Study Title: Stimulation to Improve Memory: Alzheimer's Disease Biomarker Education, Decision-Making, & Disclosure

NCT: NCT04818255

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STIM+ Bioethics Supplement Study Protocol

PARENT STUDY TITLE: **Treating Mild Cognitive Impairment with Transcranial Direct Current Stimulation**

PARENT STUDY SHORT TITLE: Stimulation to Improve Memory (STIM)

FULL STUDY TITLE: **Stimulation to Improve Memory: Alzheimer's Disease Biomarker Education, Decision-Making, & Disclosure**

SHORT STUDY TITLE: **Stimulation to Improve Memory: PET Disclosure (STIM+)**

Protocol Amendment Number: 01

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Trial Sponsor: NIH/NIA

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Public Title: Alzheimer's Disease Biomarker Education, Decision-Making, & Disclosure

Countries of Recruitment: United States of America

Problem(s) Studied: Alzheimer's Disease; Positron emission tomography-based amyloid and tau disclosure

Intervention: Education: Behavioral Intervention to maximize comprehension and facilitate informed decision-making

Disclosure: Behavioral Intervention to maximize comprehension and facilitate positive and adaptive psychological and behavioral reactions

Key Inclusion Criteria:	Education: Enrollment and completion of all study-related activities in one of the parent studies; complete and interpretable PET amyloid data (tau data recommended but not required); for participants with Dementia – Alzheimer's Type (DAT), the presence of a co-participant is required; for participants with Mild Cognitive Impairment (MCI), co-participants are strongly encouraged unless the participant has a legally authorized representative or power or attorney for medical/research decisions; for those completing virtual visits: laptop, desktop, or tablet (>9.7" diagonal width) and stable, secure internet connection required; prior established relationship with a PCP, geriatrician, or mental health professional. Disclosure: Same as Education portion, plus requirement for demonstrated intact decisional capacity for PET amyloid and tau disclosure
Key Exclusion Criteria:	Education: Baseline severe or untreated active depression/anxiety or other severe psychological diagnosis, other significant neurological insult or diagnosis, severe and untreated substance use disorder, severe hearing or vision impairment Disclosure: lack of participant/designated other decisional capacity
Study Type:	Interventional, single-group design
Primary purpose:	Education: Complete educational presentation about Alzheimer's Disease (AD), Dementia-Alzheimer's Type (DAT), amyloid and tau PET imaging as it relates to AD diagnosis, and risks and benefits of learning this personal health information; measure comprehension and decisional capacity for PET disclosure among symptomatic participants and/or their co-participants. Disclosure: Complete personalized PET amyloid and tau disclosure protocols with participants and family members of diverse racial-ethnic backgrounds; investigate initial outcomes including comprehension/recall of results, positive and negative psychological reactions, perceived disease stigma, and future time perspective immediately following disclosure, within 1-week post-disclosure, and at 6-weeks post-disclosure
Phase:	I/II (Part II: Disclosure)
Date of First Enrollment:	10/1/2020
Target Sample Size:	100
Recruitment Status:	Currently recruiting
Primary Outcomes:	Part I Education: (a) Interest in receiving PET amyloid and tau feedback prior to and after education (b) participant decision-making capacity for disclosure Part II Disclosure: (a) Comprehension/recall of personal risk information (b) Positive and Negative Affect Scale (c) Impact of Genetic Testing – Alzheimer's Disease (Revised) (d) Stigma Scale for Chronic Illness (e) Self-Efficacy for Managing Chronic Disease (f) Future Time Perspectives Scale

SECTION 1: Roles & Responsibilities - Contributorship

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Roles & Responsibilities:
Design conception and initiation
Mentorship of ARF
Preparation of manuscripts

Annalise Rahman-Filipiak, Ph.D. (*ARF*) – Principal Investigator

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Roles & Responsibilities:
Design conception and initiation
Preparation of protocol and revisions
Managing correspondence with clinical trials office
Publication of study reports
Preparation of manuscripts
Recruitment and screening of patients
Data collection
Data entry, verification
Statistical Analyses
Regulatory and compliance management/adverse event reporting

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Roles & Responsibilities:
Design conception and initiation
Mentorship of ARF

Marie Milliken, MSW (MM) – Research Associate/Study Social Worker

Data collection
Participant support

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Roles & Responsibilities:
Preparation of protocol and revisions
Data collection
Data entry, verification
Statistical Analyses
Preparation of study reports
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Roles & Responsibilities:
Preparation of protocol and revisions
Preparation of study reports
Preparation of manuscripts
Recruitment and screening of patients

Data collection
Data entry, verification
Statistical Analyses
Regulatory and compliance management/adverse event reporting

BMH/ARF conceived of the study, developed and refined the study protocol, and are responsible for study implementation, including data collection, entry, and management. *JSR* will oversee implementation of the education and disclosure protocols. *MM* will be responsible for outcome data collection and will be responsible for providing support and resources for participants and their families during, between, and after study sessions. *SJF* will be responsible for assisting with revisions to protocol as needed, data collection and data entry. *ML* will be primarily responsible with administrative aspects of the study, including screening and scheduling of participants and co-participants for all sessions, data collection and data entry, and preliminary statistical analyses. *BMH*, *ARF* and SJF will complete statistical analysis, prepare manuscripts and presentations, with editing input from other collaborators. *ARF* will manage the clinical trial registry, preparation of institutional review board materials, administrative duties, and auditing/reporting requirements for the various agencies associated with the study.

Roles & Responsibilities – Sponsor(s)/Funder(s)

This project was supported via a bioethics supplement award granted to BMH from the NIH/NIA, to extend the work of the parent study. The funding source had no role in the design, execution, analyses, or interpretation of the study, nor will it have a role in the decision to submit results.

SECTION 2: INTRODUCTION

SECTION 2.1: Background & Rationale

The **central goal** of this supplement is to begin addressing a vital "communication" gap that occurs between the collection of biomarker data related to Alzheimer's disease (AD) and related dementias and the absence of methods to disclose this information to patients and their care partners, as applicable. The longstanding justification that disclosure is not appropriate or necessary given the lack of pharmacologic treatment options is now thoroughly undermined by evidence that lifestyle[1-2] and other non-pharmacologic interventions[3-4] may alter clinical progression. Regardless of whether asymptomatic[5-6] or symptomatic[7-10], patients almost universally demonstrate strong interest in knowing their biomarker-based risk information, and seek to use this information to plan health behavior or lifestyle change[5,11-15]. The combination of this literature and our preliminary data below demonstrate a clear benefit of, and participant interest in, knowing biomarker status. Thus, we directly address the **first ethical dilemma** that potentially impactful information is being intentionally withheld from our participants.

The current project leverages a robust recruitment and characterization pipeline formed through the Stimulation to Improve Memory study (STIM; R01AG058724) as well as empirically-derived methods from the Sharing Alzheimer's Risk Estimates (SHARE; R03AG063222-01) study. STIM will ultimately enroll up to 240 individuals with mild cognitive impairment (MCI) and dementia of the Alzheimer's type (DAT) to evaluate the dose-response relationship associated with transcranial direct current stimulation. Each participant receives both amyloid and tau positron emission tomography (PET), which are used as participant-specific factors that may affect tDCS efficacy. We did not include biomarker disclosure in STIM because it was outside of the scope of the intervention-related focus. Moreover, it was not clear at the time of the initial submission whether participants would be interested in receiving feedback about their biomarker status. Approximately 3 recruiting quarters into the study, there is now substantial evidence that participants ***want*** the information. Thus, the STIM infrastructure provides an ideal testbed for developing/refining feedback methods for cognitively symptomatic individuals. To improve enrollment and in response to overwhelming interest in biomarker disclosure, we are also opening up this study to participants from other studies co-enrolling through the Michigan Alzheimer's Disease Research Center that include PET amyloid (and tau, if available) imaging, as long as they meet other criteria detailed above. These additional 'parent' studies include the Driving and Physiological Responses (DAPR; HUM00183327), Brain-Behavior Characterization (BBC; HUM00200763) and Dementia in African American Population Phenotyping from Potential Elevated Risk (DAPPER; HUM00152159) studies.

