges will be used to secure the participant's head and the participant will be positioned using laser guides. A 2min scout will be acquired to ensure the participant's brain is completely in the field-of-view and there is no rotation in either plane. A 2-frame by 5-min each dynamic emission acquisition will be started up to 90min post injection and immediately after a Ge-68/68-Ga source transmission scan is acquired for 7min. The transmission image will be reconstructed using back-projection and a 6mm FWHM Gaussian filter. The emission images will be processed by iterative reconstruction, 4 iterations and 16 subsets with a 3mm FWHM ramp filter. Images will be reconstructed immediately after the 10-minute scan, and if any motion is detected, another 10 minute continuous scan will be acquired.

Time: The PET scan may take up to 120 minutes, not including travel to and from the facility.

Risks

The total radiation exposure from Flortaucipir administration and subsequent PET scan is estimated to be 8.70mSv. The amount of radiation exposure is equivalent to an additional year's worth of radiation exposure experienced by individuals in the US (clinical procedures, food, environment, etc.). Because the doses of radiotracers administered are small, diagnostic nuclear medicine procedures result in relatively low radiation exposure to the participant, acceptable for diagnostic exams. The most common adverse reactions to Flortaucipir reported in the Investigational Brochure (n=273) were injection headache (2.2%), diarrhea (1.1%), hypertension (0.7%) and muscle spasms (0.7%). All others reported were <0.5% (musculoskeletal discomfort, dysgeusia, nausea, oral pain, bronchial secretion retention, epistaxis, injection site pain, dizziness, flushing, fatigue, hypotension, feeling cold, insomnia). All were reported as mild or moderate severity and all subjects recovered. Back and neck pain may be experienced from lying in the scanner. No consistent or clinically relevant changes in vital signs, laboratory values or ECG results have been observed in competed studies. Additional risks associated with this protocol are discussed in detail in the Risks/benefits section.

Feedback

Given that Flortaucipir is not FDA approved, tau cerebral burden will not be provided back to participants at this time. If Flortaucipir (1) becomes FDA approved and (2) clinical guidance's are provided for healthcare providers, we will modify the protocol at that time. If new information is released regarding Flortaucipir during the study, we will give it to the participants.

2) *Data Analysis and Data Monitoring* -

As with all Health and Aging Brain Study neuroimaging protocols (MRI, PET), all images will be directly uploaded, stored and analyzed at USC/LONI per ADNI protocols. USC/LONI has well-established protocols for analyzing cerebral tau PET scans from 1,000s of scans. All research data will be managed by our research team and stored in the Institute for Translational Research (ITR) Data Core. Periodic Quality Control checks will be conducted by our personnel and provided to the PI. All electronic records will be maintained on password protected computers behind locked doors in the ITR office space. All files will be backed up weekly, again located in the ITR office space. After data is entered the database will be transferred to the Institutional server, which will afford additional safeguards and backup. This study will enroll up to 40 Mexican Americans currently enrolled in the Health and Aging Brain Study: Health Disparities Amyloid Project (2017-165).

Standard clinical labs work will be conducted by Quest diagnostics. Samples will be labeled with a participant's medical ID number. This number is generated by the research team and is different from the participants research ID.

PET Data Processing. All PET scan images will be uploaded to the LONI server and analyzed by LONI personnel. We will perform the following processing of the scans: 1) Co-registration of frames to correct for motion; 2) Creation of an average image (90-110 min p.i.); and 3) Co-registration of the average image to the individual SPGRs (T1-weighted MRI). We will use FreeSurfer to segment the native space SPGR scan to obtain masks for whole cerebellum and four cortical regions of interest: frontal, anterior/posterior cingulate, lateral parietal, and lateral temporal cortices. We will intensity-normalize the PET images using mean PET signal in the whole cerebellum as a reference region, consistent with the standard ADNI protocol for cross-sectional studies. The global standardized uptake value ratio (SUVR) will be equal to the mean PET signal in the cortical regions of interest divided by mean signal in the whole cerebellum. We will also calculate regional SUVRs in each of the lobes, and in FreeSurfer-derived orbitofrontal, anterior and posterior cingulate

cortices, and precuneus.

