The MObile AssessMENT of Behavioral and Psychological Symptoms of Dementia in Amnestic Mild Cognitive Impairment and Alzheimer's Disease (MOMENT) Study: A Randomized Controlled Trial

Principal Investigator:
Daniel R. Bateman MD, Assistant Professor
Department of Psychiatry, Indiana University School of Medicine
Indiana University Center for Aging Research, Regenstrief Institute, Inc.
1101 West 10th Street
Indianapolis, IN 46202

Support Provided by:
National Institute on Aging (NIA)
1K23AG059914-01A1

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Abbreviations

AD	Alzheimer's Disease
AE	Adverse Event
aMCI	Amnestic Mild Cognitive Impairment
BCN	Brain CareNotes mobile application
BPSD	Behavioral and Psychological Symptoms of Dementia
COC	Certificate of Confidentiality
DOB	Date of Birth
DSMP	Data Safety Monitoring Plan
DRE	Disease-Related Event
EC	Enhanced Care
eCRF	Electronic Case Report Forms
EMA	Ecological Momentary Assessment
EMR	Electronic Medical Record
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HABC	Healthy Aging Brain Center
HIPAA	Health Insurance Portability and Accountability Act
IDE	Investigational Device Exemption
IRB	Institutional Review Board
LAR	Legally Authorized Representative
MCI	Mild Cognitive Impairment
MMSE	Mini Mental Status Exam
MRN	Medical Record Number
NCT	National Clinical Trial
NIA	National Institute on Aging
NIH	National Institutes of Health
NPI-Q	Neuropsychiatric Inventory Questionnaire
NPS	Neuropsychiatric Symptoms
OHRP	Office for Human Research Protections
PI	Principal Investigator
PSS-14	Perceived Stress Scale-14
QA	Quality Assurance
QC	Quality Control
RA	Research Assistant
SAE	Serious Adverse Event
SECBCI	Sandra Eskenazi Center for Brain Care Innovation
SILS	Single Item Literacy Screener
SO	Safety Officer
SOA	Schedule of Activities
SOP	Standard Operating Procedure
SUS	System Usability Scale
UP	Unanticipated Problem
ZBI	Zarit Burden Interview

1.0 Background & Rationale

The National Plan to Address Alzheimer's disease (AD) and the National Institute on Aging (NIA) emphasize the importance of research exploring the use of technology to assess and improve health. Researchers at the NIA 2015 AD Research Summit recommended research on "in-place monitoring" of persons living with dementia to better understand disease progression and investing "in research to develop new technologies that enhance the delivery of clinical care, caregiver support and in-home monitoring[11]." The purpose of the proposed research is to improve the day-to-day management of behavioral and psychological symptoms of dementia (BPSD) among persons living with dementia. By international consensus, behavioral and psychological symptoms of dementia (BPSD) consist of disturbed perception, thought content, mood and behavior[12]. Prevalence of BPSD range from 80% to 98%[13–17]. BPSD negatively impact a patient's quality of life[18], predict functional decline[19], and lead to greater financial costs[20]. Early onset of BPSD also strongly predicts caregiver burden[26–32].

Currently, most clinicians and investigators assess BPSD in the Alzheimer's disease (AD) population using standardized paper and pencil scales in the office setting. *The problem* is that BPSD surveillance as it stands in clinical practice today is typically episodic, cross-sectional and completed at the time of routine office visits, if it is completed at all. Recall bias and environmental setting of symptom measurement (clinic vs. home) can lead to differences in symptom reporting[7,8], as can a caregiver's emotional state and severity of caregiver burden[5,6]. Clinic-based episodic measurement may not effectively capture, nor allow timely treatment of, emerging or changing BPSD. Indeed, patients and caregivers may go months without addressing BPSD until they reach a state of crisis leading to emergency department visits, overuse of high-risk psychotropic medications, or caregiver exhaustion. Many questions remain surrounding the topic of how often care teams should monitor BPSD and whether increased surveillance in the home would provide actionable data that would improve patient and caregiver outcomes.

Mobile Ecological Momentary Assessment (EMA) represents a cutting edge, technological approach to capturing symptoms in the moment that addresses a costly, national challenge of caring for persons with BPSD. Early studies examining the use of mobile EMA in caregivers with dementia suggest proof of concept and demonstrate differences in the clinic-based vs. mobile EMA symptom assessment. Technology can provide timelier, and more frequent measurements of patient symptoms than ever before. While monitoring BPSD every 6 months is likely not enough, based on end-user feedback in our pilot studies, daily symptom assessment may be too frequent.

The long-term goal of the proposed work is to improve the care of individuals with AD in the mild cognitive impairment (MCI) stage and in the dementia stage of the illness. This will be done via creation of a more effective clinical approach to the measurement of BPSD and caregiver distress that will allow for more timely and effective care.

Our proposal objectives are to determine the feasibility and the optimal frequency of mobile surveillance of BPSD among aMCI and AD patients and their family caregivers through the employment of ecological momentary assessment (EMA), a repeated sampling method of symptoms that utilizes near real-time and natural environment data collection. *The central premise is* that increased frequency of measurement of BPSD and caregiver distress will lead to timelier, actionable data which will lead to timely care and improved outcomes for persons living with dementia and their caregivers.