We have **preliminary data**, acquired from Co-I Rahman-Filipiak's R03-funded study investigating older participants' interest in biomarker-based feedback, that shows a clear majority of participants have moderate-strong interest in learning their amyloid and tau status (Table 1). In fact, these initial data indicate that participants have equal if not stronger interest in biomarker disclosure as compared to other sources of health information (Table 1). Furthermore, 100% of participants interviewed to date would elect to learn their Alzheimer's-related biomarker status if it were available, regardless of race, gender, or whether they were cognitively symptomatic or healthy. These findings mirror preliminary data gathered from those currently

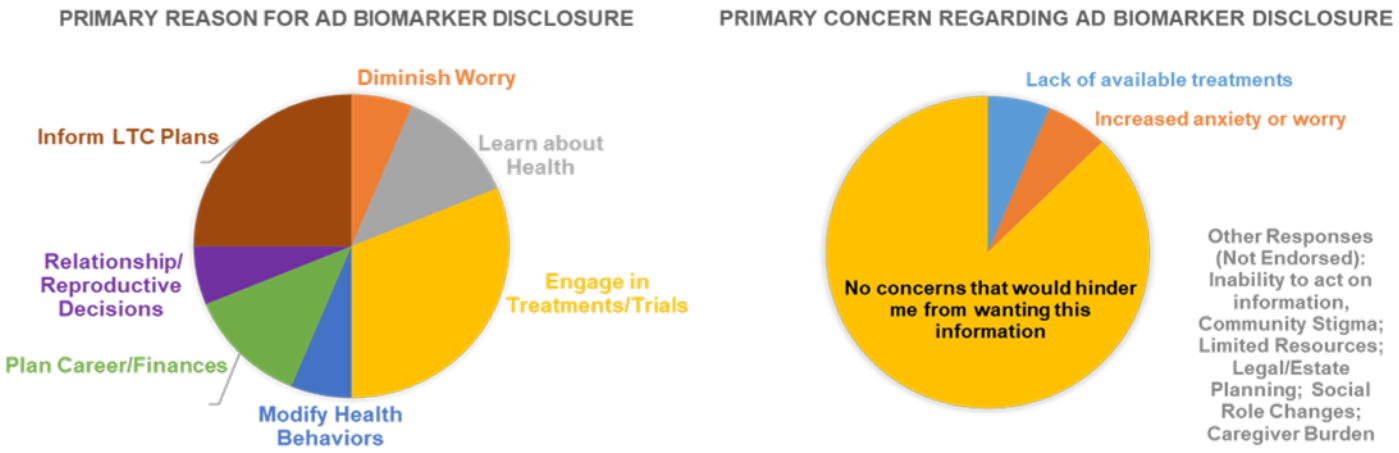
Table 1. Preliminary Biomarker Disclosure Interest Data

Interest Level	Clinical Information	Structural Neuroimaging	APO-E Genotype	Amyloid/Tau Status
No Interest	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Very Minimal Interest	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Neutral Interest	0 (0%)	1 (6%)	1 (6%)	0 (0%)
Moderate Interest	1 (6%)	1 (6%)	1 (6%)	2 (12%)
Strong Interest	15 (94%)	14 (88%)	14 (88%)	14 (88%)
Would you engage in elective disclosure about your risk for AD based on these variables?				
No	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Yes	16 (100%)	16 (100%)	16 (100%)	16 (100%)

enrolled in STIM (in which the study team does NOT mention disclosure options): of the 31 enrolled participants, 42% spontaneously requested feedback about their amyloid and tau imaging, and 23% mentioned significant disappointment or distress that the current protocol does not allow for disclosure of this information. Additionally, two participants were previously interested in the study but declined to enroll after learning that feedback was not currently provided.

The ethical principles of patient autonomy and beneficence must be carefully weighed against non-maleficence and protection of the potentially vulnerable population of cognitively impaired older adults[16]. AD Biomarker disclosure can occur only if patients (or their designated signors) fully understand the information to be shared, and appreciate the risks and benefits of knowing this information. Preliminary data from Co-I Rahman-FIlipiak's R03 demonstrate that participants request risk disclosure for a variety of perceived benefits; however, 88% endorse having 'no concerns' about risks of amyloid or tau disclosure (Figure 1). These data, while likely reflective of a strong desire for disclosure in the larger population, indicate a **second ethical dilemma**: whether to share information with symptomatic participants who may have impaired decision-making capacity to engage in amyloid/tau disclosure.

Figure 1. Participants' perceptions of primary benefits and risks of AD biomarker disclosure (data from Co-I Rahman-Filipiak's R03)



Finally, results of the prior literature suggest that disclosure of biomarker information related to AD is both safe and well-tolerated among cognitively healthy participants. Studies examining post-disclosure psychological reactions are very limited in individuals with mild cognitive impairment, and non-existent for individuals already diagnosed with DAT. Further, no prior study has examined the impact of symptomatic patients' biomarker information on care partners who are likely impacted by their partners' health information related to AD and who are also likely to have a pivotal role in their partners' health care and future care in the event of worsening cognitive impairment. Additionally, prior studies have exclusively considered the negative psychological effects of risk disclosure, rather than the full range of emotional reactions and the empowering results that may follow disclosure. Therefore, we address this **third ethical dilemma** by evaluating both positive (e.g., relief, happiness, satisfaction, empowerment) and negative (e.g., depression, anxiety, anger, distress) effects of biomarker disclosure on symptomatic participants and their co-participants (e.g., care partners).

SECTION 2.2: Objectives & Hypotheses of the study

Preliminary data gathered from the Stimulation to Improve Memory (STIM) study and an associated research project have highlighted several unforeseen but compelling needs in regards to sharing of Alzheimer's disease (AD) biomarker information with research participants and patients alike. The proposed ethics supplement addresses three of these needs, each of which represents an ethical dilemma underlying the communication gap in AD biomarker research: 1) the withholding of biomarker information from interested participants, 2) the unknown ability of cognitively symptomatic patients to appreciate risks and benefits of biomarker disclosure, and 3) the psychological ramifications of biomarker disclosure in cognitively impaired patients. We will leverage STIM infrastructure to systematically address these questions through three specific aims:

Aim 1 investigates interest in, and follow through with, amyloid and tau status disclosure in individuals diagnosed with MCI and DAT. At the time of study enrollment, we will offer all parent study participants the opportunity to learn their amyloid and tau status upon completion of parent study procedures; recording preference as appropriate. We will then examine follow through rates (i.e., interested vs. completed disclosures) thereby extending the literature. We predict *an equally high interest in, and completion of, disclosure regardless of diagnosis*.

Aim 2 examines whether cognitively symptomatic participants demonstrate decision-making capacity as it relates to biomarker disclosure. The question of whether research participants can demonstrate decision-making capacity for biomarker disclosure has, to our knowledge, never been addressed in cognitively symptomatic individuals. Thus, we fill a critical void by evaluating whether such "patients" adequately demonstrate the fundamental elements of decision-making capacity (understanding, appreciation, rationale, communication)[17]. Prior to disclosure, we will use a standardized, clinician-rated measure to evaluate capacity. *We predict a main effect of diagnosis where DAT participants demonstrate poorer decisional capacity relative to MCI*. Importantly, we overcome this predicted difference by providing disclosure to either the impaired participant's legally authorized representative or their healthcare provider. In this way, we ensure the desired information is relayed to each interested participant while still achieving the study aims.

Aim 3 will determine immediate and prolonged psychological reactions to biomarker disclosure among participants with MCI and DAT and their respective co-participants (e.g., care partners). We will assess changes in psychological status (both positive and negative) at two time points following disclosure relative to baseline. While one could predict changes in either direction, the above noted paucity of data in this area undermine the validity of such predictions. Thus, this aim is more descriptive in nature and provides critical information about cognitively symptomatic participants' response to biomarker disclosure that will guide future research and translational efforts.