The de-identified PET scans data will be analyzed at the Laboratory of Neuroimaging (LONI) at USC. All imaging data will be labeled with the participant's medical id number. The imaging data will be uploaded from the imaging center into the IDA (Image and Data Archive) run by the USC LONI. This is a secure server and all data will be de-identified. After analyses are completed, the LONI team will provide our staff with a secured file to merge the data into our master database. LONI provides such services to the top neuroimaging research studies across the globe and the database currently contains over 32,000 scans from over 80 different research studies. LONI currently manages all MRI data from the Health and Aging Brain Study HD: Health Disparities protocol and the Health and Aging Brain Study: Health Disparities Amyloid Project. Additionally, our team collaborates with LONI for all imaging studies collected as part of the Alzheimer's Disease in Primary Care (ADPC) study (MRI and PET). Other examples of studies managed by LONI are the Alzheimer's Disease Neuroimaging Initiative (ADNI), Longitudinal Evaluation of Familial Frontotemporal Dementia (LEFFTDS), Huntington's Disease Neuroimaging Initiative (TRACKHD), Australian Imaging, Biomarkers and Lifestyle flagship study (AIBL), Transforming Research and Clinical Knowledge in TBI (TRACK-TBI) and the Parkinson's Progression Markers Initiative (PPMI). The LONI is an IDA repository. The LONI will keep a copy of the de-identified scans and other data for the IDA research repository.

3) *Data Storage and Confidentiality* –

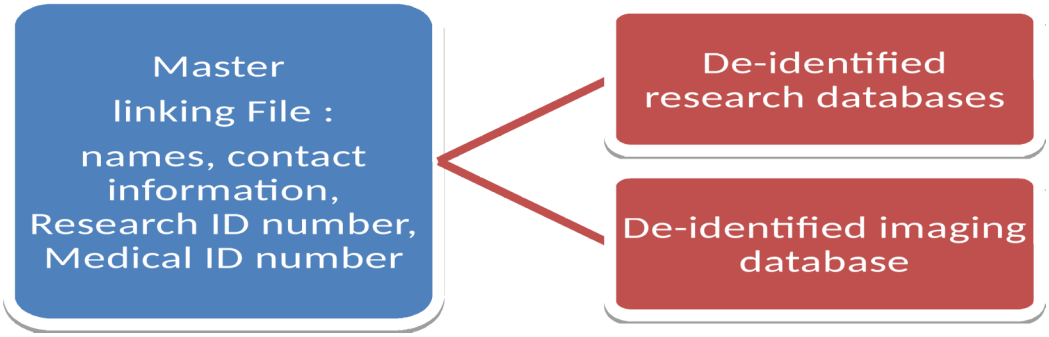
Research data will be stored and managed in a secure manner following NIH guidelines and according to state and institutional policies. Only authorized key personnel shall have access to research related documents. All personnel will be properly trained and supervised regarding the management and handling of confidential materials. The Principal Investigator assumes full responsibility for such training, supervision, and conduct.

All electronic files will be stored on the research team's computers and backed up on the Institutional server. All paper data will be stored in locked file cabinets. The results of this study will be added to the participant files for the Health and Aging Brain Study HD: Health Disparities (2016-128) and The Health and Aging Brain Study: Health Disparities Amyloid Project (2017-165).

The Master Linking File will be a separate password-protected file maintained by authorized research personnel. This file will hold the link between the research ID numbers and individually identifying information on each participant. Only authorized research personnel will have access to this file. This linking file will enable accurate tracking of research participants across multiple visits. Each participant has a Medical ID number assigned.

The imaging facility may require the participant name, date of birth, and medical ID number to complete research scans. This protocol is in place for safety and insurance purposes to protect the participant as well as the radiologists and center. To protect confidentiality the site will de-identify the results of the scan (using the medical id number), which will make it impossible to connect the participant's name to the findings. Additionally, the imaging facility will not be provided with the participant's research id number.

See diagram below.



This study has a Certificate of Confidentially from the National Institutes of Health.

4) *Setting* - Describe briefly where the study will be conducted, e.g., private outpatient clinics, physicians' offices.