The study design randomizes assignment of 154 patient-caregiver dyads (n=308 human subjects) to an active or control group; and, a 2 x 6 cross over design within the active group, wherein patient-caregiver dyads who are assigned to the active group are further randomly assigned to start with either weekly or monthly surveillance frequencies. They then cross-over every month to the other frequency condition, over a 6-month time horizon wherein each dyad will act as their own control. Subjects will be recruited from the Eskenazi Health, Sandra Eskenazi Center for Brain Care Innovation (SECBCI). The surveillance will be paired with standard SECBCI clinic BPSD treatment protocols in order to:

AIM 1: Quantitatively and qualitatively, determine the feasibility of collecting responses on an ecological momentary assessment (EMA) version of the Neuropsychiatric Inventory Questionnaire (NPI-Q), via the Brain CareNotes Mobile Application (BCN), from caregivers randomly assigned to using smartphone technology at differing frequency intervals, compared with a control group with data collected without the mobile health version and only at baseline and 6 months). **H1:** Caregivers in the intervention groups will complete the assessments via smartphone and report an acceptable response burden.

AIM 2: Determine whether more frequent surveillance of BPSD yields more actionable data. **H2:** We expect there to be more occurrences of “actionable data” in the groups (i.e., intervention vs control) or conditions within a group (i.e., weekly vs monthly condition within the intervention group) that have more frequent monitoring. We define actionable data as data that could lead to a change in care plan. This was operationalized by setting “clinically significant” thresholds for NPI-Q symptoms

AIM 3: Explore whether different surveillance intervals are associated with greater improvement in BPSD and caregiver distress. **H3:** Groups or conditions within a group that receive more frequent surveillance paired with response to “clinically significant” symptoms will have greater improvement in BPSD and in caregiver distress.

The expected outcomes are data that support an optimal measurement frequency of BPSD, demonstration of the feasibility of collecting these data in-home using widely available mobile technology, and early evidence that these assessments provide opportunities to improve BPSD. We expect these data will also be used to assess for associations between BPSD surveillance intervals (weekly or monthly), actionable data and characteristics. Data pertaining to feasibility and usability and to the impact of the intervention on BPSD and caregiver distress we expect will support an R01 application

to trial monitoring and just-in-time interventions in a fully powered RCT where the primary outcomes will be emergency room, hospital and psychotropic medication utilization.

Significance: The National Institute on Aging (NIA), the National Plan to Address Alzheimer's disease (AD), and the NIH all emphasized the value and prioritization of using technology to assess and improve health. Researchers at the NIA 2015 AD Research Summit formulated many recommendations on AD and technology. They included (1) supporting the development and use of in-place monitoring of patients to better understand disease progression, (2) integrating pervasive computing approaches into AD clinical trials to allow for continuous data capture of everyday symptoms and activities, (3) integrating mobile health (mHealth) technologies for assessment and disease monitoring into the healthcare system and (4) investing "in research to develop new technologies that enhance the delivery of clinical care, caregiver support and in-home monitoring[11]." The 2015 update to the National Plan to Address AD stressed the use of health information technology to support the needs of individuals with AD and related dementias. The NIA and National Plan to Address AD are not alone, the NIH listed the application of mHealth technologies to enhance health promotion and disease prevention as a priority in their NIH-Wide Strategic Plan for Fiscal years 2016-2020[33].

Studies estimate that over 5.5 million people in the U.S. suffer from ADRD[34]. By 2025 the number of adults age ≥65 with AD will increase to 7.1 million, a 35% increase over 2017 estimates[34,35]. Experiencing at least one BPSD in the course of dementia is almost universal, with BPSD prevalence ranging from 80% to 98%[13–17], meaning that somewhere between 4.4 and 5.4 million people with ADRD will suffer from BPSD. Persons with BPSD experience a more rapid disease progression, greater mortality[21–23] and earlier nursing home placement[23–25]. One study estimates that BPSD accounts for 30% of annual expenditures on ADRD care[36]. Morris et al identified the cost associated with agitation, one of the most distressing and potentially dangerous types of BPSD, to have a mean excess cost of $5539 per person with ADRD annually[37,38].

Not only does BPSD carry a financial cost, there is a significant psychological and physical cost to caregivers. Caregivers of persons with dementia report higher rates of depression, lower subjective wellness and worse physical health as compared to non-caregivers[39]. A meta-analysis estimated caregiver prevalence rates of depressive and anxiety symptoms to be 34 and 44%[40]. Multiple longitudinal studies show that onset of BPSD early in the disease course increases in BPSD strongly predict caregiver burden[26–32]. A meta-analysis of 228 studies calculated the BPSD correlational co-efficient for caregiver burden and depression to be 0.37 and 0.27 respectively[30,41]. For perspective, the cognitive impairment correlational co-efficient for the same meta-analysis were lower at 0.18 and 0.16[30,41]. BPSD is a much greater contributor to caregiver burden and depression than cognitive impairment.