Aim 4 examines the impact of biomarker disclosure on co-participants as it relates to caregiving readiness and self-efficacy. We will assess changes in perceived readiness to provide care (to the participant) and caregiving self-efficacy at two time points following disclosure relative to baseline among co-participants who are either currently providing care to participants with MCI/DAT or who will hypothetically take on the caregiving role should the need arise. We predict that caregiving preparedness will be associated with the participant's disclosed amyloid/tau result; specifically, an 'elevated' biomarker result is hypothesized to be associated with greater caregiving preparedness. Conversely, it is hypothesized that co-participants will have lower perceived readiness for caregiving if the participant's amyloid/tau result is 'not elevated.'

SECTION 2.3: Trial Design

The Education portion of the study is considered a Phase I/II Behavioral Intervention clinical trial without randomization. The Disclosure portion of the study is considered a Phase I/II Behavioral Intervention clinical trial without randomization, with the disclosure feedback serving as the intervention. The study will use a single-group design. All 100 participants (and any co-participants attending the first session) will complete the educational presentation and undergo an assessment of comprehension and decisional capacity. Those participants or dyads who meet criteria and demonstrate intact decisional capacity will be offered feedback about the participant's PET amyloid and tau results. Outcomes will be measured immediately following feedback, within one week of disclosure, and at six-weeks post-disclosure. For more information regarding design, see *Methods* section.

SECTION 3: METHODS

SECTION 3.1 Participants: Inclusion & Exclusion Criteria

The proposed supplement directly extends STIM study infrastructure (Figure 2). All participants will complete parent study procedures (including amyloid and tau PET) before engaging in the activities of this supplement.

Participants: All participants (i.e., those with MCI and DAT) enrolled in STIM (HUM00146180) will express their interest in biomarker disclosure (Aim 1); however, only those who actually complete PET imaging will be eligible to receive this information (otherwise there is no information to disclose). Specific inclusion and exclusion criteria for STIM are included below:

STIM Inclusion Criteria:
(1) Diagnosis of MCI or DAT
(2) Age 55 and older
(3) MRI-compatible
(4) Stable on medications for 4 weeks prior to study enrollment

STIM Exclusion Criteria:
(1) Other neurologic disease (e.g., epilepsy, stroke, traumatic brain injury)
(2) Psychiatric conditions (e.g., moderate-severe depression, bipolar disorder, schizophrenia)
(3) Sensory impairments that limit the ability to take part in the study
(4) A significant history of, or current alcohol or drug abuse/dependence
(5) Are left-handed with right hemisphere language lateralization

We will additionally invite participants who have completed PET amyloid (and ideally tau) scans through other MADRC-co-enrolled studies (DAPR [HUM00183327], BBC [HUM00200763] and DAPPER [HUM00152159]) to take part in this bioethics supplement, provided they have a diagnosis of MCI or DAT and meet with the additional study-specific criteria below.

Additional inclusion/exclusion criteria for the Education portion of the study are included below:

Part I Education Inclusion Criteria:
(1) Complete and interpretable PET amyloid and tau imaging
(2) For those completing virtual sessions: Laptop, desktop, or tablet with 9/7" diagonal diameter and stable, secure internet connection
(3) Established relationship with a primary care provider, geriatrician, and/or mental health professional
(4) Co-Participant – required for individuals with DAT; strongly encouraged for participants with MCI

Part I Education Exclusion Criteria:
(1) Baseline active depression or anxiety or clinically elevated scores on Geriatric Depression Scale – 15 (GDS-15)[25-26] or Beck Anxiety Inventory (BAI)[27-28]
(2) History of significant neurological disease
(3) Current severe or untreated substance use disorder

Part II Disclosure Inclusion Criteria:
(1) Demonstrated intact decisional capacity for amyloid and tau PET disclosure

Part II Disclosure Exclusion Criteria:
No additional criteria

For the proposed study, we will offer all of the participants who have completed all parent study procedures up to and during this one-year supplement funding period (we estimate up to 100 individuals) the opportunity to enroll in the supplement-related procedures.

Co-Participants: Co-participants are required for all participants with a diagnosis of DAT, given the likelihood that participants may have impaired decision-making capacity and/or need additional support following disclosure. Co-participants are also strongly recommended, though not required, for participants with a diagnosis of MCI except in the event a participant with MCI demonstrates impaired decision-making capacity, thus requiring a co-participant. Co-participants are defined as (a) those who are currently serving as a

caregiver to the participant, or would hypothetically serve in this role should the need arise; (b) individuals who know the participant well, as demonstrated by a relationship lasting at least five years, and contact (any modality) at least once per week. Co-participants must also be age 18 years or older, English-speaking, cognitively healthy, and without current severe or untreated depression and/or anxiety.

Of note, if participants have a dedicated legally authorized representative (LAR) or durable power of attorney (DPOA) for medical and/or research decisions, this individual must serve as the co-participant in order for the participant to take part in the study. Documentation of this legal designation must be provided.

SECTION 3.2 Recruitment Strategy

Participants for Part I: Education will be recruited from parent studies via invitation only. The study team will review participants who completed the parent study, screen these cases for any interim changes that might impact eligibility of the participant (or co-participant, if there is one), and contact dyads to determine interest in engaging in STIM+ Education.

All participants who demonstrate decisional capacity for disclosure (or have a co-participant or LAR/DPOA who demonstrate decisional capacity for disclosure) will be invited to take part in Part II: Disclosure by study team invitation.

SECTION 3.3 Procedures

In light of the 2020 global COVID-19 pandemic, we have adapted our procedures to include **the option for virtual, video-conferencing sessions**, to reduce the risk of exposure for our vulnerable study population. The virtual option will be the default offered to all participants. Participants and co-participants must utilize a desktop or laptop computer, or a tablet with a screen at least 9.7 inches in diagonal width to ensure that they are able to view the materials for Part I Education and Part II Disclosure completely. Additionally, participants/co-participants must have access to a stable, secure internet connection (not public Wi-Fi) and a quiet, private space where they will be uninterrupted for the duration of their appointment(s). Those enrolled in the study will be sent private links to engage in a secure video conference session through the Zoom for Health application, a free, HIPAA-compliant service through the University of Michigan.

Participants who do not have access to or comfort with the above technology will be offered the opportunity to take part in an in-person visit following strict Covid-19 safety precautions that include preliminary, day-before, and day-of screening for symptoms using the University of Michigan ResponsiBLUE screening, PPE for participants and study team members, distancing while in the laboratory, and rigorous cleaning and contact tracing procedures. In-person visits and associated procedures will follow recommendations from the Office of Research.

3.3.1 Part I Education Procedures

At the time of enrollment in the parent study, participants will be asked whether they would be interested in receiving feedback about amyloid and tau positivity or negativity from their PET scans (Aim 1). Following parent study completion, up to 100 interested participants and their co-participants (if designated) will be approached for the Education Session. A summary of Part I procedures is included in Table 2.

> Preliminary Screening of STIM Participants: Following study team review of the participant's and co-participant's medical record to ensure no interim changes make either part ineligible, the study team will access the participant's prior parent study involvement to determine whether they have adequate information for risk disclosure. If the participant meets these criteria, the study team will send an email introducing the study (see 'STIM+ Education Script') and begin contacting the participant via phone (see 'STIM+ Part I Oral Script').
>
> Preliminary Screening of Participants from Other Parent Studies: For studies within the Research Program on Cognition and Neuromodulation Based Interventions (BBC), the study team (BMH, ARF, ML) are all part of the larger program and approved study team members on the IRB. For additional

studies [(DAPR (HUM00183327) and DAPPER (HUM00152159)], we will utilize the current MADRC protocol for sharing of eligible participants through the MADRC Data Core.