Participants will be seen in the Health and Aging Brain Study offices in the Institute for Translational Research for the consenting and medical exam and ECG. They will go to the clinical laboratories for the blood draw (Quest), and then they may be accompanied by a member of the research team to the imaging center for the brain scans. The particular center will depend on availability of scanners.

Since we may contract with multiple imaging sites we will submit an addendum for each site that outlines the site specific requirements for research and a copy of the requisition forms.

5) *Laboratory methods and facilities* –

As outlined above, each study participant will undergo brain PET scan at an imaging center. The imaging center(s) will conduct the scans as a fee-for-services contract, similar to the process we already have in place where Quest Diagnostics (or another lab) conducts clinical labs for our research participants. See Procedures Section above for description of imaging procedures to be completed.

6) *Estimated Period of Time to Complete the Study* – Rough estimates of the time can be found below:

Consent and screening visit: 30 minutes -1 hour
PET Scan: up to120 minutes

F. Human Subjects - Describe the characteristics of the research population:

1) *Description of subjects* is to include the projected sample size, plans for the selection of subjects, and inclusion and exclusion criteria.

This study seeks to obtain PET tau imaging on n=40 Mexican American participants within known amyloid status currently enrolled in the Health and Aging Brain Study: Health Disparities Amyloid Project (2017-165). Bilingual research assistants will be utilized to interact with Spanish speaking only participants. Participants will be recruited directly from the Health & Aging Brain Study: Health Disparities Amyloid Project protocol. Only those who have been consented for re-contact will be recruited for this study. It should be noted that the Inclusion criteria for the parent study is age 50 and older. The majority of participants in the study are 60 and older.

2) *Sample Size*: Up to 40 Mexican American participants from the Health & Aging Brain Study: Health Disparities Amyloid Protocol (2017-165) will be enrolled in this imaging study.

3) Describe both *Inclusion / Exclusion Criteria*.

Inclusion Criteria

1. Enrolled in the Health and Aging Brain Study: Health Disparities Amyloid Protocol (2017-165)
2. Self-identified as Mexican American
3. Provided consent to re-contact

Exclusion Criteria:

1. Inability to provide informed consent by self or by proxy.
2. Pregnant or breast feeding women*
3. History of risk factors for torsades de pointes
4. Taking medications known to prolong QT interval.**
5. Clinically significant findings on ECG, specifically Bazett's[19] corrected QT (QTcB) interval exceeding accepted values (458 msec in males, 474 msec in females).***
6. Have clinically significant infectious, cardiac, hepatic, renal, pulmonary, metabolic or endocrine disturbances as defined by medical history and clinical lab values.
7. Presence of other conditions or medications deemed to put the subject at risk by the study physician.
8. Participants may not be in this study if they do not meet the safety criteria to undergo imaging procedures.
   Note: Participants will be pre-screened by both the research staff and the imaging facility staff before they are scanned.

Additional information for the bulleted exclusion criteria.

*Women who are pregnant or breast feeding will not be allowed to enroll in this study. Additionally, women of child bearing age, who have experienced a period in the past two years, will be asked to undergo a urine pregnancy test. Women of childbearing potential will be required to use a reliable birth control or refrain from sexual activity for 24 hours following the scan to be included in the study. **[Please note: Based on a review of the records from Amyloid project, no female participants were required to undergo a urine pregnancy test due to not having a period within a 2-year time. However, all subjects will be re-assessed for the current study.]**

** Please see the attachments for a list of excluded medications. This is not a comprehensive list. **The study doctor will review all medications and make a decision regarding eligibility in conjunction with a patient's clinical labs, ECG, medical history.**

***Until additional human cardiovascular safety data are available, participants with a history of risk factors for torsades de pointes, including clinically significant findings on ECG, or taking medications known to prolong QT interval will be excluded from this study. Medical history, ECG, and a list of medications will be reviewed by appropriate medical personnel to determine participant's eligibility. Clinical labs will be obtained on all participants. The study doctor will review all the information collected during the medical exam to determine eligibility. **[Please note references ranges for the QT intervals and medications are consistent with other trials utilizing this tau tracer.]**

4) Describe intended *gender, age range, and intended racial and ethnic distribution*. If any vulnerable subjects are involved in this study

Participants will be men and women age 50 and older, and self-identified as Mexican American. Only individuals who are participants in Health & Aging Brain Study: Health Disparities Amyloid Project will be enrolled. Participants may have cognitive impairment and Alzheimer's disease. For individuals with Alzheimer's disease who are unable to provide independent consent, informed consent will be obtained from caregivers and consent from the participant will be obtained.