Only in the past 20 years have clinicians, investigators and nursing home administrators come to recognize the importance of assessment and treatment of BPSD. Previously,

cognitive symptoms and functional impairment were the focus of ADRD research. In 1996, a consensus conference of dementia specialists developed a consensus statement on BPSD current knowledge and implications for research and treatment[12]. They defined BPSD as an integral element of the dementia disease process, consisting of signs and symptoms of disturbed perception, thought content, mood and behavior[12]. The consensus concluded that BPSD symptoms present significant problems to all those who interact with persons with dementia, for society and health systems. Observational studies support this claim.

Until curative treatment of ADRD is available, non-pharmacologic and pharmacologic interventions are the only options for symptom management of BPSD. Only after clinicians are able to accurately assess BPSD, can they effectively apply interventions to help improve outcomes for ADRD patients.

Innovation*:* The integration of health technology with ADRD assessment and treatment interventions is a national priority. Currently, most clinicians and investigators assess BPSD via interview and standardized scales in the office setting. Using mobile EMA to measure BPSD in real-time and real-place (natural environment) provides an opportunity for clinicians to understand BPSD symptomatology through a richer and potentially more accurate source of data. Repeated sampling has the advantage of decreased measurement error. These data can provide more meaningful opportunities to treat BPSD and to measure treatment response.

A mobile surveillance approach also leverages the science of behavioral economics, a field that merges the schools of psychology and economics to better understand human behavior and decision making. Psychologists Barbara Fredrickson and Daniel Kahneman, demonstrated that 94% of the variance in subjects' global evaluations of recalling past experiences of discomfort was attributable to the combination of peak discomfort and discomfort at the time of last measurement[1]. They described this as the *Peak-End Rule.* This was seen in a study of patients receiving colonoscopies (n=682) randomized to a modified procedure that reduced pain at the end of the procedure. Those with reduced pain at the end of the procedure rated their whole experience as less painful[2]. In another experiment, subjects were exposed to the aversive event of placing their hand in cold water. Subjects expressed a preference for a longer exposure to cold water (longer duration of pain) over a shorter exposure to colder water (shorter duration with more intense pain)[3]. We often assume that patients or caregivers fill out scales using a weighted average during the past time interval, yet the *Peak-End Rule*, argues against this assumption and provides the underlying logic for using more frequent measurement to assess experiences closer to real-time.

Mobile surveillance represents a cutting edge, technological approach, to addressing a costly, national problem of BPSD. The studies examining the use of mobile surveillance in caregivers with dementia and older adults are small in number and more work needs to be done in this area.

2.0 Objective(s)

AIM 1: Quantitatively and qualitatively, determine the feasibility of collecting responses on an ecological momentary assessment (EMA) version of the Neuropsychiatric Inventory Questionnaire (NPI-Q), via the Brain CareNotes Mobile Application (BCN), from caregivers randomly assigned to using smartphone technology at differing frequency intervals, compared with a control group with data collected without the mobile health version and only at baseline and 6 months). **H1:** Caregivers in the intervention groups will complete the assessments via smartphone and report an acceptable response burden.

AIM 2: Determine whether more frequent surveillance of BPSD yields more actionable data. **H2:** We expect there to be more occurrences of "actionable data" in the groups (i.e., intervention vs control) or conditions within a group (i.e., weekly vs monthly condition within the intervention group) that have more frequent monitoring. We define actionable data as data that could lead to a change in care plan. This was operationalized by setting "clinically significant" thresholds for NPI-Q symptoms

AIM 3: Explore whether different surveillance intervals are associated with greater improvement in BPSD and CG distress. **H3:** Groups or conditions within a group that receive more frequent surveillance paired with response to "clinically significant" symptoms will have greater improvement in BPSD and in caregiver distress.

3.0 Outcome measures and mobile application

3.1 Primary outcome measures

3.1.1 The Neuropsychiatric Inventory Questionnaire – (NPI-Q): was developed as a more clinically relevant version of the original neuropsychiatric inventory. It is a self-administered questionnaire completed by a person who cares for a patient with AD or dementia. There are 12 domains in the NPI-Q each focused on a different and specific BPSD. The domains are as follows: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, motor disturbance, nighttime behaviors and appetite/eating. Each is noted as present "yes" or absent "no". If the informant answers "yes" to a symptom question they then are asked follow up questions on the symptom severity (mild, moderate, severe) and the amount of distress the symptoms causes them (the caregiver) on a 5-point scale[19]. On average the NPI-Q takes 5 minutes to complete.

3.1.2 The Brain CareNotes mobile application (BCN) was developed by Regenstrief Institute investigators Drs. Bateman, Holden and Boustani, and Cathy Alder. BCN takes all of the questions of the NPI-Q and delivers the questions from the scale to the caregiver through a smartphone mobile app that pings the caregiver on their phone at a set frequency, prompting the caregiver to complete the questionnaire. The app is designed for ecological momentary assessment (EMA) and is HIPPA compliant with secure transfer of data from the app to a secure cloud-based database. Ecological

momentary assessment is the approach to gathering survey data from individuals in real time in the individuals' real environment. Our study will be surveying individuals at different intervals, making it similar to an EMA approach.