Virtual Informed Consent: The informed consent document will be emailed to participants and co-participants at the time of scheduling (or earlier by request), to provide the recipient enough time to review the document. Prior to other study activities, a study team member will set up a phone call or video session to review the consent paperwork together. At this phone appointment, a study team member will explain each section of the informed consent document, pausing to answer questions or clarify misunderstandings. The study team member will also use the Consent Decision-Making Capacity Tool to ensure that the individual providing consent is able to fully understand the decision they are making prior to providing consent. After the informed consent document has been reviewed, eligible participants or LARs/DPOAs will review the STIM+ Disclosure Packet Request Form to determine whether they would like to receive a written copy of their results post-disclosure, and whether they'd like to receive them via US mail system or office pickup. After reviewing the forms, participants will be asked to provide electronic signatures on each form. These can be completed through two methods: (a) the patient can download, sign, scan, and email the form back to the study team member, who will additionally sign as witness and study representative, or (b) the Signnow platform will be used to provide electronic consent. SignNow is a secure platform offered through University of Michigan, which is HIPAA-compliant and approved by Health Information Technology Services (HITS). A copy of the forms, with all signatures, will be emailed to the participant/co-participant or made available through SignNow.

In-Person Consent: Participants completing in-person sessions will be encouraged to follow the above procedures to complete the consent paperwork via phone or Zoom prior to their in-person session, even if they choose to sign the consent in person. This will allow the study team to assess consent decisional capacity and walk through the consent form thoroughly before the participant comes into the lab (which may be more burdensome).

Additional Screening & Scheduling: Following receipt of the signed informed consent documents, both the participant and any co-participants will be asked to complete the GDS-15 and BAI via phone or video (these can be conducted on the same call used to complete the consent documentation). Any individuals who score above the clinical cutoffs (GDS ≥ 9; BAI ≥ 16) for these measures will be ineligible to take part in the study, per eligibility criteria noted above. Additionally, all co-participants must be cognitively intact based on screening or recent evaluation. Co-participants whose scores fall below the cutoff for impairment will be considered ineligible for study participation. Their respective participants will also be asked to delay scheduling of their virtual visit until they can identify another interested and eligible co-participant. Once this secondary screening of the subjects has been completed, the study team will schedule the Education session.

Education & Decision-Making Assessment Session: Participants (and co-participants, as applicable) will take part in a single 90-minute session via video conference (see Table 2).

1. Participants and co participants will complete a baseline assessment of their knowledge and understanding of AD biomarker testing procedures, results, risks, and benefits (Disclosure Decision-Making Assessment Tool; see below). Immediately following this assessment, participants will be shown an interactive educational presentation reviewing. AD, DAT, available treatments, and the risks, benefits, and limitations of PET Aβ and tau disclosure in regard to assessing AD pathology and risk for DAT development.

2. Educational Module – The psychoeducation module will consist of a brief, instructor-led Power-point presentation. This didactic will cover the following topics: (a) definition of Alzheimer's disease and dementia due to Alzheimer's; (b) the role of amyloid and tau in Alzheimer's disease; (c) how amyloid and tau were measured in the parent study (i.e., PET imaging, what 'positivity' means in this context); (d) limitations of these measurements; (e) basic AD risk associated with amyloid and tau; (f) potential benefits of knowing one's biomarker status; (g) potential risks of knowing one's biomarker status. This module will include multiple opportunities for the participants and their loved

ones to ask questions. These materials were adapted from existing materials currently used in the Risk Evaluation and Education for Alzheimer's Disease (REVEAL) study, of which Co-I Roberts is Co-PI, as well as Co-I Rahman-Filipiak's R03. Participants will also be provided with written materials summarizing this information. Materials will be written in lay language to accommodate all participants in the study.

3. Disclosure Preferences & Decision-Making Capacity Assessment – The educational module contains several 'checks for understanding' that parallel the questions on the **Disclosure Decision-Making Assessment Tool (DDMAT)** after each section to determine whether the participant fully demonstrates decision-making capacity for risk disclosure (Aim 2). Specifically, to demonstrate *understanding* of the decision, participants or their designated DPOA/LAR will be asked to describe, in their own words, the purpose and procedures involved in personal biomarker disclosure. To demonstrate *appreciation* of the decision, they will be asked to describe possible risks and benefits of personal biomarker disclosure. To evaluate *reasoning*, they will be asked to discuss their personal weighing of these risks and benefits, and alternatives to participation. Finally, they will be asked to *communicate*, either aloud or in writing, whether they would like to move forward with biomarker disclosure. Participants' responses will be recorded and subsequently transcribed for later evaluation of themes and foci. After each question, the clinician will evaluate the response for completion, ensuring it complies with necessary standards. If respondents provide an erroneous or incomplete response (e.g., acknowledging only one of several risks), the examiner will return to the section of the Education module reviewing the missed information, present it again, and then repeat the DDMAT question. If respondents are not able to provide a full, accurate response after such review, the question will be considered 'failed'. To address Aim 2, we will record not only who was able versus unable to demonstrate disclosure decision-making capacity, but also the specific element(s) of decisional capacity that were failed. Such information provides important information about how to better structure content so as to maximize comprehension in future efforts.

   <u>If the participant does not demonstrate disclosure decision-making capacity and does not have a co-participant or LAR/DPOA</u>, the participant's involvement in the study will be complete after this session, and they will not be invited to take part in the Part II Disclosure portion.

   <u>If the participant has a LAR/DPOA co-participant</u>, that individual must demonstrate decision-making capacity for the participant to receive risk disclosure and agree with this decision. Participant decision-making capacity will still be assessed. Regardless of whether the LAR/DPOA wants the participant to complete risk disclosure, the study team will not move forward with sharing the participant's risk information with either party unless assent is provided by the participant. If the participant or designated LAR/DPOA does not demonstrate full decision-making capacity, the study team will not move forward with risk disclosure, and the dyad's involvement in the study will be complete.

   <u>If the participant brings a co-participant who is not the designated LAR/DPOA</u>, the participant may allow that individual to make the decision regarding PET disclosure for them. If this option is selected, the co-participant will undergo disclosure decision-making capacity assessment. Participant decision-making capacity will still be assessed. Regardless of whether the co-participant wants the participant to complete risk disclosure, the study team will not move forward with sharing the participant's risk information with either party unless assent is provided by the participant. If the participant or designated co-participant does not demonstrate full decision-making capacity, the study team will not move forward with risk disclosure, and the dyad's involvement in the study will be complete.

4. Baseline Outcome Measurement (for Part II): In order to gather baseline measurements of the constructs of interest for Part II of the study, all participants in Part I will complete the five outcome measures listed in Section 3.4.

Table 2. Proposed Components of Part I Education
1. Consent for Education (may be completed pre-session; separate)

2. Education Presentation (participant with co-participant)
3. Participant Decision-Making Capacity Assessment (separate)
4. Co-Participant or LAR/DPOA Decision-Making Capacity Assessment (separate)
5. Participant& Co-Participant Baseline Outcome Measurement (separate)
6. Post-Session study team review of responses to determine Disclosure eligibility

Both participants and their respective co-participants who complete the Education session will each be compensated with $10 paid via check after the session.

3.3.2 Disclosure Procedures

Following the Part I Education session, participants/co-participants who are deemed eligible will be invited to take part in a 90-minute virtual Part II Disclosure session. Study team members will contact the participant or dyad via phone to introduce the study (see 'STIM+ Disclosure Oral Script'). Disclosure procedures are summarized in Table 3.

1. Consent – Interested participants will undergo a separate consent procedure for Disclosure, given the differing level of risk in this portion as compared to the Education portion. Consent will be completed virtually following the same procedures as detailed above in the Education Procedures section.