5) Identify the *source(s) from which you will obtain your study population*.

Participants will be recruited from the Health and Aging Brain Study: Health Disparities Amyloid Project (IRB protocol 2017-165).

6) Describe plans for *recruitment of subjects*.

To be included in this study a participant must be currently enrolled in the Health and Aging Brain Study: Health Disparities Amyloid Project (IRB protocol 2017-165), self-identified as Mexican American, and consented for recontact. No new recruitment material will be created for this study.

G. Risk/Benefit Assessment

1) Describe the *level of risk*, and if more than minimal, describe how this research holds the prospect of a *direct benefit for the subjects*.

Overall this study is more than minimal risk to participants. Participants may not receive any direct benefits for participating in this study.

Participants who undergo PET scans will be exposed to low levels of radiation. Because the doses of radiotracer administered are small, diagnostic nuclear medicine procedures result in relatively low radiation exposure to the participant, and are considered acceptable. The most common adverse reactions to Flortaucipir reported in the Investigational Brochure (n=273) were injection headache (2.2%), diarrhea (1.1%), hypertension (0.7%) and muscle spasms (0.7%). All others reported were <0.5% (musculoskeletal discomfort, dysgeusia, nausea, oral pain, bronchial secretion retention, epistaxis, injection site pain, dizziness, flushing).

Currently there are no FDA approved tau tracers on the market. Therefore, this study is considered investigational. Flortaucipir has been tested in over 2400 individuals in completed or ongoing studies. It has

been generally well tolerated with a low risk of adverse events. However, as Flortaucipir is not FDA approved, there may be risks that are unforeseen. Therefore, numerous safeguards are built into this protocol to reduce the risk to subjects. All participants will be required to complete a medical exam which includes a medical history, medication review, urine pregnancy test (if necessary), blood work and ECG. The study doctor will review the results of the medical exam and determine if the subject is eligible to participate.

Due to the unique nature of the research, some members of the research team have significant financial interests in the outcome of the Health and Aging Brain Studies (patent pending the AD blood test, and UNTHSC has licensed these pending patents to a company. Drs. O'Bryant and Johnson have a financial interest in this company). Information regarding this financial interest is incorporated in the consent document in order to inform the subject. Additionally, the investigators have disclosures and management plans on file with the University's Research Conflict of Interest Committee.

2) Describe how the anticipated benefit justifies the risk.

To date, the scientific community does not know if our current pathological understanding of AD is relevant to Mexican Americans. The 2018 AT/N Framework provides, for the first time, a comprehensive biological framework/construct for studying the disease. This is the first-ever study to fully examine the 2018 AT/N Framework among Mexican Americans, even at a pilot level. The community is here offered the opportunity to contribute to the advancement of scientific knowledge about aging health and, in particular, Mexican American aging. Through the efforts of this, and other work, UNTHSC can contribute substantially to the advancement in aging across the U.S. and globe. The establishment of ethnicity as an important demographic variable for consideration when developing biomarkers for the detection of Alzheimer's disease would be of tremendous value to the field globally. Given the recently published 2018 AT/N Framework, this work is of paramount importance.

3) Describe how the anticipated benefit of this research is at least as favorable to the subjects as that to be received by available alternative approaches for the subjects.

This work can lead to a comprehensive understanding of established biomarkers of Alzheimer's disease among Mexican Americans. Our preliminary data suggests that the patterns of these "established" biomarkers is different among this ethnic group. Therefore, the information provided by this study will be of tremendous importance to the field.

4) Describe any potential RISKS OR DISCOMFORTS in detail.

