SV2A PET Imaging in Alzheimer's Disease

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1 STUDY OBJECTIVES

Introduction: Synaptic loss is a major feature of symptomatic Alzheimer's disease (AD) [1]. Conversely, abundance of synapses may confer resilience to cognitive decline in the presence of AD pathology. The pathology-defining features of AD are amyloid plaques and neurofibrillary tangles and their presence and distribution can be spatially estimated in-vivo with amyloid and tau positron emission tomography (PET). Although these biomarkers can inform on the degree and location of pathology, they do not provide an indicator of their effect on collocated or extended in-network neural damage including synaptic density. Synaptic vesicle glycoprotein 2A (SV2A) is expressed ubiquitously in synapses and the capability of assessing SV2A *in vivo* may provide a direct indicator of synaptic health. Such information would be of high importance for staging the level of synaptic loss or conversely synaptic abundance in the AD continuum and may potentially improve prognostic precision. The PET radioligand [C-11]UCB-J is a marker of SV2A [2-4]. The overarching goal of this project is to use [C-11]UCB-J to obtain spatial information on neuronal synapse abundance and inform upon disease progression. We propose to collect longitudinal amyloid, tau and SV2A PET in participants in the Wisconsin ADRC and WRAP across the clinical stages of AD [5], including cognitively unimpaired biomarker negative, unimpaired biomarker positive, mild cognitive impairment (MCI), and dementia due to AD.

1.1 Primary Objectives

Specific Aim 1). Determine the extent to which [C-11]UCB-J provides unique information from MRI regarding neurodegeneration. Approach: We will recruit N=60 cognitively unimpaired participants, N=30 MCI participants, and N=30 participants with AD dementia to undergo PET imaging with [C-11]UCB-J. MRI will include anatomic and diffusion connectivity MRI. When available, ancillary cerebrospinal fluid (CSF) indicators of neurodegeneration and synapse function will be examined for relationships with UCB-J.

Specific Aim 2). Determine the rate of synapse loss as reflected by [C-11]UCB-J signal across all participants. Rationale: Trajectories of synaptic loss are unknown *in vivo*. Approach: We will determine the longitudinal trajectories of regional synapse loss that are observed over time among participants who undergo repeat [C-11]UCB-J (separated by two years, same participants scanned for Aim 1). We will also examine trajectories by amyloid and tau load. Quantifying longitudinal synaptic loss is expected to eventually facilitate the identification of individuals who are progressing to dementia, as well as inform upon changes that are normal for age.

Specific Aim 3). Determine the extent to which [C-11]UCB-J associates with cognitive decline. Rationale: We expect that lower baseline SV2A density and longitudinal decline in SV2A density in the medial temporal lobe will be associated with faster progression of cognitive decline. We will also test the extent to which harboring multiple pathologies (↑amyloid, ↑tau, and ↓SV2A density) contributes to cognitive decline. Approach: We will examine core indices of cognitive status and continuous measures of cognitive function from the source cohorts and utilize mixed effects models to ascertain the effect of UCB-J amyloid and tau on

cognition.

Specific Aim 4). Determine factors which impact synapse loss. Rationale: Several risk factors for cognitive decline and dementia have been identified including potentially modifiable factors such as insulin resistance and vascular risk factors. Approach: We will determine cross-sectional and longitudinal trajectories of regional synapse loss in relation to risk factors for cognitive decline and dementia. In order to determine insulin resistance, we will perform blood draw and assess fasting glucose and insulin values to determine the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR). The impact of potentially modifiable risk factors on synapse loss in vivo is currently unknown. This aim will address this gap in knowledge, results which may translate to strategies for reducing dementia risk.

2 BACKGROUND AND STUDY CONTEXT

2.1 Background

A critical gap in the field is the ability to predict with greater certainty who with AD pathology will progress to symptoms, and when. This project will focus on synaptic degeneration as an early marker of neurodegeneration and will address important as yet unanswered questions regarding the temporal occurrence of synaptic decline in relation to amyloid and tau pathology. There are clear implications of such new knowledge from this project in concepts relating to brain resiliency as embodied by synapse health, and to improved accuracy of cognitive prognosis.

Synapse loss in AD. Synaptic loss is a key feature of AD, associated with progression from healthy cognition to dementia, and preceding neuronal degeneration [6-8]. Even early in the disease, synapse density is reduced by up to 30%[8]. Neurogranin, a postsynaptic protein primarily localized to the cortex, hippocampus, and amygdala, has been used as a cerebrospinal (CSF) biomarker of synapse loss in AD. Using CSF neurogranin, several in vivo studies indicate that synapse loss is a feature of dementia and prodromal AD. CSF neurogranin levels are elevated in patients with AD and MCI compared to controls [9-11] and this elevation appears specific to AD compared to other neurodegenerative diseases [12]. Moreover, higher CSF neurogranin levels predict conversion from MCI to AD and correlate with a greater rate of cognitive decline in MCI [13,14] and older controls [15]. While CSF biomarkers may inform upon development of AD pathology, they do not provide regional information concerning brain areas affected by disease. Regional information obtained in vivo will be especially important given mixed literature[16-19], and limitations in regional sampling imposed by the logistics of post-mortem examination. Imaging measures, such as PET, can inform upon specific regions affected by disease, as well as the heterogeneity of disease progression. The temporal relationship between the development of amyloid and tau pathology and synapse loss in AD is unknown. This project will begin to address this gap in knowledge.

PET imaging of synapses. PET imaging of synapses is a newly developed methodology but expected to lead to substantial gains in knowledge of the progression of AD. Development of synapse imaging was born out of a medicinal chemistry program to identify antiepileptic drugs

with increased affinity at synaptic vesicle glycoprotein 2A (SV2A) which is expressed in synaptic vesicles throughout the brain. Research focused on developing PET ligands with high SV2A affinity and desirable absorption, distribution, metabolism, and excretion properties led to the development of several compounds with favorable in vivo imaging characteristics [3]. Of these, [C-11]UCB-J is the most recently developed and demonstrates high brain uptake, fast kinetics, rapid metabolism, and is safe for multiple administrations[3,20].

3 STUDY DESIGN

Design: Participants will be recruited to participate in this longitudinal imaging protocol and be scanned with [C-11]UCBJ (synapse abundance), [F-18]MK6240 (tau tangles), [C-11]PiB (fibrillar amyloid). Additionally, participants will undergo an MRI (if one has not been done in the last 12 months), have genetic testing (if not already done with ADRC/WRAP), and plasma/serum will be collection for storage. Participants will, also, have the option of completing a lumbar puncture and FDG PET scan. Procedures occurring at baseline may be repeated approximately 24 months later. See table 1 in section 5: Study procedures.

Patient groups: We will study approximately 120 participants who all fit within two broad cognitive groups: 1) cognitively unimpaired, or 2) with cognitive impairment spanning the MCI to mild dementia clinical stages due to presumed underlying AD etiology.