BCN is not intended to function as a medical device. BCN does not meet the software definition of a medical device as clarified in the updated 2019 *FDA Policy for Device Software Functions and Mobile Medical Applications Guidance for Industry and Food and Drug Administration Staff.* Section 201 (h) of the FD&C ACT defines a medical device as *"…an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory", that is "… intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man …" or "… intended to affect the structure or any function of the body of man or other animals…" and "does not include software functions excluded pursuant to section 520(o) of the FD&C Act."* (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/policy-device-software-functions-and-mobile-medical-applications).

BCN is intended to be used as a mobile application that helps facilitate communication between caregivers and members of a patient's treatment team. It is not a treatment onto itself.

3.1.3 Feasibility will be measured 5 different ways:
1) Completion rate of the NPI-Q through the BCN app by the aMCI or AD caregiver over the 6-month intervention period.
2) Quantitative answers to the burden of scale completion question will be asked every time the NPI-Q is completed. *"How burdensome was completion of the prior scale (Answer options: not at all burdensome, mildly burdensome, moderately burdensome, or extremely burdensome)".*
3) Completion rate of the semi-structured BPSD phone questionnaires triggered by "clinically significant" symptoms entered by the caregiver into the BCN application.
4) aMCI and AD Caregiver Feasibility and Usability Survey (3mo, 6mo, quantitative).
5) aMCI and AD Caregiver Feasibility and Usability Semi-Structured Interview (3mo, 6mo, qualitative).

3.1.4 Usability will be measured 3 different ways:
1) System Usability Scale
2) aMCI and AD Caregiver Feasibility and Usability Survey (3mo, 6mo, quantitative)
3) aMCI and AD Caregiver Feasibility and Usability Semi-Structured Interview (3mo, 6mo, qualitative)

3.1.5 Other relevant outcome measures
1) Caregiver and Patient Demographics
2) Zarit Burden Interview (baseline, 3mo, 6mo) – Validated measure of caregiver burden
3) Perceived Stress Scale 14 (PSS-14, baseline, 3mo, 6mo) – Validated measure of stress

4) Healthy Aging Brain Center Caregiver Version (HABC-CG) – Validated measure of BPSD developed by faculty at the Sandra Eskenazi Center for Brain Care Innovation (SECBCI), and used routinely in their memory subspecialty clinic.

3.2.0 Secondary outcome measures

3.2.1 Actionable data - we define actionable data as data that could lead to a change in care plan (e.g. diagnostics, medication change, etc.). This was operationalized by setting "clinically significant" thresholds for NPI-Q symptoms and caregiver distress (see research design and methodology overview) that when reached leads to contact and interval assessment of the caregiver by the research team. Clinical teams are then notified by research team about findings. We will compare groups and conditions on the percentage of participants in each group or each condition that met at least one "clinically significant" threshold per month.

3.3.0 Exploratory outcome measures

3.3.1 Change in rating of BPSD - calculated by the difference in NPI-Q total scores (baseline, 3-mo, 6-mo). The intervention group will be compared to the control group for the same time intervals.

3.3.2 Change in caregiver distress - calculated by the difference in NPI-Q caregiver distress total scores (baseline, 3-mo, 6-mo). The intervention group will be compared to the control group during the same time intervals.

4.0 Eligibility criteria

4.1.1 Inclusion criteria

To be eligible for participation in this study, a patient caregiver dyad must meet the following inclusion criteria:

1. The patient has received a diagnosis of Amnestic Mild Cognitive Impairment (aMCI) or probable or possible Alzheimer's disease (AD) and receives his or her care at the Eskenazi Health, Sandra Eskenazi Center for Brain Care Innovation.
2. The patient has a caregiver who is willing to participate in the study.
3. The caregiver is at least 18 years of age and does not have visual impairment significant enough to interfere with the use of a smartphone.
4. Both the patient and caregiver live in the community setting in Indiana.
5. The patient is also eligible if they live in an independent or assisted living facility.
6. In cases where the patient with AD lacks capacity to consent to research, he or she must have a legally authorized representative (LAR) to consent on his or her behalf.
7. In cases where the patient lacks capacity to consent to research, he or she will be given an opportunity to provide assent. If the patient is unable to provide assent, an observable dissent will be honored.
8. The caregiver reports having contact with the patient with aMCI or AD at least weekly on average. The reported contact can be in person, over the telephone, or via a video call, like Zoom or FaceTime.

4.2.1 Exclusion Criteria

1. The patient and/or caregiver have a history of serious mental illness (schizoaffective disorder, schizophrenia, bipolar disorder)
2. The participant is participating in another caregiver intervention research study
3. The participant lacks both the capacity to consent and a legally authorized representative (LAR)
4. The potential participant with a diagnosis of either aMCI or AD communicates observable dissent.
5. If the patient lives in a long-term care facility.