Procedural Risks (and how they will be managed):

Potential risks and safeguards:

PET Scan with Flortaucipir

Flortaucipir is not FDA approved, there may be risks that are unforeseen. Therefore, numerous safeguards are built into this protocol to reduce the risk to subjects. All participants will be required to complete a medical exam which includes a complete medical history, medication review, urine pregnancy test (if necessary), blood draw, and an ECG. The study doctor will review the results of the medical exam and determine if the subject is eligible to participate. Below is more detailed description of the risks and safeguards.

Participants will be exposed to low levels of radiation due to the injection of the radiotracer. The dose is small and considered safe for diagnostic procedures. Participants will be informed of the risk of radiation exposure in the consenting process and may refuse to participate. The most common adverse reactions to Flortaucipir reported in the Investigational Brochure (n=273) were injection headache (2.2%), diarrhea (1.1%), hypertension (0.7%) and muscle spasms (0.7%). All others reported were <0.5% (musculoskeletal discomfort, dysgeusia, fatigue, nausea, oral pain, bronchial secretion retention, epistaxis, injection site pain, dizziness, flushing). Some participants may feel uncomfortable having to lie still on a table for the length of the scan. The technician will try to keep the participants as comfortable as possible throughout the scan. Allergic reactions may occur but are extremely rare. The imaging center staff are trained to address these issues and have safety protocols in place to address these instances. The injections may cause slight pain and redness. Additionally, participants will be instructed to notify the research team if they experience any side effects.

Women who are pregnant or lactating will be excluded from the study. Additionally, women of childbearing age, who have experienced a period in the past two years, will be asked to undergo a urine pregnancy test. Women of childbearing potential will be required to use a reliable form of birth control or refrain from sexual activity for 24 hours following the scan to be included in the study. As noted previously, participants will be recruited from the Amyloid project. None of the female participants enrolled in the amyloid project were of childbearing age.

Until additional human cardiovascular safety data are available, participants with a history of risk factors for torsade de pointes, including clinically significant findings on ECG, or taking medications known to prolong QT interval will be excluded from this study. Medical history, ECG, and a list of medications will be reviewed by appropriate medical personnel to determine participant's eligibility.

ECG risks

Electrocardiograms (ECGs) are safe, noninvasive, painless tests and have no major risks. The electrodes (sticky patches) that connect the sensors do not send out electric shocks. Participants may develop a mild rash or skin irritation where the electrodes were attached. If any paste or gel was used to attach the electrodes, they may have an allergic reaction to it. This irritation usually goes away once the patches are removed, without requiring treatment. The procedure will be performed by our study nurse practitioner and she will assess for any reactions during the procedure.

Blood draw risk

Participants will undergo a blood draw during this study. During the blood draw, the participants may experience discomfort, bleeding, and/or bruising from having blood drawn. Participants may feel dizzy or even faint. We will minimize this risk by scheduling blood draws in the morning and offering snacks. On a rare occasion, an infection could develop at the site the blood was collected. We will instruct the participant to notify us immediately if this event occurs. Potential risks associated with the blood draw will also be minimized by using trained personnel and aseptic technique.

Clinically relevant findings from medical exam

Participants will be notified if the results of the medical exam yield clinically relevant findings. This may result in the participant becoming distressed. The study doctor will ask the participant to follow up with their personal medical providers.

Informational Risks

Flortaucipir is not currently FDA approved and, therefore, results from this study will not be provided back to participants or their healthcare providers. If new information is released regarding Flortaucipir during the study, this information will be provided to participants.

Another risk related to the research is breach of confidentiality, which we will minimize to the extent possible. All files will be stored behind locked doors in locked file cabinets and on password protected computers. Only the PI and the core research team will have access to the master database that contains all research information.

Unknown Risks

Since this tracer is not FDA approved, there may be risks that are unknown. All SAEs will be reported to the FDA, Avid, and the IRB. This study will also be registered on clinicaltrials.gov.

H. Payment/Compensation-This study pays a flat rate for PET scans, which is as follows:

PET Scan with Flortaucipir: **$150**

Participants must complete the scan to receive payment. No partial payments will be given.
**The imaging center may refuse to scan a participant if they identify a reason that the person cannot be scanned safely.