Study Location: The entire study including subject recruitment, imaging and analysis will take place at the University of Wisconsin-Madison medical campus including the following sites:

- Waisman Center Laboratory for Brain Imaging and Behavior: where PET and MRI imaging will occur as well as analysis.
- Wisconsin Institute for Medical Research WIMR: where MRI may occur and backup PET scanners are located.
- Alzheimer's Disease Research Center (ADRC) Imaging Core in the CSC J5/Mezz; K6/3 and K6/4 areas of the CSC. At the ADRC Imaging Core, the images will be backed up, maintained, and analyzed.
- Clinical Research Unit: where blood draws and lumbar punctures will be performed.
- Virtual visits for completing questionnaires, the consent addendum, disclosure, and optional disclosure follow up visits, if applicable, may occur via phone call or UW approved HIPAA compliant video conferencing software, in addition to UW locations.
- Dr. Pryzbelski's clinic: where biomarker disclosure visits may occur

Enrollment Window and Study Duration: Recruitment and enrollment will require as much as 2.5 years. Applicable longitudinal imaging may occur about 104 weeks plus/minus 16 weeks after baseline imaging.

4 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

Cognitively unimpaired adults:

- Age: Between 55 and 89

- Normal Cognition: Results of most recent testing with the source cohort indicate the participant is cognitively unimpaired as judged by consensus or expert review
- General health: Good general health with no conditions/medications affecting cognition or imaging
- Commitment to imaging: Willing to undergo [C-11]UCB-J, [C-11]PIB, [F-18]MK6240 PET scans
- An adequate MRI exam within 12 months prior to baseline. An MRI will be performed if not already available.

Mild Dementia and amnestic Mild Cognitive Impairment

- Age: 50 years or older
- Abnormal cognitive status of MCI or dementia as judged by consensus or expert review using NIA-AA 2018 criteria[5]
- MCIs must be affected in the memory domain but may also have other affected domains
- Commitment to imaging: Willing to undergo [C-11]UCB-J, [C-11]PIB, [F-18]MK6240 PET scans. An adequate MRI exam within 12 months prior to baseline. This MRI exam will come from ADRC/WRAP studies. Clinical MRI's (ones obtained outside of our research program) will not be adequate. An MRI will be performed if not already available from within the research program.

4.2 Exclusion Criteria

Candidates meeting any exclusion criteria at screening are not eligible for inclusion:

- For women: pregnant, lactating or breastfeeding or intention to become pregnant
- Evidence of unstable or untreated clinically significant gastrointestinal, cardiovascular, hepatic, renal, hematological, neoplastic, endocrine, alternative neurological, immunodeficiency, pulmonary, or other disorder or disease. Stable, treated chronic medical conditions like hypertension, hypercholesterolemia, diabetes mellitus, non-metastatic dermatologic or prostatic cancer, etc. are acceptable as long as they do not, in the study investigator’s opinion, contribute to cognitive dysfunction or limit participation in study procedures.
- Any illness or other consideration that makes it unlikely that the subject will be able to complete the 24-month study
- Current or prior history (within past 5 years) of significant alcohol or substance abuse as determined by the investigator
- Psychiatric disorders that may interfere with the study including current major Axis I DSM-V disorders including but not limited to severe Major depression, current or history of bipolar I disorder, or schizophrenia
- Current use of the anti-seizure medication Levetiracetam, also known as Keppra, Spritam or Roweepra
- Lack of decisional capacity at the time of informed consent
- MRI exclusion criteria include:

  - Findings from previous MRIs within the ADRC/WRAP research program that may be responsible for neurologic status of the subject such as significant evidence of cerebrovascular disease with multiple infarcts, infectious disease, space-occupying lesion, normal pressure hydrocephalus, CNS trauma, or any other structural abnormality that may impact cognition or image analysis, as judged by the investigator
  - MRI-incompatible implants or devices such as certain cardiac pacemakers or defibrillators, insulin pumps, cochlear implants, metallic ocular foreign body, implanted neural stimulators, CNS aneurysm clips, and other medical implants that have not been certified for MRI, or history of claustrophobia in MRI that prevents completion of MRI protocol
- Lumbar puncture exclusion criteria include:
  - Previous lumbar spine surgery
  - Taking blood-thinning anti-platelet medications
  - Taking immunosuppressive medications
  - Being treated or were recently treated for an infection or virus within the last 2 to 3 months

4.3 Study Recruitment Plan and Enrollment Procedures

- Participants may already be in the ADRC clinical core cohort (2015-0030), the WRAP cohort (2016-0634), or other relevant ADRC-linked studies. Participants may have had an applicable MRI with the ADRC, WRAP, or appropriate linked study. When this is the case, we will accept the prior MRI instead of repeating to alleviate subject burden. When participants consent to the ADRC clinical core study and WRAP, they agree to be contacted about participation in other studies associated with the Alzheimer's Disease Research Center or WRAP. Participants may, also, be recruited from the ADRC Registry (2016-0735), UW memory clinics, the community, and social media. Subjects will be invited to participate via letter, phone, or in-person discussions around the time of their baseline or regularly scheduled visit. IRB-approved informational materials may be used.

- For participants already in an ADRC-linked study, we will conduct database queries and screens for participants who meet criteria for controls or patient groups.

- From this general pool, case records will be examined further for eligibility criteria and availability of usable MRI.
  - Data reviewed from source protocol records may include memory diagnosis, age, visit date(s), sex, race, education level, parental family history of Alzheimer's disease, cognitive test results that indicate dementia or MCI, cognitive test results on memory and executive function such as list learning, story learning, digit symbol tests, and trails tests. Data reviewed may include prior brain imaging and cerebrospinal fluid test results that indicate possible risk for dementia, genetic test results such as *APOE* allele carrier status, and other medical history that may affect eligibility for MRI and PET imaging such as metal-containing implants, significant neurologic disease or significant medical illness.

- Candidates who are ostensibly eligible on the record review may be recruited into the study in the following ways:
  1. *If the participant is not due for an in-person ADRC-linked study in the near future:* Participants will first be sent a letter in the mail to introduce them to the study. This letter will be followed up with a phone call. The screening questionnaire will be completed if the participant agrees, and then a study visit will be scheduled in which the participant will go over the consent form with a study coordinator.

  2. *If the participant has an upcoming ADRC-linked study visit:* The participant will be approached for recruitment at their study visit. They will be given a study Information Sheet and will go through the screening questionnaire if they agree. If participant would like to take more time to consider, a PET coordinator will contact them at a later date.

  3. *If the participant has an upcoming ADRC or WRAP study visit:* Participants will be sent a reminder letter in the mail for their upcoming appointment, and the letter may include information about this PET scan study opportunity and that they will receive more information at their study visit with either WRAP or ADRC. Participant may also be approached for recruitment at their WRAP or ADRC study visit.

- Reasons for non-participation of eligible unscreened candidates will be logged.

- Interested candidates will be screened for eligibility using a screening form, either over the phone or in person. If all eligibility criteria are met, the participant proceeds to the scheduling of a research visit. A screening log will be kept to record reasons for screen failures.

- Women of childbearing potential will have a urine pregnancy test within 24 hours prior to undergoing each PET scan. The test must be negative to proceed with the scan.