5.0 Study Design

The purpose of the following randomized control trial is to determine: 1) the feasibility and usability of the Brain CareNotes mobile application (BCN) intervention to deliver ecological momentary assessment (EMA) surveillance of Behavioral and Psychological Symptoms of Dementia (BPSD) and caregiver distress in amnestic mild cognitive impairment (aMCI) or Alzheimer's Disease (AD) caregivers, 2) the optimal surveillance frequency and 3) whether improved BPSD surveillance can improve opportunities to intervene.

The BCN intervention delivers the Neuropsychiatric Inventory Questionnaire (NPI-Q) to caregivers of patients with either aMCI or AD to monitor BPSD and caregiver distress. During the study caregivers in the intervention group will be asked to answer an EMA version of the NPI-Q on the BCN intervention at differing intervals (weekly or monthly).

We propose to enroll 154 aMCI and AD patient-caregiver dyads from our memory care practice at Eskenazi Health, Sandra Eskenazi Center for Brain Care Innovation (SECBCI), an urban safety net hospital in Indianapolis in a 6-month randomized controlled trial of EMA assessment to monitor BPSD compared to enhanced care. Subject dyads will be randomized to either the intervention or control group in a 1:1 ratio (77 per group). The control group will not receive the BCN intervention. However, the caregivers in the control group will be administered most of the same assessments at the baseline, 3-month and final (6-month) visit as the caregivers in the intervention group, except for the two assessments that ask questions related to the mobile application. Caregivers will also participate in semi-structured interview at the baseline visit, final visit and when triggered by "clinically significant" BPSD.

The study design includes six 1-month periods. Those in the intervention group will be nested in a 2 x 6 cross-over design in which they will be randomly assigned to start with 1 of 2 schedules of EMA surveillance frequency (1) weekly or (2) monthly. The intervention participants will then cross-over at the end of each and every month to the other surveillance frequency condition, over a 6-month time horizon. The crossover design allows efficient sample size reduction for the comparison between two higher frequency arms by allowing persons to serve as their own controls for a within person intervention effect. According to standard analysis of cross-over trials, the comparison

of the two EMA surveillance frequency conditions within the intervention group will be tested with a within-subjects test**.** Co-variates and biological variation including sex will be incorporated into the analysis.