2. PET Disclosure: All parent studies utilize the expertise and methods of Dr. Robert Koeppe (head of PET imaging at University of Michigan) for PET analysis; this will ensure consistency across methods and interpretive messaging regardless of the parent study. Each participant's PET imaging will be reviewed by Dr. Robert Koeppe, who will provide both region-specific and total standardized uptake value ratio (SUVr) calculations of amyloid and tau burden and determinations of whether these ratios surpass normatively-referenced thresholds to indicate amyloid or tau positivity. We will share only positive vs. negative status and simplified qualitative risk estimates (e.g. positivity = 'increased risk/likelihood of Alzheimer's etiology'), given the current lack of validated quantitative models of AD risk based on amyloid and tau. The study team have developed a flexible disclosure protocol that provides written and graphic representations of the participant's amyloid results (see 'STIM+ Disclosure Slides'). The protocol will be adapted using standardized instructions prior to the session, to personalize each protocol to the participant. Personalization will be based on demographic factors and geographic location of the patient's home (to ensure identified resources are close by and accessible), and PET results (to ensure that appropriate recommendations and resources are given). PET results will be provided as a qualitative interpretation (i.e., Elevated vs. Not Elevated) of the presence or absence of significant burden for either of the abnormal proteins. Disclosure will also involve discussion that elevation on either/both proteins may indicate underlying AD pathology that may explain their current cognitive/behavioral symptoms. Following this summary, the protocol includes general recommendations and next steps for healthy aging (e.g., taking care of physical and emotional health, staying cognitively and socially engaged) and a list of informational and support resources. As with the Education Module, the disclosure protocol will include multiple 'checks for understanding' after each section to ensure that information communicated is being comprehended accurately by the participant and co-participant.

3. Outcome Assessment: Immediately following risk disclosure, the participant and co-participant (if present) will complete outcome measures with a study team member and, as needed, a brief psychological risk assessment with a clinical psychologist and/or social worker. Both parties will receive a packet of personalized resources or supports from the region- and service-specific list developed in ARF's prior work, through the Michigan Alzheimer's Disease Research Center, or through the NIA.

Participants will also be asked whether they would like a written summary of the information provided; if so, this report will be prepared after the visit and sent via mail to the participant or LAR/DPOA. No results will be uploaded in the participant's medical record; however, they are welcome to share the results with their medical providers independently. If the participant or LAR/DPOA wishes the study team to contact the participant's medical providers to discuss any of the findings, an Authorization to Release Information will be filled out and signed by the participant/LAR/DPOA, specifying exactly which information should be shared or discussed, in what format, to whom, and for how long.

Table 3. Proposed Order & Components of Disclosure Sessions
1. Consent for Disclosure (may be completed pre-session)
2. Personal Risk Disclosure (participant and co-participant)
3. Recommendations (participant and co-participant)
4. Participant & Caregiver Resources (participant and co-participant)
5. Risk Assessment & Follow-Up (as needed; separate))
6. Outcomes Assessment (separate)

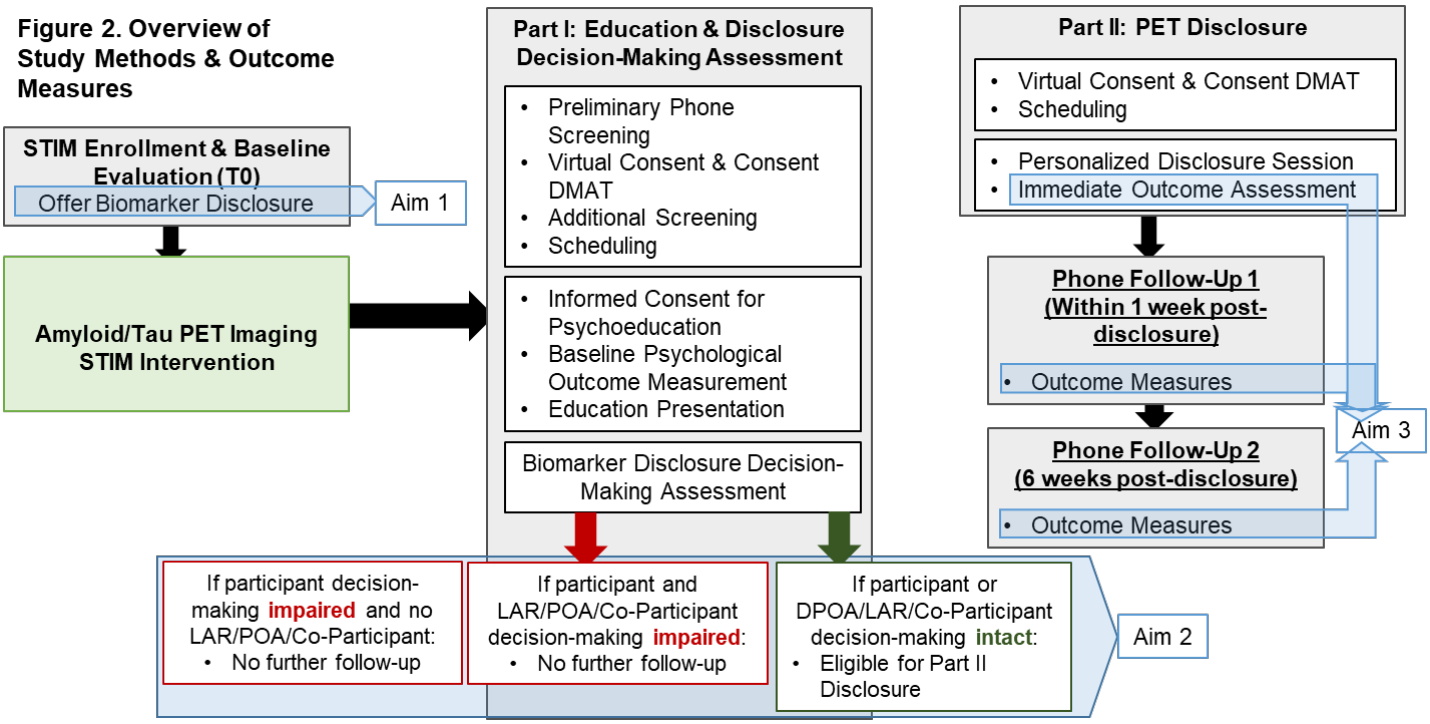
Participants who complete the Disclosure session will be compensated with $20 paid via check after the session. Likewise, co-participants who complete the Disclosure session will also be compensated with $20 paid via check following the session.

3.3.3. Follow-Up Procedures:

1. Formal Follow-Up Sessions: Within one week of disclosure, the social work team member will contact all participants and co-participants (as applicable) to assess psychological reactions to, and coping with, biomarker disclosure (Aim 3). These measures will be repeated at 6-weeks post-disclosure. These measures will be conducted via phone or video conference based on participant preference.
2. Informal Between-Session Follow-Up: Participants and DPOAs/LARs will be provided with contact information for the social worker and clinical psychologists at the time of disclosure; we will also track any additional requests for information, support, or resources between assessment sessions and provide such information as appropriate.

Participants and co-participants will each be compensated with $10 per follow-up session completed, paid via check after the session.

Figure 2. Overview of Study Methods & Outcome Measures



3.4 OUTCOMES

In addition to measuring **preliminary interest in PET disclosure after STIM activities (Aim 1, Primary Outcome 1**) and **Disclosure Decision-Making Capacity (overall and by component; Aim 2, Primary Outcome 2**), we will collect the following outcome measures post-disclosure for participants who complete this step (Aim 3). These measures will be completed over the phone or via virtual visit to allow for maximum flexibility. Of note, we will also administer the GDS-15 and BAI at each time point for the purpose of safety monitoring (see DSMP); these are not considered primary outcomes. A summary of the outcome measure respondents and timeline is provided in Table 4.

Primary Outcome 3.1 - Comprehension & Recall: The Personal Information and Meaning of Information accuracy scores will be totaled for all participants and co-participants. Mean, median, and standard deviation will be calculated. Exploratory analyses will evaluate trends in whether specific types of feedback information (e.g., neuroimaging vs. amyloid/tau burden) were better understood than others, and whether group differences exist (i.e., participants vs. co-participants, by race, by cognitive status).

Primary Outcome 3.2 - Positive and Negative Affective Scale – Short Form (PANAS-SF[18]): This 20-item scale asks respondents to rate the extent to which they are experiencing positive (e.g., excited, inspired) and negative (e.g., distressed, ashamed) emotions on a Likert-style scale ranging from '1 = Very Slightly or Not at All' to '5=Extremely.' The two subscale scores range from 10-50, with higher scores indicating higher positive or negative emotions, respectively. The PANAS has demonstrated strong psychometric properties for assessing emotions in older adults[19]. This measure will be administered to both participants and co-participants.