- Informed consent will be required prior to procedures. Only individuals with capacity to consent will be included. Our center has procedures built into the IRB approved consenting process to ensure participants have capacity to consent.

- Exceptions to eligibility criteria are rare but may occur at the discretion of the principal investigators. For example, exceptions may be made related to a participant's potentially confounding data. Exceptions will not be made related to a participant's safety.

5 STUDY PROCEDURES

5.1 Schedule of Evaluations

See Table 1. Completion of study procedures at baseline and potential follow-up visits will take 1-4 days depending on procedures due and the schedules of participants, staff, and facilities.

Table 1. Overview of study design and timeline

Screening by Staff	Baseline	24 months
Prior to baseline	0 weeks (day 0)	104 weeks (±16 weeks)
Medical history, medication review, eligibility determination	Review of medical/surgical history, medications, allergies, family history	Review of medical/surgical history, medications, allergies, family history
	MRI (if not available within 12 months)	MRI (T1, T2, DTI)
	[^{11}C]PiB PET	[^{11}C]PiB PET
	[^{18}F]MK-6240 PET	[^{18}F]MK-6240 PET
	[^{11}C]UCB-J PET	[^{11}C]UCB-J PET
	[^{18}F]FDG PET (optional)	[^{18}F]FDG PET (optional)
	Lumbar puncture (optional)	Lumbar puncture (optional)
	CDR interviews and NPI-Q, GDS, FAS, IQCODE questionnaires (if not done with ADRC/WRAP)	CDR interviews and NPI-Q, GDS, FAS, IQCODE questionnaires (if not done with ADRC/WRAP)
	Diabetes questionnaire	Diabetes questionnaire
	Genetic testing (if not done with ADRC/WRAP)	Genetic testing (if not done with ADRC/WRAP)
	Blood draw: 1. Plasma and Serum: all participants 2. Glucose and insulin: all participants unless performed by parent study (ADRC or WRAP) in last 6 months 3. Whole blood for ApoE: only community/clinic participants	Blood draw: 1. Plasma and Serum: all participants 2. Glucose and insulin: all participants unless performed by parent study (ADRC or WRAP) in last 6 months 3. Whole blood for ApoE: only community/clinic participants
	Physical and Neurological Exam (community/clinic participants or those participating in LP)	Physical and Neurological Exam (community/clinic participants or those participating in LP)
	Neuropsychological testing (community/clinic participants): MoCA, Craft Story (recall immediate & delayed, Benson Complex Figure Copy (immediate & delayed), Number Span test (Forward & Backwards), Category Fluency (Animals & Vegetables), Trails Making Test (A & B), MINT (Multilingual Naming test), Verbal Fluency: Phonemic Test (F,L & C), RAVLT– Version 2 (Immediate, Delayed & Recognition tasks), WAIS-R Digit Symbol	Neuropsychological testing (community/clinic participants): MoCA, Craft Story (recall immediate & delayed, Benson Complex Figure Copy (immediate & delayed), Number Span test (Forward & Backwards), Category Fluency (Animals & Vegetables), Trails Making Test (A & B), MINT (Multilingual Naming test), Verbal Fluency: Phonemic Test (F,L & C), RAVLT– Version 2 (Immediate, Delayed & Recognition tasks), WAIS-R Digit Symbol
	Disclosure of PET scan results (if consented)	Disclosure of PET scan results (if consented)

5.2 Description of Evaluations and Procedures

5.2.1 Screening Evaluation

Screening assessment: After appropriate subjects are identified who meet study criteria, they will be contacted by phone or mail by trained study coordinators and invited to participate. A screening discussion will be completed on the phone or in person. The screening is done to determine whether the participant continues to meet all study inclusion and none of the exclusion criteria and assess eligibility for MRI if applicable.

5.2.2 Consenting Procedure

Before any study procedures are performed, informed consent will be obtained. A single consent form and process will be used. The study coordinator or one of the study

investigators will obtain written informed consent, and the original document is stored in each participant's study binder/folder. The coordinator will review the consent form with participants at the study visit in person. Once review is complete, an assessor will either provide a capacity assessment in person or via phone/internet. Consent and capacity will therefore take place at the same time.

Participants who would like to know their amyloid result will also complete the consent addendum for disclosure of PET scan results. The consent addendum may be completed in conjunction with the main informed consent or after initial study consent and visits if they would like more time to consider the option or would like to opt in after previously opting out of disclosure in the informed consent. The consent addendum may be conducted in-person, via phone call, or via UW approved HIPAA compliant video conferencing software. If the consent addendum is not completed in person, participants will be instructed to electronically sign the document via an FDA Part 11 compliant software. If the participant is unable to electronically sign the consent, the participant will be instructed to mail the signed consent to the study team. In instances of remote consent, in which the study is not able to witness the signing of the consent, the study team will verify the identity of the signer by confirming personal information such as date of birth and current address. Capacity assessment will be completed by study clinician or nurse practitioner for individuals with dementia, as applicable, before a participant with dementia consents to disclosure of results with the consent addendum. If the capacity assessment indicates that the participant lacks decision-making capacity at this point, the participant's assent and surrogate consent may be obtained.

5.2.3 MRI Protocol

If the participant otherwise meets all inclusion and no exclusion criteria, the MRI will be performed if a suitable scan is not available from approximately the prior 12 months to baseline from an affiliated study. If participants report a possible history of metal in their eyes or a history of working with metal (grinding, welding, etc.), they will receive an orbital x-ray to ensure eligibility for MRI. This procedure includes a T1-weighted anatomic volume, a T2-weighted fluid attenuated inversion recovery (FLAIR) scan, and diffusion imaging. These sequences do not take the place of a clinical MRI examination. If clinically significant abnormalities are found, the participant is excluded and referred for further clinical follow-up.

The MRI exams will be performed using a 3T MRI scanner at the Waisman Center or WIMR. The scan duration is typically 60 minutes and no longer than 75 minutes and consists of established as well as innovative locally developed scan sequences. Participants are asked to fast 4 hours prior to MRI.

The MRI procedure is considered complete if a T1-weighted volume, FLAIR, and DWI scan are successfully acquired. When feasible, additional scans will be acquired. The additional sequences will make it possible to conduct exploratory comparisons. Sequences may include:

T1w Brain Volume: This sequence provides high-resolution volume and region quantification. This sequence is required and used for quantifying the PET images.

T2 Fluid attenuated inversion recovery (FLAIR): This is a 3D volume acquisition and is sensitive to ischemic disease and other pathology. This scan will be used to quantify white matter hyper-intensity lesion burden.

Diffusion Imaging: A diffusion-weighted may be performed used for whole brain advanced DTI studies. Diffusion encoding will be performed using multiple shells and multiple directs requisite for NODDI and advanced DTI modeling of white matter tracts.

Other non-required MRI sequences: Additional sequences from the ADRC/WRAP standard protocol may be used to maintain continuity with prior and future MRIs with the program. These are performed when time schedule and tolerability permit and will be used to conduct exploratory analyses.