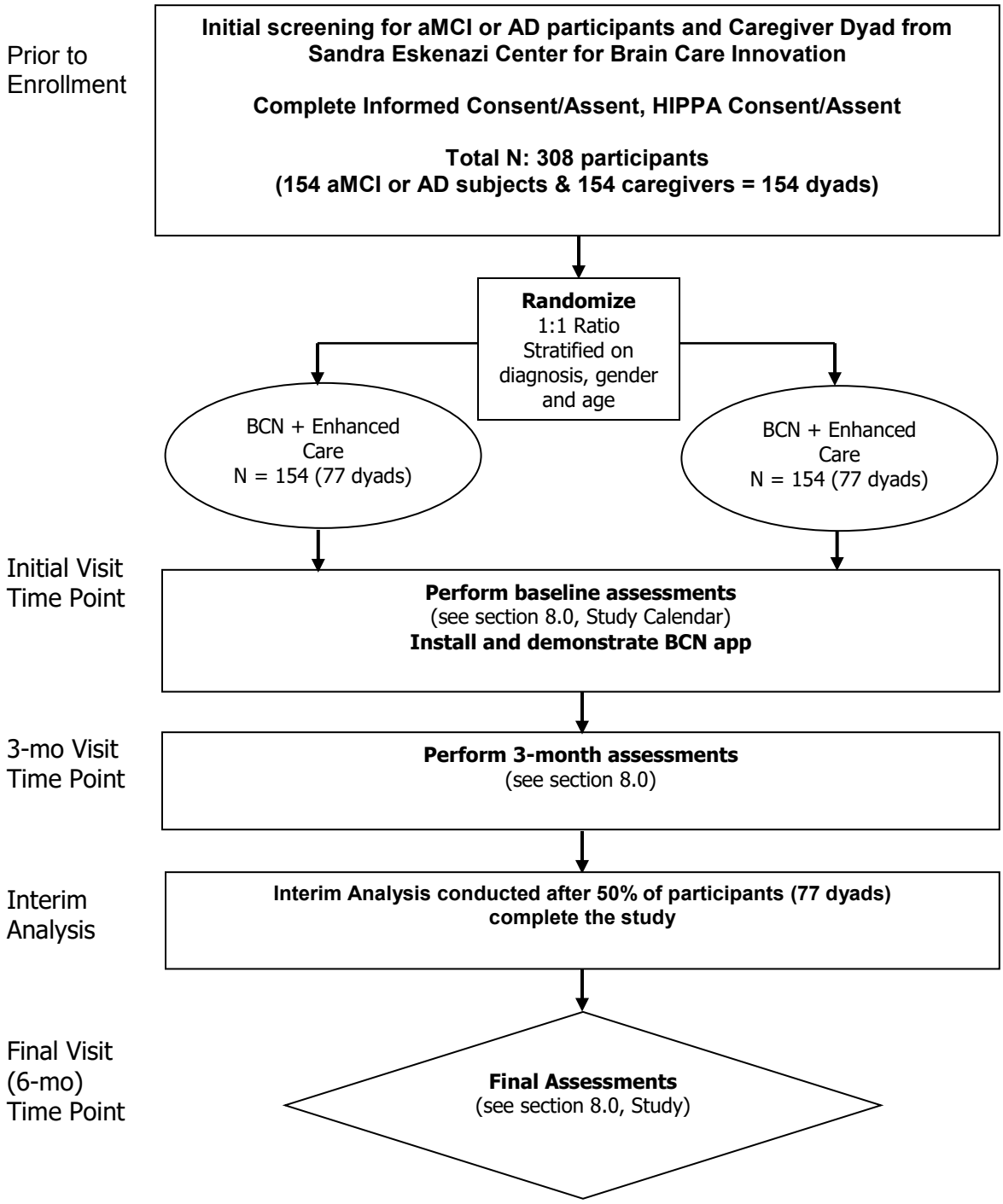
Table 1. Study Characteristics

Stage of Behavioral Intervention Development:	Stage II
NIH Phase III Clinical Trial?	No
Multiple Site Trial?	No
Brief Description of Study Design	
Study participants, 154 caregiver-patient dyads with amnestic mild cognitive impairment (aMCI) or Alzheimer's Disease (AD) Dementia (308 human subjects) will be randomly assigned to Enhanced Care (EC, 77 dyads) or the BCN Intervention + EC (77 dyads).	
Enhanced Care (EC) x (6-mo)	• Dementia collaborative care provided through the Sandra Eskenazi Center for Brain Care Innovation (SECBCI). • Services include care coordination, and evidenced based assessment and treat protocols for behavioral and psychological symptoms of dementia (BPSD).
Brain CareNotes (BCN) App + EC x (6-mo)	• The Brain CareNotes (BCN) app was developed with a user centered design for patients with MCI and AD, caregivers and healthcare team members. • The BCN app will deliver the Neuropsychiatric Inventory Questionnaire (NPI-Q) to the caregiver to report on the patient's BPSD severity and associated caregiver distress severity. • The NPI-Q delivery frequency will alternate every 30 days between conditions of weekly or monthly delivery. These set frequencies of weekly and monthly, will be re-evaluated and possibly modified based on feedback from the first 10 participants in the intervention arm. • If BPSD as measured by the NPI-Q rises to a set severity threshold then this data will be shared with the patient's treatment team who will contact the caregiver for further evaluation.

Table 2. Defining Clinically Significant BPSD and Responses to BPSD

Clinically Significant BPSD Severity Threshold	• Clinically Significant BPSD will be defined as when any NPI-Q severity domain = 3 regardless of caregiver distress, or whenever NPI-Q caregiver distress is marked as “moderate” “severe” or “very severe”.
Response to Clinically Significant BPSD	1. Automatic free response follow up questions (via BCN). 2. Automatic notification of research team. 3. Automatic notification of SECBCI clinical team. 4. The research team to contact the caregiver and complete a semi-structured interview and the Caregiver & Environment Assessment for Neuropsychiatric Symptoms. 5. The research team member documents findings and notifies PI and SECBCI clinical team.
BCN Triggered Free Response Follow Up Questions	1. Please describe the behavior or symptom that is most distressing to you. 2. What about this behavior or symptom makes it distressing to you? Why is it distressing? 3. Please describe anything that you think may have led to the behavior or symptom. 4. Describe anything you tried to address the behavior or symptom. Did it help?

Figure 1. Flow Diagram for The MOMENT RCT



6.0 Enrollment/Randomization

6.1 Patient Population and Setting: Our research center has 20 plus years of experience developing interventions to improve the care of older adults with AD and their caregivers. The PREVENT study applied the concepts of collaborative care to persons with AD in the primary care setting in a safety-net hospital system with in Indianapolis, IN[43]. At 12 and 18 months, results of the PREVENT study demonstrated improvements in BPSD frequency and caregiver distress from BPSD[43]. The results and experiences with PREVENT, as well as subsequent work by our research team and others led to the creation of the Sandra Eskenazi Center for Brain Care Innovation. This memory care practice serves as both a diagnostic and longitudinal care center for persons living with dementia and their family caregivers.

6.2 Preliminary Work: Neuropsychiatric Inventory Questionnaire (NPI-Q) – Ecological Momentary Assessment (EMA) Caregiver Pilot: We successfully pilot tested the NPIQ-EMA app in four AD patient-caregiver dyads without any attrition. The time horizon for the pilot differs from the proposal in that the caregiver was asked to fill out the smartphone survey (NPIQ-EMA) daily for a 2-week time period. Patient ages ranged from 63 to 95, and caregiver ages ranged from 63 – 82. Three of four caregivers identified as African American. All four caregivers found answering the NPIQ-EMA questions to "Not be burdensome." Several caregivers reported that the NPIQ-EMA improved their awareness of the patient's BPSD. Three of four answered that they would prefer weekly monitoring rather than daily and the last caregiver expressed a preference for daily monitoring. All caregivers agreed that the system was easy to use.