Primary Outcome 3.3 - Impact of Neuroimaging in Alzheimer's Disease (INI-AD): This measure assesses both positive and distressing reactions to disclosure of PET amyloid and tau results. The measure is adapted from the original Impact of Genetic Testing in Alzheimer's Disease scale[20] (used to measure reactions to genetic susceptibility testing results for AD genes), the scale was adapted to PET biomarker disclosure. This scale has been previously developed and used as part of the REVEAL study, and has the strength of assessing both positive and negative reactions and being specific to Alzheimer's disease. This measure will be administered to both participants and co-participants.

Primary Outcome 3.4 - Stigma Scale for Chronic Illness (SSCI-8[21]). The SSCI-8 demonstrates strong reliability for the measurement of both internalized and enacted stigma perceived by individuals with chronic neurological conditions. Respondents complete 8 items about experiences of stigma, rated on a Likert-style scale from 1 = 'Never' to 5 = 'Always.' This measure will be administered to participants only.

Primary Outcome 3.5 - Self-Efficacy for Managing Chronic Disease Scale (SECD[22]): The SECD is a 6-item scale that measures perceived ability to self-manage the physical, emotional, and cognitive symptoms associated with their chronic disease. Items are listed on a 10-point scale ranging from 1 = 'Not at all confident' to 10 = 'Totally confident'. Though not previously applied to Alzheimer's disease specifically, psychometric properties for the assessment of self-efficacy across chronic conditions were strong (reliability ranging from 0.88-0.95[23]. This measure will be administered to participants only.

Primary Outcome 3.6 - Future Time Perspective Scale (FTP[24]): This 10-item scale measures the extent to which respondents feel that they have potential for productive and functional years ahead of them. Statements regarding positive and negative future time perspective are rated on a 7-point Likert-style scale, ranging from 1= 'Very untrue' to 7='Very true.' This measure will be administered to both participants and study partners.

Primary Outcome 4.1 - Preparedness for Caregiving Scale (PCS[29,30]**):** This 8-item measure assesses the degree to which care partners of persons with cognitive impairment (e.g., MCI, DAT) perceive they are prepared for and able to manage various domains of caregiving such as providing physical care and emotional support, setting up in-home support services, and coping with stress due to caregiving. Items use a 5-point likert scale ranging from 0 = 'Not at all prepared' to 4 'Very well prepared'. The PCS has demonstrated strong psychometric properties for assessing perceived readiness for caregiving among family members of persons with Alzheimer's disease dementia. This measure will be administered to study partners only.

Primary Outcome 4.2 - Revised Scale for Caregiving Self-Efficacy (RSSE[31]): The Revised Scale for Caregiving Self-Efficacy is a 15-item scale consisting of 3 sub-scales, each containing 5-items, designed to measure perceived ability to manage aspects related to caregiving among caregivers of persons with dementia. A single subscale consisting of 5-items will be used to measure co-participant's perceived ability to manage the emotional stresses associated with caregiving. This measure will be administered to study partners only.

Table 4. Outcome Measure Summary

Construct/Measure	Group (Participant, Study Partner, or Both)	Data Collection Timepoint			
		Pre-Disclosure (Education Session)	Immediate Post-Disclosure	1-week	6-weeks
Positive and Negative Affective Scale – Short Form	Both	X	X	X	X
Impact of Neuroimaging in Alzheimer's Disease	Both		X	X	X
Future Time Perspective Scale	Both	X	X	X	X
Stigma Scale for Chronic Illness	Participant	X	X	X	X
Self-Efficacy for Managing Chronic Disease Scale	Participant	X	X	X	X
Revised Scale for Caregiving Self-Efficacy	Study Partner	X		X	X

Preparedness for Caregiving	Study Partner	X		X	X

SECTION 3.5 DATA MANAGEMENT & ANALYSIS

3.5.1 Data Management & Entry

Only IRB approved study personnel will have access to study documents/data. Signed consent paperwork and will be uploaded into the participant's medical record according to IRB standards. Electronic consent forms will be saved under password protection on the secure lab drive. Copies will be printed and stored in the aforementioned binder, away from all other study data. Data are kept in a locked file cabinet within a locked, private office in an office suite (i.e., behind two locked doors). The participant's study ID number will be recorded on every paper page of the study documents. A centralized database for all outcomes will be saved on the University of Michigan secure server as a password-protected file only accessible by approved study personnel.

The participants' PET amyloid and tau data will not be requested or added to this database until completion of Part I Education & Decision-Making Assessment, to ensure no implicit bias in the manner in which Part I procedures are conducted based on participant risk. At this time, data from eligible participants enrolled in the Part II Disclosure will be accessed. De-identified participant information, coded with the parent study ID number, will be shared with the study team as a secure excel database and transferred to the centralized study database.

3.5.2 Statistical Design

Data Screening

Prior to statistical analyses, data screening will be conducted. Initial steps will include a missing data analysis to determine randomness of missing data and range checks to assess for data quality. Additional screening for univariate and multivariate outliers, skewness and kurtosis will be conducted to inform needs for data transformation and statistical approach.

Statistical Approach

To assess Aim 1, we will compare the proportion of individuals in each diagnostic group who request vs. completed disclosure using a chi-squared test. Similarly, we will test hypotheses associated with Aim 2 (*greater disclosure decisional capacity in MCI than DAT*) by comparing the proportion of individuals in the DAT and MCI groups who demonstrate 'pass' scores on the DDMAT using a chi-squared test. We will also explore which particular elements of decision-making capacity may be more impaired in each group by comparing proportion of each diagnostic group who can adequately demonstrate understanding, appreciation, rationale, and communication on the DMAT using the same statistical strategy. To evaluate Aim 3, (*psychological reactions based on biomarker status*) we will compare participants' and co-participants' responses on outcome measures, based on amyloid and/or tau positivity vs. biomarker negativity. As we expect outcome measures to be correlated, we will utilize a 2 (diagnosis: MCI vs. DAT) by 2 (biomarker status: positive vs. negative) repeated measures analysis of variance (rmANOVA) approach for each follow-up time point. We will also compare differences in psychological reactions between participants and co-participants by diagnosis (MCI vs. DAT) using a paired t-test on all continuous items and a chi-squared test on categorical items. To evaluate Aim 4 (*impact of biomarker disclosure on co-participant caregiving readiness and self*-efficacy), we will similarly compare co-participants' responses, based on amyloid and/or tau positivity vs. biomarker negativity. As we expect outcome measures to be correlated, we will utilize a 2 (participant's diagnosis: MCI vs. DAT) by 2 (biomarker status: positive vs. negative) repeated measures analysis of variance (rmANOVA) approach for each follow-up time point.

SECTION 4: MONITORING

4.1 Risk Monitoring

4.1.1 Part I: Education & Decision-Making Assessment

Participants who endorse current/active depression, anxiety, or other significant psychological disorder will be excluded from the study. Prior to other study activities but after informed consent has been provided, participants will be screened using the Geriatric Depression Scale – 15 Item version (GDS-15)[1] and the Beck Anxiety Inventory (BAI)[2] to ensure no active depressive/anxiety symptoms. Each of the measures have empirically supported cut-off scores (GDS-15 ≥ 9; BAI ≥ 16) for determining clinically significant depression, anxiety, and event-related distress; individuals who endorse clinically significant depression or anxiety on the GDS-15 or BAI will be withdrawn from the study prior to further participation. These measures will be repeated at each of the three follow-up time points (immediate, within 1 week, 6 weeks) to assess change in mood or anxiety symptoms; those with elevations at or above the cutoffs noted above will complete an additional assessment with a clinically licensed team member to determine next steps, adverse events, and resources. Additionally, participants complete the INI-AD at the immediate, one-week, and six-week follow-up sessions. Any participants scoring 24 or higher on the distress subscale of the INI-AD will complete a follow-up assessment by a clinically licensed study team member.