Quantitative T1 Mapping with MPNRAGE: This is a locally developed anatomical sequence for detailed T1-mapping and tissue segmentation. This is a non-standard sequence conducted in Research mode.

Pseudo-continuous arterial spin labeling (pCASL): This provides a perfusion weighted scan used to assess flow and aspects of neurovascular function.

4D flow: We will use a novel high-resolution flow-sensitive MRI approach to quantify macroscopic CBF in all extracranial and intracranial arteries in a single acquisition. The method developed at UW uses radial undersampling and significantly reduces otherwise prohibitively long scan times for a vascular examination uses *no* exogenous contrast agent. The method allows for coverage of the entire brain, providing high spatial resolution and flow dynamics within an approximately 7-minute exam. This is a non-standard sequence conducted in Research mode.

5.2.4 PET Scans

PIB: The synthesis and PET scanning with [C-11]PiB will be consistent with the methods described in the drug IND. A target dose of 8-15 mCi +/- 10% of PiB bolus is injected over ~30 second infusion with the participant positioned in the scanner. A 70 minute dynamic PET scan will be initiated with the injection of radiotracer. An alternative abbreviated imaging session of 50-70 minutes post-injection may be used if the participant is unable to complete a full 70 minute scanning procedure. If an acceptable PiB scan conducted with our research program is available within approximately 12 months of baseline, this scan will not be repeated.

MK6240: The synthesis and PET scanning with [F-18]MK6240 will be consistent with the methods described in the drug IND. A target dose of 5-10 mCi +/- 10% of MK6240 bolus is injected over ~30 second infusion. Uptake occurs at rest for approximately 70 minutes

followed by imaging across the interval of approximately 70 to 110 minutes from time of injection (thus, approximately 40 minutes of imaging). A 20-minute frame within this window will be considered sufficient for a successful scan. If an acceptable tau scan conducted with our research program is available within approximately 12 months of baseline, this scan will not be repeated.

UCB-J: The synthesis and PET scanning with [C-11]UCB-J will be consistent with the methods described in the drug IND. A target dose of 5-15 mCi +/- 10% of UCB-J bolus is injected over ~30 second infusion with the participant positioned in the scanner. A 70 minute dynamic PET scan will be initiated with the injection of radiotracer. An alternative abbreviated imaging session of 40-70 minutes post-injection may be used if the participant is unable to complete a full 70 minute scanning procedure. If an acceptable UCB-J scan conducted with our research program is available within approximately 12 months of baseline, this scan will not be repeated.

If there is any tracer synthesis failure, we will reschedule the visit to a later date.

PET Scanner: PET imaging may be collected using either a PET scanner or a PET/CT scanner, depending on scanner availability. Participants are positioned headfirst and supine with the canthomeatal line parallel to the in-plane field of view. The CT or a transmission scan is acquired for attenuation correction.

It is possible that this scan will need to be repeated (whether a chemistry issue arose, there was a problem with the scan itself, etc.). An additional CT transmission scan contributes a radiation dose of 0.2mCv, which is less than 1% of the dose received from the entire protocol.

Blood pressure: A participant's blood pressure will be taken before and after each PET scan they participate in.

Disclosure of Biomarker findings to participants: Amyloid PET scan results may provide important helpful information pertinent to a person's diagnosis, clinical care, and personal planning goals. Results of amyloid PET may be disclosed to participants who consent to this and who want to know their results by a trained clinician with expertise in dementia/geriatrics. Study staff will contact participants to determine their interest in learning their amyloid results with a phone call and follow up with a letter, if needed. The study staff will provide and review an educational pamphlet and/or educational PowerPoint slides. They will also conduct psychological screening assessments and a pre-disclosure semi-structured interview to gauge the emotional readiness of the participant to receive these results and to ensure safety after disclosure of results which may include the following: PHQ-4 (Patient Health Questionnaire – 4), C-SSRS (Columbia-Suicide Severity Rating Scale), Alzheimer's Disease Suicide Questionnaire, and INI-AD (Impact of NeuroImaging in Alzheimer's Disease; completed post-disclosure). If the psychological screening assessments

exceed set thresholds, the study team will determine if the participant will either be excluded from disclosure or re-screened at a later date by a clinician prior to disclosure.

These assessments are only applicable for disclosure of PET scan results to participants. If during any of the participant interactions (whether in person, by phone, or video conferencing) the participant expresses concerns, hopelessness, or suicidal ideation, the study coordinator will involve relevant clinical expertise to address participant concerns and issues. Follow up will be initiated by the clinical team when warranted. Participants that exceed set thresholds or do not have emotional readiness at clinician's discretion will be excluded from the disclosure procedure. Participants will be made aware that a study coordinator or clinician will provide a follow-up phone call approximately 24-72 hours post-disclosure to follow up and address any further questions or concerns. Any concerns will be immediately followed up by a study clinician. Participants may be provided with referrals for mental health treatment or encouraged to follow-up with their primary care provider. We are equipped to handle potential negative effects from disclosing amyloid status; however, we anticipate that, similar to other studies, any negative effects will be mild and temporary.

The disclosure of PET results occurs within approximately 12 months of PET scanning visits or consenting to the disclosure process. The disclosure will be completed in-person or via UW approved HIPAA compliant video conferencing software by an experienced clinician, practitioner, or social worker within the ADRC research program. This role will be documented in the delegation of duties log. Standardized talking points will be followed for the disclosure, and the participant will be offered support including clinical referrals as needed, a follow-up letter reiterating the results, and any recommendations, and informing the participant's physician if requested. Participants will be offered optional supportive follow up visits, including a session to discuss lifestyle/risk reduction and/or a session to review community resources and referrals, and participants will be provided with an optional satisfaction measure for quality improvement purposes.

Due to the recent progress of anti-amyloid therapies, participants with a diagnosis of MCI or dementia and with a positive amyloid PET scan may now receive those results at anytime. PET result disclosure may occur with participants who received their PET scan under the ADRC, WRAP, an ADRC-affiliated study, or a WRAP-affiliated study when disclosure under the protocol conducting the scan isn't feasible (e.g. the protocol is in data analysis)

5.2.5 (Optional) Lumbar puncture (LP)

Participants who agree to this procedure will have cerebrospinal fluid (CSF) acquired via LP at baseline (if no sample from the past 18 months is available) and at the end of the potential 2-year follow-up (if no sample from the past 18 months is available). An experienced clinician will collect CSF on all willing and eligible participants according to well-established procedures and the infrastructure of the ADRC. The procedure will be done in the Clinical Research Unit (CRU) after a 4 hour fast. Though, exceptions to the fasting requirement may be made on a case-by-case basis in consultation with a study clinician or PI.

All CSF collection is completed according to the guidelines put forth in the "Biospecimens Best Practice Guidelines for the ADCs" published by the National Alzheimer's Coordinating Center (NACC) and available on their website. CSF collection occurs at approximately the same time at each visit to help control for diurnal variability. LPs will be performed using Sprotte spinal needles, drip method and/or gentle extraction technique. Participants are placed in the sitting position and asked to maximally flex their knees, hips, back, and neck. The skin over the L3-L4 or L4-L5 vertebrae is prepped. 1% lidocaine is used as a local anesthetic, followed by insertion of a spinal needle with an introducer into the L3-L4 or L4-L5 interspace using sterile technique. Approximately 25 mL of CSF will be collected using sterile polypropylene collection tubes. Fresh CSF will be analyzed on the Roche analyzer in-house, and the remainder of the extracted CSF will be aliquoted, frozen, and stored as usual for future assays.