6.3 Recruitment, Screening, Informed Consent, and Enrollment: The Sandra Eskenazi Center for Brain Care Innovation provides longitudinal care to ~ 600 patients; 38.7% are Black; and 70.4% are female. In addition, each of five clinicians completes an initial assessment on 1-3 new patients per week. We anticipate a recruitment number of 154 dyads over 27 months and believe this to be achievable. Half of the dyads would be randomized to the intervention or treatment as usual group. Our group has a recruitment rate of approximately 50% of eligible subjects in this environment[43].

6.4 Randomization Scheme: Participating dyads will be randomized to the two groups (intervention vs control) using a randomization list that contains group assignment in blocks, thus ensuring that the groups have comparable sample sizes throughout the study. We will use a stratified block random assignment following the Kernan strata determination formula (Kernan et al. 1999) listed as, *# of strata < n / B x 4,* where *B* is block size and *"…n is the sample size at the first planned interim analysis and 4 is a safety factor that accounts for unequal distribution of patients among strata."* Using *n=154* and *B=4*, then, the *# of strata < 9*. In this study, we will use *8 strata = 2 Diagnosis (aMCI, AD) x 2 Gender (M, F) x Age (< 65, ≥ 65).* Sealed envelopes with randomization assignments will be prepared by a research team member not involved

with enrollment. Sealed envelope preparation will follow calculations and instructions made by the study biostatistician.

Participants in the intervention group will be further randomly assigned to start with 1 of 2 schedules of EMA surveillance frequency (1) weekly or (2) monthly. The intervention participants will then cross-over each month between the two surveillance frequency conditions, yielding 6 periods for their 2 x 6 cross-over design.

6.5 Potential Sources of Biological Variation and Co-variates: The experimental design allows us to explore moderators of response.

Table 3. Baseline Potential Sources of Variation

Subject	Obtained from caregiver	Obtained from EMR
aMCI/AD Subject	**Sex,** age race, ethnicity, education level, medical status, insurance type	Age, diagnosis, cognitive function, physical function, illness severity, problem list & med list
Caregiver Subject	**Sex**, age, race, ethnicity, education level, relationship to person with aMCI/AD, # of hours caregiving, caregiver burden, and perceived stress	None

7.0 Study Procedures

- Subjects will be identified from a list generated with patients who receive care at the Eskenazi Health, Sandra Eskenazi Center for Brain Care Innovation (SECBCI) and have a diagnosis of either Amnestic Mild Cognitive Impairment (aMCI) or possible or probable Alzheimer's disease (AD). Patients will also be referred by SECBCI providers. The screening portion of enrollment will be done either face-to-face in the SECBCI clinic or over the phone prior to the patient's SECBCI appointment.

- This study is seeking to recruit 154 patient-caregiver dyads (n=308 human subjects).

Inclusion Criteria:

1) The patient has received a diagnosis of Amnestic Mild Cognitive Impairment (aMCI) or probable or possible Alzheimer's disease (AD) and receives his or her care at the Eskenazi Health, Sandra Eskenazi Center for Brain Care Innovation.
2) The patient has a caregiver who is willing to participate in the study.
3) The caregiver is at least 18 years of age and does not have visual impairment significant enough to interfere with the use of a smartphone.
4) Both the patient and caregiver live in the community setting in Indiana.
5) In cases where the patient with AD lacks capacity to consent to research, he or she must have a legally authorized representative (LAR) to consent on his or her behalf.

6) In cases where the patient lacks capacity to consent to research, he or she will be given an opportunity to provide assent. If the patient is unable to provide assent, an observable dissent will be honored.
7) The caregiver reports having contact, in person, over the telephone or via video call with the patient with aMCI or AD at least weekly on average.

Exclusion Criteria:

1) History of serious mental illness (schizoaffective disorder, schizophrenia, bipolar disorder)
2) The participant is participating in another caregiver intervention research study
3) The participant lacks both the capacity to consent and a legally authorized representative (LAR)
4)

4.) The potential participant with a diagnosis of either aMCI or AD communicates observable dissent.

5) 5.) The patient lives in a long-term care facility.

- Using this research subject list the research team will access the patient electronic medical record to obtain contact information and other necessary screening data elements. This will be recorded on paper and destroyed as soon as the dyad declines interest in the study. If the subjects are enrolled in the study then this data will be inputted into a REDCap database.

- Data Elements to be pulled from patient's record prior to screening
  1) Patient name, DOB, MRN and contact information
  2) Primary caregiver name and contact information
  3) Diagnosis of either aMCI or possible or probable AD.
  4) Associated SECBCI physician name
  5) Most recent SECBCI visit date
  6) Next scheduled SECBCI visit date
  7) Most recent MMSE score and date

- Once an eligible patient has been identified the study team member will notify the respective SECBCI provider, that their patient will be approached for recruitment and request their' opinion of the patient's capacity to consent to research. The study team member will allow a week for the provider to respond before moving forward with contacting the patient-caregiver dyad. Only study team members will have access to the patient list. All study team members have completed CITI training.
- The study team member will attempt to contact the patient-caregiver dyad by phone to see whether they would be interested in learning more about and possibly participating in the research study. A verbal recruitment screener will be used.