Subject Costs –

The participant will not incur any costs related to this study.

J. List of KEY PERSONNEL

Sid E. O'Bryant, PhD
Dr. O'Bryant is PI of the Health and Aging Brain Study and will provide project oversight and

management. Dr. O'Bryant will participate in all aspects of the study.

Leigh Johnson, PhD

Dr. Johnson is a Co-PI and will manage the daily operations of the project, as well outreach operations. Additionally, she will conduct data analysis, blood draws, and participant feedback sessions. Dr. Johnson will participate in all aspects of the study.

David Mason, DO

Dr. Mason will provide medical oversight for the study and be involved in all research activities. Dr. Mason may perform some or all elements of the medical exam. Dr. Mason will review the information collected during the screening visit and determine participant eligibility.

Stephanie Large, NP

Mrs. Large is a licensed nurse practitioner and will conduct the medical exam during the screening visit. She will conduct the ECGs, urine pregnancy test, medical history, consensus reviews, and other study procedures. Mrs. Large has worked on numerous FDA and NIH funded clinical trials and has significant experience conducting ECGs.

She will provide Dr. Mason with the results of the medical exams.

Kim Brown, RN

Ms. Brown may recruit, complete study protocols and assist with the medical exam. Mrs. Brown will assist with all regulatory and IRB submissions. She will participate in outreach activities, recruitment and consent of participant, completion of study protocols, blood draws, scheduling, consensus reviews, and enter data into the research database.

Jill Rhodes, Research Specialist, Bilingual

Ms. Rhodes will serve as project coordinator. She will provide daily oversight to the staff working on this project. She may also participate in outreach activities, recruitment and consent of participants, completion of study protocols, scoring of participant testing, consensus reviews, and enter data into the research database.

Raul Vintimilla, Research Scientist, Bilingual

Mr. Vintimilla will participate in outreach activities, recruitment and consent of participant, completion of study protocols, blood draws, consensus reviews, and enter data into the research database. Mr. Vintimilla will also coordinate scheduling of research participants and serve as primary English to Spanish translator for all research materials.

Haydee Izurieta Munoz, Research Assistant, Bilingual

Ms. Izurieta Munoz will participate in outreach activities, recruitment and consent of participant, completion of study protocols, blood draws, scheduling, consensus reviews, and enter data into the research database.

Miguel Reyes, Research Assistant, Bilingual

Mr. Reyes will participate in outreach activities, recruitment and consent of participants, completion of study protocols, blood draws, biobank processing, consensus reviews, and enter data into the research database.

Daisy Ruiz, Bi-lingual Research assistant

Ms. Ruiz will participate in all research activities including outreach, recruitment and consent of participants, completion of study protocols, blood draws, scheduling, consensus reviews, and enter data into the research database.

Jennifer Loya, Bilingual Research assistant

Mrs. Loya will participate in all research activities including outreach, recruitment and consent of participants, completion of study protocols, blood draws, scheduling, consensus reviews, and enter data into the research database**.**

Lydia Cacho, Bilingual, scheduling

Mrs. Cacho will assist with scheduling, communicating to the imaging facility, and paperwork.

Hilem Gardea, Bilingual, administrative assistant

Mrs. Gardea will participate in outreach, recruitment, scheduling, data entry, and other administrative tasks.

Marcela Davila, Data entry

Mrs. Davila will assist with data entry, database management, participants tracking, research and other project activities.

Chris Conger, IT and Database

Mr. Conger will assist with database creation and management and all other IT needs for the study.

Sean Davidson, IT and Database

Mr. Davidson will assist with database creation and management and all other IT needs for the study.

Denise Duarte, Research Assistant, Bilingual

Mrs. Duarte will participate in all research activities including outreach, recruitment and consenting participants, completion of study protocols, blood draws, scheduling, consensus reviews, and enter data into the research database.

Antonio Casas, Research Assistant, Bilingual

Mr. Casas will participate in all research activities including outreach, recruitment and consenting participants, completion of study protocols, blood draws, scheduling, consensus reviews, and enter data into the research database.

K. Literature Cited – If any, the references should be limited to relevant and current literature pertinent to the proposed research.

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