Vitals will be taken at any CRU visit.
CSF samples may be sent to Dr. Henrik Zetterberg—an internationally recognized leader in CSF biomarker analysis—at his laboratory at the Sahlgrenska Hospital Goteborg University in Sweden as a fee-for-service analysis. (APOE genotyping will not be shared outside). All samples will be coded with a unique identifier to keep the laboratory blinded to factors such as subject identity or group.

CSF samples will also be released to the University of Bristol, Dementia Research Group, Bristol, England (Dr. Scott Miners). Dr. Miner's lab will be running new assays to look at Alzheimer's disease and vascular markers.

CSF samples, along with plasma and serum, may also be sent to the Center for Biomedical Research, Ulm, Germany (Dr. Patrick Oeckl) for measurement of markers related to Synapses. Samples will be coded with a unique identifier to keep the laboratory blinded to factors such as subject identity or group.

5.2.6 (Optional) FDG

Participants are studied after an approximately 4hr fast (water is allowed). The blood sugar will be tested (via finger puncture) before an FDG PET scan. Following the 5 mCi (± 20%) injection with [F-18]FDG compound, participants rest in a quiet room. Imaging begins approximately 30 minutes post injection and takes place over an interval of 30 minutes. Our team has obtained PET images for several NIH funded protocols (including the Alzheimer's Disease Neuroimaging Initiative), and thus we are experts in obtaining both of these scans. Amyloid, tau and synaptic density PET images will not typically be clinically evaluated as the clinical relevance of a positive scan is yet unknown. Approximately 30% of cognitively healthy individuals are amyloid positive, and the diagnostic relevance of a positive scan is yet to be determined. FDG-PET scans will not typically be evaluated by a clinician because the clinical utility of this scan in a healthy participant is not known. FDG is an FDA approved tracer; however, this is being used outside of its clinical labeling indications as it is being used for research purposes only.

5.2.7 Genetic Testing

Genetic testing (for the APOE gene) will be conducted on participants who have not had this testing with the ADRC. The result of this test will not be shared back with the participant. Blood will be drawn from subjects for the purpose of genotyping various SNP sequences, including Apolipoprotein E (ApoE), at their baseline visit only (who do not have this information on file). Genotyping will be performed on batches of stored samples of DNA extracted from buffy coat derived from blood collected at baseline. Buffy coat and DNA not used for genotyping will be stored for future use. Results of this genotyping will not be reported to subjects, nor will it be included in their medical records, as the results of this genotyping do not yet aid the participant in future treatment options.

5.2.8 Blood Labs

Blood plasma and serum will be collected from all participants to be stored for future research to look at markers for AD risk factors. Additionally, fasting glucose and fasting insulin will be tested if not already completed by the WRAP/ADRC study the same day. Blood will still be drawn if the participant is not fasting. Both procedures will be done at baseline and the potential follow-up to allow for the analysis of changes that occur over time. This procedure will be done at CRU.

5.2.9 Neuropsychological testing and assessments, physical and neurological exam

Participants who have not undergone neuropsychological testing or physical/neuro exams with the WADRC or WRAP or participant, such as those who are recruited from the memory clinic or community, will be required to do so with this study at baseline and the potential follow up visit. The neuropsychological testing will consist of a multidimensional set of brief measures assessing cognitive, emotional status that can be used as a “common currency” across diverse study designs and settings. These will be supplemented by measures that are consistent with other national studies of AD, such as the NIH-funded Alzheimer's Disease Neuroimaging Initiative (ADNI). Participants will also complete: MoCA, Craft Story (recall immediate & delayed), Benson Complex Figure Copy (immediate & delayed), Number Span test (Forward & Backwards), Category Fluency (Animals & Vegetables), Trails Making Test (A & B), MINT (Multilingual Naming test), Verbal Fluency: Phonemic Test (F,L &C), RAVLT–Version 2 (immediate, delayed & recognition tasks), and WAIS-R Digit Symbol.

For completion of certain assessments, such as the Clinical Dementia Rating [CDR] Scale and IQCode, a family member or a friend will be asked to provide information via the telephone.

All tests will be given by trained personnel and will be standardized for reliable administration. In some cases, the tests may be audio-recorded to make sure we accurately document the participant’s responses.

Physical and neurological exams will be completed by ADRC clinicians. Information on family history, medical/surgical history, medications, and allergies will be collected from participants

from the community, memory clinic, or those without current information with WRAP or ADRC. Participants will be provided forms at a visit. Forms can be completed at a visit, after a visit by phone, or at home then returned by mail.

5.2.10 Consensus Diagnosis (for those not in WRAP or ADRC)

After each study visit, our expert clinician(s) and research staff will meet to review the information we collect about the participants and give their opinion about their diagnostic status. In this meeting, all data will be reviewed from all participants including those with Alzheimer's disease, mild cognitive impairment, and the healthy older controls. Participants' diagnostic status will be reviewed after every study visit since cognitive function might change year after year. No matter the cognitive status, if the memory tests performed in this study reveal something unexpected that is of clinical concern, a study team clinician, with expertise in diagnosing memory disorders, will contact the participant by phone to discuss the results and refer them for clinical evaluation.

5.3 Data collection from source study

This study recruits from WRAP, ADRC, the ADRC Registry, UW memory clinics, linked studies, and the community. Relevant information from those sources will be obtained for analysis under this protocol. Data collected will be both retrospective and prospective. Information to be collected includes the following:

- **Cognitive data** including all relevant psychometric assessments and alpha-numeric results from serial cognitive assessments. Cognitive test results may indicate dementia or MCI. Data collected also includes cognitive test results on global cognitive tests, memory, and executive function such as list learning, story learning, digit symbol tests, and trails tests. Rationale: Using these collected data will facilitate analysis of relationships between disease burden and the presumed cognitive effects.

- **Clinical data** including diagnostic consensus conference summaries. Primary diagnoses (such as MCI or dementia due to AD) and any relevant secondary diagnoses (such as vascular disease) would be captured. Rationale: Diagnosis is a main grouping variable.

- **CSF lab test results** if participants have provided CSF. We will access the results of those tests. Values will include AD-related assays such as tau and amyloid, inflammation assays such as YKL40, neurodegeneration assays such as neurogranin and neurofilament light, and other proteins that are relevant to synapse loss, aging, and Alzheimer's. Rationale: These assays are used to cross-validate the molecular PET scans.

- **Prior imaging** such as existing MRI, PIB and MK6240 images. They will be utilized in analyses. Rationale: Reduce participant burden, minimize exposure to procedures and radiation (e.g., repeating an MRI or PET scan) when existing data is already available, and evaluate longitudinal change in amyloid and tau burden.