It is not expected that discussing AD, DAT, and PET disclosure will cause significant distress or exacerbation of mood symptoms; however, any participant who appears distressed during the session will undergo risk assessment and intervention as needed according to the study safety plan (Appendix A). Of note, for video or phone sessions, at the start of each session, the participant/co-participant will be asked to provide a call-back number in case he/she is disconnected from the technology, as well as current location; this information will not be stored after study completion in the participant's/co-participant's file, but will be used as a reference in case of emergency or safety issue.

4.1.2 Part II: Disclosure

It is possible that participants may experience psychological distress as a result of hearing their PET results, particularly if this feedback indicates elevated risk. Although DAT risk and biomarker disclosure has been found to be generally safe and well-tolerated in the literature[3,4], we will conduct careful screening of mood, anxiety, and event-related distress utilizing psychometrically sound evaluations. Specifically, each participant and co-participant will repeat the GDS-15 and BAI, and complete the INI-AD[5] post-disclosure as well as both follow-up sessions. Any clinically significant elevation of scores on these measures, and/or other indication of new or exacerbated mood symptoms will result in a more advanced evaluation by a licensed clinical psychologist (ARF, BMH) or licensed social worker (MM; see Appendix A). In addition, participants and co-participants will be given contact information for the study team and encouraged to call ARF or MM with any concerns or needs related to their reactions to the disclosure session.

4.2 Safety Assessment: At the beginning of each session, the study team member completing the visit will confirm the participant's current location and call-back number to use in case of emergency. In the case of safety concerns in either part of the study, a risk assessment and follow-up will be conducted. A licensed psychologist (*ARF*, *BMH*) or social worker (*MM*), who will be available to join the sessions virtually or via phone, and are also available via page, will evaluate the severity of the participant's (or co-participant's) psychological symptoms and risk for self-harm. The clinician will take additional action as needed to either provide immediate transfer to emergency care (in the case of active threat), or facilitation of clinical care or supportive resources, per participant request (in the absence of active threat). All participants will also be provided with emergency contact cards with local, 24/7 resources if emergent mood issues arise between sessions. A summary of the project safety plan is included in Appendix A.

4.3 Adverse Events Reporting: Participant and co-participant mood and distress will be carefully assessed at baseline (prior to study activities), following disclosure, and at all follow-up time points using the GDS-15 and BAI. These measures will be used to determine (a) whether changes in mood or distress occur, and (b) whether these changes are likely attributed to study participation. Each of the measures have empirically supported cut-off scores (outlined above) for determining clinically significant depression, anxiety, and event-related distress; scores will therefore be used to define the nature of any events (unanticipated vs. anticipated, adverse vs. serious adverse) and relationship of these events to study participation (related vs. unrelated).

The independent safety officer (SO) for this project is Dr. Joshua Grill (jgrill@hs.uci.edu). Dr. Grill is a Professor in the University of California Irvine Department of Psychiatry & Human Behavior and Neurobiology & Behavior and specializes in Alzheimer's disease. He has previously served in this capacity for *ARF*'s risk disclosure studies. Information regarding non-serious adverse events (i.e., an elevation in mood or anxiety symptoms as a result of study participation) will be reported directly to the PI, who will compile and submit a report to the SO. Similarly, serious adverse events that are determined to be unrelated to study participation will be reported to the PI, recorded in a secure study database, and reported to the SO. These summary reports will be submitted to the SO on a **quarterly** basis.

Unanticipated adverse events or serious adverse events deemed related to study participation (i.e., acute exacerbation or onset of severe depression or anxiety, hospitalization for emotional reasons, and/or preparation for or engagement in self-injurious behavior as a result of risk disclosure results) will be reported immediately to the study PI. Consistent with Office of Human Research Protection, Institutional Review Board guidelines for the study's parent institution, and NIA standards, serious study-related adverse events resulting in life-threatening outcome or death will be reported to the SO and NIA program officer as soon as possible, and within 24 hours of study PI knowledge of the event. Other serious study-related adverse events and unanticipated adverse events will be reported as soon as possible, and within 48 hours of study PI knowledge of the event. The PI, in conjunction with the SO, will review the case and relevant study data to determine whether the study should be halted or how it may be altered to promote safety.

Additionally, the SO will meet at least twice per year via telephone or video conferencing to review adverse events and their outcomes, and to generate recommendations for study protocol alteration for improved safety (or termination of the study, if deemed necessary).

SECTION 5: ETHICS AND DISSEMINATION

5.1 Research Ethics Approval & Protocol Amendments

All procedures detailed above fall within the parameters approved by the University of Michigan institutional review board. Any changes to these parameters or procedures will be proposed to and approved by the IRB through formal amendments prior to implementation.

5.2 Consent or Assent

All consent forms and others requiring authorized signatures will be approved by the University of Michigan IRB. There are separate consent forms for Part I: Education & Decision-Making Assessment and Part II: Disclosure. A study team member will review the appropriate consent form with the participant and their LAR/DPOA as applicable. The team member will pause after each section to solicit and answer questions. Comprehension of the procedures, risks, benefits, and other aspects of the study will be checked using the Consent Decision-Making Assessment Tool (CDMAT), a brief measure asking the participant to use their own words to review the contents of each section of the consent form before signing. If the participant no longer retains the ability to provide informed consent, the designated LAR/DPOA will be asked to provide consent, and the participant will be asked to provide assent. Alternatively, if the participant no longer retains the ability to provide consent but brings a co-participant who is not a designated LAR/DPOA, the participant may allow that individual to provide consent, and the participant will be asked to provide assent.

As detailed above, these procedures will be completed virtually prior to the first visit to ensure sufficient time to answer all questions. The participant will then print, sign, scan, and return the consent form or utilize the SignNow modality to electronically sign the document and return it to the study team member, who will sign it.

The study team member will then download the completed form, and store electronically under password protection in the network secure drive. As mentioned above, a copy of the consent form is uploaded into the participant's University of Michigan electronic medical record as a 'Research Document' to communicate current research participation to medical providers.

5.3 Confidentiality

Information gathered from individuals contacted for initial screening is entered into a recruitment database file that is stored in the shared drive (accessible only to approved lab personnel) and password protected. This centralized file will contain only the necessary information for contacting and determining eligibility and interest in the study, as well as assigned ID numbers for enrolled participants and any co-participants. For information regarding security and confidentiality of data from enrolled participants/co-participants, see '**Data Management & Entry**'.

Participants will be made aware prior to enrollment in Part I that they will not receive feedback regarding their PET amyloid and tau status during this stage of the study. This option will not be offered to participants until completion of and evaluation of responses from Part I.

5.4 Declaration of Interests

None of the study investigators have any financial or competing interests to declare.

5.5 Access to Data

Physical study data will remain housed within *ARF's* private office at the University of Michigan and will only be available to authorized study team members or members of oversight committees (e.g., IRB).

5.6 Ancillary and Post-Trial Care

As noted above, there are procedures in place to alert the principal investigator and take any needed action to deal with serious adverse events or harms that occur during the study session. As stated in the consent form, participants and co-participants are instructed to seek immediate medical attention for any serious adverse events that arise after the study session, rather than waiting to contact or hear back from study personnel. Participants are instructed that any medical appointments that are attended after the study will be billed through the patient's regular insurance avenues.

As this study is investigating PET disclosure, which is not considered part of the standard of care for older adults, there is no obligation to provide a waitlist control or delayed access to treatment to individuals assigned to the sham condition.

5.7 Dissemination Policy

A summary of results from the current study will be uploaded within one year of study completion to clinicaltrials.gov. At this time, there are no plans to grant public access to the participant level dataset or statistical coding used to analyze data. Findings will be communicated in the form of scientific presentations at national meetings and publications in peer-reviewed scientific journals. There are no restrictions on publications. Authorship will be based on study contribution, considering efforts towards study design, data collection and management, statistical analysis and interpretation, and production of presentations and manuscripts.