- **Questionnaire data** including previously and prospectively collected self-report and informant report data from ADRC and WRAP, such as symptom checklists and surveys such as clinical dementia rating, quick dementia rating scale, informant questionnaire on cognitive decline in the elderly (IQCODE) and independent activities of daily living (IADL). May also include survey results such as sleep surveys, diet surveys, and physical or cognitive activity surveys. Rationale: These questionnaires provide support for diagnostic groups and provide an index of symptom severity and resiliency.

- **Genetics** including *APOE* genetic status. Rationale: *APOE4* is a risk factor for AD and will be analyzed as a predictive marker.

5.3.1 Visit Sharing

Participants in this study are also eligible to enroll in LEAD, ALERTT, LIFE, PREDICT3 and the ADRC/WRAP PET Study. To reduce participant burden, visits may be shared with other studies. In other words, participants may complete more than one study during a single visit. Subjects who enroll in Synapse and ALERTT, PREDICT3, ADRC/WRAP PET Study, LEAD, LIFE, ADRC, or WRAP may undergo shared study visits, in which the relevant collected information will be analyzed in both studies. The synchronization of study visits will be handled by each protocol's primary study coordinator. PET imaging data will be shared amongst studies to reduce the PET imaging burden placed on participants. We will not repeat a PET scanning procedure if a participant has recently had a tau or amyloid PET scan with another study. Participant comfort is assessed at regular intervals. The results of lab tests will be shared across protocols. This will reduce subject burden. Only data and samples approved for collection under the other study's protocol will be transferred from this study. Likewise, only data and samples approved for collection under this protocol will be transferred from the aforementioned studies. Study coordinators of the other protocol will be listed as key personnel on this study. Participants will be enrolled and consented for all studies that are conducted at the shared visit. Study staff from those protocols will already have access to this study's code-name links. As a step to protect confidentiality, data and samples will be labeled with study ID numbers and not names.

5.4 Data Banking:

Data banking is a required component of the study; participants must agree to data banking at the time of consent. Participants may request to have their data withdrawn from the bank, and then, study personnel will remove their data from the bank and will discontinue using it for further research. Data collected from this study will be stored on Department of Medicine computer servers that are password-protected. Banked data is coded with a subject ID. Only approved study personnel have access to the key linking subject ID and identifiable subject information. Unless staff are listed as key personnel on this study, they will not be given access to the code linking subject identity with subject ID.

5.5 Data Sharing:

Banked images and their meta-data from this study will be managed by the ADRC imaging core. Images may be uploaded to the National Alzheimer's Coordinating Center or other NIH-specified repository. The images will be shared back with the ADRC UP protocol (2013-0178), the ALERTT study (2018-1348), the ADRC, and WRAP to address the major specific aims of this project. Once the data is shared with the ADRC UP protocol, the data may be used to address future unspecified research. Other investigators who wish to use these data may contact Dr. Bendlin, and she will collaborate with Dr. Christian and Dr. Johnson to decide how the data from this study are shared. Investigators from other departments within UW, institutions outside UW, and private companies may contact Dr. Bendlin and request the data. Only coded data are shared with researchers that are not listed as key personnel on the projects. The multi-PIs (Bendlin, Christian, Johnson) hold ultimate responsibility for data sharing oversight and will review all requests.

Coded images and AE data pertaining to MK6240 will also be sent to Cerveau Technologies, Inc., the provider of the MK6240 drug precursor. Cerveau will use these data for image quality assurance and drug safety profile tracking. Cerveau maintains safety data for all sites using the MK6240 drug and is responsible for Investigational Drug Brochure updates. In addition to images, Cerveau will have access to brain MR images, unique subject identifiers, amyloid images and status, cognitive metrics consisting of MMSE, ADAS-COG and CDR, weight/height, scan time, MK6240 dose, scan date, clinical diagnosis, demographic information, and smoking status.

Cerveau will provide secure storage of the study data described above, be responsible for transferring MRI and PET images, perform Image data quality control, and ensure consistent image acquisition and transfer via an electronic image submission system. The electronic image submission system is in compliance with 21 CFR Part 11, electronic records, electronic signatures and predicate rules. Compliance is achieved through a combination of SOP adherence and a structured validation system. Security of this system includes the use of passwords that limit user access according to their job responsibilities. Throughout the study, an image data back-up will be performed on data storage systems. Off-site image data back-up will also be performed. Other electronic data (electronic CRFs, audit trails, database contents, electronic documents, etc.) will be stored on a dedicated database server and saved daily throughout the study. Access to the data at the clinical site is restricted to authorized personnel only.

6 SAFETY CONSIDERATIONS

6.1 PET Imaging ([C-11]PiB, [F-18]MK6240, [C-11]UCB-J, and [F-18]FDG radiotracers)

Radiation exposure: PET Imaging ([C-11]PiB, [F-18]MK6240, [C-11]UCB-J, and [F-18]FDG radiotracers) involves exposure to small amounts of ionizing radiation, which has no known or expected harmful effects. The possibility exists for a rare reaction to any of the substances or procedures to which the subject is exposed.

People who live in the US receive on average a total of 6.4 mSv per year. 50% (3.2 mSv) comes from natural background sources (e.g., food we eat, air we breathe) and 50% (3.2 mSv) from human sources (e.g., dental and medical exams).

This study consists of up to 8 PET scans including 4 at baseline and 4 at the potential 2-year follow up. The scans may take place on a PET/CT or just PET machine. The radiation dose calculations include the low dose CT procedure.

C-11 PiB brain scan (2.9mSv at each of two scans = 6.8mSv)
F-18 MK-6240 brain scan (12 mSv = 24 mSv)
C-11 UCB-J brain scan (2.0 mSv at each of two scans = 4.0 mSv)
F-18 FDG brain scan (4.2 mSv at each of two scans- 8.4 mSv)

The four scans together = 42 mSv total potential exposure over the two-year study (baseline and potential follow-up). This is below the guidelines established in 21CFR §361.1 for occupational whole body (Annual Limit - 50 mSv) exposure.

6.2 Risks related to disclosure of PET scan results to participants

Although several studies suggest minimal acute psychological consequences to disclosure of beta-amyloid results or other AD risk information, there is a risk of increased depression, anxiety, or potential for suicidality associated with learning beta-amyloid results. Additionally, there is a risk that participants will make decisions based on beta-amyloid results that impact other psychosocial outcomes (e.g., financial/retirement plans, long-term care plans) that will take longer to fully evaluate. There is a risk that beta-amyloid results will be shared by participants with individuals who are also impacted by the information regarding risk for development of AD, such as family members. If that happens, there could be consequences (emotional, stigma etc.) for both the participant and recipient of the information. It could affect relationships with family and friends, affect employment, or make it harder to get insurance or a job. Although we will not add study information to medical records, we will communicate results to providers at the participants' request, and it is possible that participants could share the information with their healthcare providers who may add it to their medical record. Participants will be informed that this has the potential to impact long-term care insurance applications or other unforeseen consequences regarding medical care.

We will ensure that a number of safeguards are in place to protect participants from any serious, negative effects of disclosure such as completing the psychological screening assessments to assess depressive symptoms, anxiety, and suicidality, the pre-disclosure questions, the post-disclosure questions, providing follow up, and offering optional follow-up support visits to discuss lifestyle/risk reduction and/or community resources and referrals. Participants that exceed set thresholds or do not have emotional readiness at the clinician's discretion will be excluded from the disclosure procedure.

6.3 Adverse Events and Serious Adverse Events Monitoring

The PIs will be apprised of any adverse events and will report any SAEs experienced in the study to the IRB. Although no study related serious adverse events or significant trends have been reported in the combined experience of our institution and other institutions for either radioligand, we will examine AEs for study related trends. If needed, we would modify the consent form after consulting with the CTRC Research Subject Advocate and the IRB.

Vitals are assessed prior to and after the PET scans. The participant is given the study team's contact information so that they may report any adverse events that may occur within the next 24 hours. If any adverse events are discovered, a clinician will continue to follow up with the participant until resolved.

An **adverse event (AE)** is any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome, or disease which either occurs during the study (having been absent at baseline) or, if present at baseline, appears to worsen. Adverse events will be recorded regardless of their relationship to the study.

A **serious adverse event (SAE)** is generally defined as any untoward medical occurrence that results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly.

Participants will be advised to inform us of any adverse events following PET scans.

6.4 Follow-up for Adverse Events

The investigator is obliged to follow subjects with AE's until the events have subsided, the conditions are considered medically stable, or the participants are no longer available for follow up. Subjects who discontinue due to adverse events will be treated and followed according to established medical practice.

7 STATISTICAL CONSIDERATIONS

7.1 Sample Size Justification

Approximately 120 participants will be enrolled. This will provide a sufficient number of cases to achieve the aims described above.

Prospective power was estimated using MedCalc version 18.2.1[30]. Assuming an AUC of 0.73 for discriminating MCI and Control participants [31], and a correlation of 0.77 between synaptic density and cognition [32], with our proposed sample of N_{MCI}=30 and N_{Ctrl}=60, we will have 80% power to detect a 10% improvement in AUC with [C-11]UCB-J. A sample of 30 participants with dementia due to AD will be imaged to obtain qualitative information concerning synapse density loss in phenotypic and biomarker confirmed disease.

8 DATA COLLECTION

8.1 Data Collection Forms

The study coordinator works with the participant at the study visit to collect all relevant data. Case report forms will be generated to record the data. CRFs and all participant specific data are stored hard copy in an individual binder/folder.

9 PARTICIPANT RIGHTS AND CONFIDENTIALITY

9.1 Institutional Review Board (IRB) Review

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the University of Wisconsin-Madison Health Sciences IRB.

9.2 Informed Consent Forms

A signed consent form will be obtained from each participant. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy will be given to each participant and this fact will be documented in the participant's record. Only participants with cognitive capacity to provide consent will enroll in this study.

This study enrolls participants with cognitive capacity, but it cannot be predicted in advance who will lose decision-making capacity over the course of the study. We need to enroll those who are at risk for losing capacity to determine if the synaptic density significantly varies or changes at this stage in the disease. The longitudinal study aims require collecting data on synapse density at time points two years apart.

If the subject has lost capacity to consent during the study, we would request a surrogate to re-consent in their place. Surrogates may include a court appointed guardian or next of kin (in the order of priority): spouse, adult child (18 or older), parent, adult sibling, grandparent, or adult grandchild. If surrogate consent is required, the consent form will be modified to specify surrogate consent and instruct surrogates that their decisions should be based on what the surrogate believes would be desired by the subject. If that cannot be determined, the surrogate would decide based upon what s/he believes is in the subject's best interest.

9.3 Participant Confidentiality

Any data, forms, reports, PET images, and other records will be identified with minimum PHI necessary. A participant ADRC identification number (Participant ID, PID) is used to maintain confidentiality, and the key to the ID code is never released outside the study team. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using PIDs only. Identifying information will not be released without written permission of the participant, except as necessary for monitoring by IRB, the FDA, the NIA, and the OHRP.

9.4 Study Discontinuation

The study may be discontinued by the IRB, the NIA, the OHRP, the FDA, or other government

agencies as part of their duties to ensure that research participants are protected.

10 DATA SAFETY MONITORING PLAN (DSMP)

10.1 Internal Audit and Data Safety Monitoring:

Refer to the Study Monitoring Plan, which is a separate document, for the Data Safety Monitoring Plan. This observational cohort study does not meet the definition of a clinical trial, and an external DSMC is not required from a design standpoint. Further, the radioligand is delivered in tracer quantities and has no pharmacological effect.

The Study Monitoring Plan describes the strategy, responsibilities, and quality management activities in place to ensure adequate protection of the rights, welfare, and safety of human subjects and the quality and integrity of the resulting data, in compliance with applicable laws, regulations, policies, and guidance.

11 DATA MANAGEMENT TOOLS

11.1 CoRRIE – CRM database

Directly identifiable information and indirectly identifiable (identified by study ID number) information will be stored in CoRRIE.

CoRRIE is a contact database that is used by all ADRC-linked studies. It is a web-based, electronic database for contact management that is password-protected and managed by DOM.

In addition to storing the names of those who enroll in this study, the CoRRIE database will also help the staff to manage their contacts with participants. The database allows for the storage of participants' relationship to our program by stating which studies in our program they are enrolled in or have been enrolled in the past. This allows staff to answer the phone call of someone with a memory disorder and be able to tell them when their next visit is and who they will be seeing. The database also allows us to track and assign activities that take place during the course of research (phone calls, letters, screenings). This helps to ensure that participants are not needlessly contacted and overall improves the customer service provided to our participants by the members of our research program. The purpose of storing this data is for programmatic cohesion in working with subjects with memory problems. It is important to know which subjects are enrolled in which studies so that we may provide appropriate coordination of their study visits.

UNIVERSAL IDENTIFIER

An internal ID number is generated by the ADRC CoRRIE database and will have "RMRaic00" added to it to create a unique participant identifier that will remain with the participant from study to study. This number will be used to label brain images collected in affiliated ADRC protocols. This will allow physicians who are reviewing the brain scans to look for brain changes over time.

11.2 PANDA and PACS

Image data management tool: Image data are electronically transferred and stored on servers at the ADRC imaging core, and metadata is inserted into an imaging database called PANDA. Image headers by protocol do not contain identifying information. Additionally, each image is automatically inspected, and any PHI is removed. These resources are maintained by the Department of Medicine. Some derived numeric image data and cognitive and questionnaire data may be maintained in PANDA. User access is protocol specific such that only users authorized to see this study's data will have access.

MRI and PET images labeled with only study IDs as identifiers may also be uploaded to the Dept of Radiology PACS directly from the scanner for radiology over-reads.