References

1. Kivipelto, M, Mangialasche, F, & Ngandu, T (2018). Lifestyle interventions to prevent cognitive impairment, dementia, and Alzheimer's disease. *Nat Rev Neurol, 14*(11), 653-666. PMID: 30291317
2. Bhatti, GK, Reddy, AP, Reddy, PH, & Bhatti JS (2020). Lifestyle modifications and nutritional interventions in aging-associated cognitive decline and Alzheimer's disease. *Frontiers in Aging Neuroscience, 11.*
3. Buss, S. S., et al. (2019). Therapeutic noninvasive brain stimulation in Alzheimer's disease and related dementias. *Current Opinion in Neurology*, *32*(2), 292–304. PMID: 30720478.
4. Hill. NTM et al. (2017). Computerized cognitive training in older adults with Mild Cognitive Impairment or Dementia: A systematic review and meta-analysis. *Am J Psychiatry, 174,* 329-240. PMID: 27838936.
5. Caselli, RJ et al. (2014). Public perceptions of presymptomatic testing for Alzheimer's disease. *Mayo Clin Proc*, *89*(10), 1389-1396. PMCID: PMC4369785
6. Ott, BR et al. (2016). A survey of knowledge and views concerning genetic and amyloid positron emission tomographic status disclosure. *Alzheimer's Dement, 2*(1), 23-29. PMCID: PMC4804344
7. Wake, T et al. (2018). Disclosure of amyloid status for risk of Alzheimer's disease to cognitively normal persons with subjective cognitive decline. *Alzheimer's Dement, 14*(7), P1620. PMCID: PMC6064628
8. Vanderschaege, G et al. (2017). Amnestic MCI patients' perspectives toward disclosure of amyloid PET results in a research context. *Neuroethics, 10,* 281-297. PMCID: PMC5486502
9. Vanderschaeghe, G et al. (2017). Amnestic MCI patients' experiences after disclosure of their amyloid PET result in a research context, *Alzheimer's Research & Therapy, 9,* 92-108. PMCID: PMC5712105
10. Lingler, JH et al., (2018). Amyloid positron emission tomography candidates may focus more on benefits than risks of results disclosure. *Alzheimer's Dement, 10*, 413-420. PMCID: PMC6072672
11. Roberts, JS et al. (2014). Direct-to-consumer genetic testing for risk of Alzheimer's disease (AD): The psychological and behavioral impact of APOE. *Alzheimer's Dement, 10*(4), 209. PMCID: PMC3772971
12. Chao, S et al. (2008). Health behavior changes after genetic risk assessment for Alzheimer's disease: The REVEAL study. *Alzheimer Dis Assoc Disord, 22*(1), 94-97. PMCID: PMC2483341
13. Vernarelli, JA et al. (2010). Effect of Alzheimer disease genetic risk disclosure on dietary supplement use. *Am J Clin Nutr, 91,* 1402-1407. PMCID: PMC2854909
14. Christensen, KD et al. (2015). Associations between self-referral and health behavior responses to genetic risk information. *Genome Medicine, 7,* 1-11. PMCID: PMC4311425
15. Taylor, DH et al. (2010). Genetic testing for Alzheimer's and long-term care insurance. *Health Aff(Millwood), 29*(1), 102-108. PMCID: PMC2931337
16. De Wilde, A et al. (2018). Disclosure of amyloid positron emission tomography results to individuals without dementia: A systematic review. *Alzheimer's Research & Therapy, 10,* 72.
17. Appelbaum, PS, & Grisso, T (1988). Assessing patients' capacities to consent to treatment. *N England J Med, 319*(25), 1635-1638. PMID: 3200278
18. Watson, D et al. (1998). Development and validation of brief measures of positive and negative affect the PANAS scales. *Journal of Personality and Social Psychology, 54*(g), 1063.
19. Humboldt, S. et al. (2017). Validation of the PANAS: A measure of positive and negative affect for use with cross-national older adults. *Review of European Studies, 9*(2), 10-19.
20. Chung, WW, et al. (2009). A new scale measuring psychologic impact of genetic susceptibility testing for Alzheimer's disease. *Alzheimer Dis Assoc Disord, 23*(1), 50-56. PMCID: PMC2743905
21. Molina, Y. et al. (2013). The Stigma Scale for Chronic Illnesses 8-Item version (SSCI-8): Development, validation, and use across neurological conditions. *Int J Behav Med, 20*(3), 450-460.
22. Lorig, K.R. et al. (2001). Effect of a self-management program for patients with chronic disease. *Effective Clinical Practice, 4*, 256-262.
23. Ritter, PL & Lorig, K (2014). The English and Spanish self-efficacy to manage chronic disease scale measures were validated using multiple studies. *Journal of Clinical Epidemiology, 67*(11), 1265-1273.
24. Lang, F. R., & Carstensen, L. L. (2002). Time counts: Future time perspective, goals and social relationships. *Psychology and Aging, 17*, 125-139. PMID: 11931281
25. Yesavage, JA, et al. (1982-1983). Development and validation of a geriatric depression screening scale: a preliminary report. *Journal of Psychiatric Research, 17*(1), 37-49.
26. Sheikh, JI, et al. (1986). Geriatric Depression Scale (GDS): Recent evidence and development of a shorter version. *Clinical Gerontologist: The Journal of Aging and Mental Health, 5*(1-2), 165-173.

27. Beck, AT, et al. (1988). An inventory for measuring clinical anxiety: Psychometric properties. *Journal of Consulting and Clinical Psychology, 56*, 893-897.
28. Wetherell, JL, & Arean, PA, (1997). Psychometric evaluation of the Beck Anxiety Inventory with older medical patients. *Psychological Assessment, 9*(2), 136-144.
29. Archbold, Patricia G., et al. (1990). Mutuality and preparedness as predictors of caregiver role strain. *Research in nursing & health* 13(6) 375-384.
30. Archbold, P. G. (1992). The clinical assessment of mutuality and preparedness in family caregiver to frail older poaple. *Key aspects of elder care*, 328-339.
31. Steffen, A. M., McKibbin, C., Zeiss, A. M., Gallagher-Thompson, D., & Bandura, A. (2002). The revised scale for caregiving self-efficacy: Reliability and validity studies. *The Journals of Gerontology Series B: Psychological sciences and social sciences*, *57*(1), P74-P86.

Appendix A. Safety Plan

***Note: For virtual visits, study team members will verify participants'/co-participants' call-back number and address of their current location at the outset of each session.**

Potential Suicidal Ideation indicated by:

- Negative answer to GDS #11, 'Do you think it is wonderful to be alive now?'
- Score ≥ 9 on GDS-15 and/or Score ≥ 16 on BAI
- Participant direct or indirect reference to suicidal ideation, intention, plan, or preparatory behaviors (e.g., giving away personal items, stock-piling medications)
- Informant concerns about changes in the participant's thoughts/speech/ actions consistent with depression

Risk Assessment & Safety Planning

1. Principal Investigator completes assessment of:
    a. Current/past suicidal thoughts
    b. Current/past suicidal intention or plans
    c. Current/past preparatory behaviors
    d. Current/past suicidal actions or attempts
    e. Access to means
    f. Current supports/barriers to carrying out suicidal thoughts/plans
    g. Current reasons for living
    h. Current/past treatment for psychiatric issues, including contact information if available
2. If needed, consultation with Co-Investigators
3. **Study team determines whether active threat to self (need for hospitalization).**

Active Threat

<u>Virtual Visit Protocol:</u>

1. Confirm participant phone #/current location.
2. If participant has friend/family present to safely transport to emergency department, proceed.
3. If no friend/family member present, stay on call with participant & call UM PES Care Manager:
    a. 8am-5pm: Page #34832 with your location, means of contacting you (phone, IM)
    b. After-hours: Call local police or SW at 734-936-5900 (will assist with contacting police).

No Active Threat

1. **Provide resources:**
    a. Depression brochure
    b. <u>Ann Arbor</u> - Mental Health Resources and Washtenaw County Senior Resources lists
    (OR)
    <u>Detroit</u> - Community Resources for Seniors list
2. **Complete Safety Plan with patient**
3. **Encourage participant to follow up with own health care provider.**