11.3 BOOKED

Directly identifiable information and indirectly identifiable (identified by study ID number) information will be stored in Booked. A participant scheduling web application, Booked, has been developed by extending the Booked (PHP) free, open source project. The Booked application can prevent double booking of staff and resources, provide email notification to staff when they are added to appointments, provide email notification if an appointment has been cancelled, and provide email reminders before an appointment starts. Staff can be linked to multiple roles in appointments. The calendar view can be filtered by resource, staff, and study participant. The appointments are color coded by appointment type and staff member. Booked reports can track cancelled appointments, cancellation reasons, appointment types, resource usage, staff hour totals, and staff appointment counts. Booked is limited to https ssl connections. Only users granted protocol specific permissions can log into Booked and view study participant information. It is also important to note that the Booked software is installed on the DOM production server in the DOM server room; therefore, all Booked data will be on the DOM server. Access to Booked via the web is limited to UW Networks. Booked is a free, open source project; therefore, there are no connections or relationships with the Booked software manufacturer. Participant Name, phone number and ADRC Registry ID (2016-0735) are identifiers used in Booked. Booked is an appointment scheduling application, so the participant's name, phone, and Study ID are needed to identify the participant. These identifiers will only be visible to users who are on the protocols that the participant is enrolled in.

12 PRIVACY

12.1 Privacy and Data Storage

Physical data will be kept in locked cabinets in our lab which has space at the UW Hospital. Other data will be kept on the Department of Medicine's secure server and at the Waisman Center server which comports with HIPAA security requirements. Only individuals in our labs will have access to these computers and any PHI. Any data shared with individuals outside of our lab (i.e., papers or presentations) will be coded or anonymized. Each subject will also have an individual study number to code their study data. Names are never entered at the scanner console, only study numbers. Study numbers are used on data collection forms.

Directly identifiable information and indirectly identifiable (identified by study ID number) information will be stored on CoRRIE and Booked.

12.2 CoRRIE

CoRRIE refers to the ADRC Registry Protocol (2016-0735); however, it is also an electronic database/contact management system that stores information (inclusive of PHI) from the 'First Contact Form' as described in 2016-0735 and tracks study participation. The electronic database is web-based, though only accessible within the DOM server, and is password-protected. Data are not stored in temporary files. Registered accounts must be approved by our research staff supervisors, and access/activity in the database will be monitored. Only those listed on the 2016-0735 protocol will be allowed access.

12.3 Booked

Booked is a participant visit scheduling web application that has been developed by extending the Booked (PHP) free, open source project. Booked software has been installed on the DOM production server in the DOM server room. All Booked data will be on the DOM server. Access to Booked via the web is limited to UW DOM Networks. Booked is a free, open source project; therefore, there are no connections or relationships with the Booked software manufacturer, and data will not be stored online with the software manufacturer. Booked is limited to https ssl connections. Only users granted protocol specific permissions can log into Booked and view study participant information. Booked is an appointment scheduling application, so the participant's name, phone number, and Registry ID are needed to identify the participant. These identifiers will only be visible to users who are on the protocols which the participant is enrolled in. The DOM IT department has been consulted with regard to HIPAA security requirements.

12.4 PANDA

PANDA (PAN = Greek prefix meaning 'all'; Data Archive) is a data and imaging management tool that has received IRB approval for use in other ADRC and WRAP linked protocols. Data and images are electronically transferred to PANDA, which is maintained by the ADRC imaging core. PANDA is a Ruby on Rails application using a MySQL backend database, which provides secure web interfaces to a repository of MRI, PET and project-specific variables including neuropsychology, lab results, questionnaires, and participant properties. Security of the database uses best practice guidelines. Viewing and editing data are separately granted permissions and are access-controlled at the project level. Editing of data will be locked to all but the DBA. In all cases, this also requires a user to be listed on the IRB-approved protocol (via ARROW study team list). For security, all login and query downloads are logged and traceable by user and date. Further, any logged query, including table fields and selection criteria, may be reconstructed at a later date for auditing if needed. The DBA has an interface to view the queries by user/time. As imaging data cannot be uploaded, it is the image metadata that are uploaded into the SQL database; the images themselves are stored on a secure DOM server in the imaging core as well as in Waisman Center brain imaging lab. Data

are transferred to database users using https downloads of queries in CSV text files that can subsequently be imported into statistical analysis software.

12.5 REDCap

REDCap is an electronic data management system that will be used to capture, edit, manage, and export study data (inclusive of PHI) for analysis. REDCap is a mature, secure web application that can be used to collect virtually any type of data; it is specifically geared to support data capture for research studies. The REDCap Consortium is composed of 2,514 active institutional partners in 116 countries who utilize and support REDCap in various ways. All communication between the clients and the REDCap application takes place via Hypertext Transfer Protocol over Secure Socket Layer or HTTPS. HTTPS provide the ability for normal web-based communication over an encrypted Secure Socket Layer (SSL) connection. This ensures that data passing between the client and REDCap is protected.

The REDCap server is housed in a state-of-the-art data center managed by the UW SMPH network staff. The levels of security for the server are fivefold and include:

1. Physical Security
   The server is located in a secure data center under control of UW School of Medicine and Public Health (SMPH) ITS. The server is in a dedicated computer machine room (passkey access only) containing emergency backup power, an uninterruptible power supply (UPS), and an automatic fire detection and suppression system. SMPH ITS does not have access to the DOM REDCap server.

2. Access controls
   Data access is limited to DOM Faculty and staff-approved individuals.

3. Domain access restrictions
   Access to DOM computing resources, including the DOM REDCap Server, is restricted to individuals with a login ID for the DOM Domain. Login IDs are issued only upon approval of the Administrator or Principal Investigator (Data Custodian). Login IDs are only issued upon confirmation that the individual has completed appropriate training.

4. Authentication
   Password protection is used at the network level for all transactions that allow entry and editing of data, provide access to EPHI data, or administrative activities.

5. Firewall
   The DOM REDCap server is located behind the UW-Madison SMPH firewall. The SMPH firewall does not allow outside access to the server itself. Outside access to the application is allowed through a combination of firewall rules, reverse proxy access, and directory level user authentication.

The REDCap database is backed up hourly, daily, weekly, and monthly. These backups are stored in an offsite datacenter. The files on the REDCap server are backed up daily and stored in an offsite datacenter.

Within the REDCap software itself, there is an audit trail that includes all operations performed on the data. Viewing data or exporting data will trigger a record in the audit log. Each audit record includes the operation, date, time, and the user who performed the operation.

At the server level, logs are compiled to track users who login to the server. The server is only accessed directly by administrators for administrative or maintenance purposes. Any failed login attempts are tracked in order to log potentially malicious activity.

12.6 FreezerPro

FreezerPro is a sample management system created by Brooks Automation, Inc. that will link each participant's study visits and their associated biological sample collection kits. The application and data will be hosted on the DOM server. Access to the web application is managed through DOM LDAP authentication and FreezerPro's role-based authorization. Access to the system is encrypted via HTTPS/TLS secure handshake certificate, and it is not accessible from outside the DOM network. Registered accounts must be approved by our research staff supervisors, and access/activity in the database will be monitored by system-specific supervisors. Additionally, the database will be accessible to a limited number of users (coordinator, PI, and other laboratory personnel) with password protection.

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