- The study team member will explain the study and review the informed consent process. If both the patient and caregiver are interested they will proceed with scheduling a time for the patient-caregiver dyad to talk over the phone to conduct the informed consent review. At that time the research team member will mail out copies

of the informed consent and assent, the HIPAA authorization form, and the COVID-19 risk handout. This handout will inform the patient and caregiver of the risks related to COVID-19 which should help them when making the decision to meet in person or complete the assessments over the phone.

- The informed consent document and HIPAA authorization form will be reviewed over the telephone, rather than in-person, to minimize COVID-19 exposure. Once the participants have had time to ask questions and their understanding of the study is assessed, verbal consent will be attained. At this point in time, the study team member will ask the caregiver their appointment type preference, whether they want to meet in person the Eskenazi Health, Fifth Third Building or complete the assessments over the phone.
- Before verbal consent is obtained, the patient will be assessed to determine their capacity to consent to research.
    - The provider reports the patient lacks the capacity to consent.
    - The MMSE score is </= 17
        - If neither of the aforementioned measures have been met, the study team will ask the patient the following 4 questions:
            - What do you understand is wrong with your brain health right now?
            - Can you please explain in your own words the choices I have presented to you (choice to consent)?
            - If you decide to participate in this study, what good things might happen and what harm might occur?
            - Can you please explain how you decided to participate (or not participate) in this study?
        - The determination to have the capacity to consent to research the patient must answer these 4 questions correctly.
- The patient's Legal Authorized Representative (LAR) will consent on the patient's behalf if any of the following conditions are met:
    - The patient lacks the capacity to consent to research.
    - The patient is unable to communicate verbally or through another method due to the progression of their disease.
    - The patient has a court appointed guardian.

  As a part of the informed consent process, once capacity to consent has been established, the study team member will ask four teach back questions related to the study to both the caregiver and the patient. These questions are asked to ensure the caregiver and patient understand what they are consenting to, as well as making them aware that we have safety procedures in place to minimize their exposure to COVID-19.

- If the caregiver chooses to complete the assessments remotely, the study team member will schedule a time to deliver study supplies. Regardless of what

randomization group they are in, the study team member will deliver a plastic bin which contains a binder with paper copies of the assessments and other study related materials. It will be delivered to the patient and caregiver's respective homes without direct contact from team members (left outside home). If the dyad has been randomized to Group 2- The Three Assessments and Mobile Application and request to use a study mobile phone, this will be included in the plastic bin. The purpose of the study binder is to ensure the dyad is able to follow along during the assessment. The study team members will have a mirror binder where they will indicate the caregiver's responses to the assessment questions.

- The study team member will then arrange a time for the caregiver to complete the baseline study visit. The baseline study visit will be completed over the telephone or if the caregiver prefers in-person at the Eskenazi Health, Fifth Third Building located on the Eskenazi Health Hospital Campus (the in-person visit is entirely optional).

- The patient will not be present or participate in the baseline, 3-month or Final / 6-month research visit.

    - During the informed consent visit, patients who have the capacity to consent will consent to the HIPAA authorization form, which grants the study team permission to access their Eskenazi Health medical record and to communicate with their SECBCI clinical team. If they do not have the capacity to consent, then their LAR will consent on their behalf.
    - The caregiver will also be asked to consent to a HIPAA authorization form as some of the assessments address their own personal health. In addition they will agree that data collected by the research team can be used for the purposes of research.
- If consent by LAR is necessary, the study team will also seek a separate assent to participate from the individual with aMCI or AD. If an assent isn't obtained, an audible dissent will be honored.

- The patient with aMCI or AD will not receive any assessment or participate in interviews as their participation in the study is passive. Once enrollment of the patient with aMCI or AD is complete, they have completed their portion of the study. All other activities will involve the caregiver or the caregiver monitoring the patient with aMCI or AD.

- Once enrollment is complete the study team member will schedule and conduct the baseline research visit with the caregiver and provide education to the caregiver about Behavioral and Psychological Symptoms of Dementia (BPSD).

- If the participants choose to complete their assessment in person, then the study team member will call 24-48 hours before the baseline visit to make sure that in the past 2 weeks the patient and caregiver have not been in contact with anyone diagnosed with COVID-19, and have not developed any symptoms to suggest that

they currently have COVID-19. If they choose to complete their assessment over the telephone, then the study team will not make this call.

- If either the patient or caregiver have had a recent COVID-19 exposure or symptoms of COVID-19 then the research visit will be rescheduled and the patient and/or caregiver will be referred to resources to help address the patient's or caregiver's COVID-19 exposure and/or symptoms.

- The study team will follow Eskenazi Health policy by wearing a mask and gloves during any in-person research visit.

- The study team will sanitize all research supplies and research visit space before and after every research visit.

- **The baseline visit includes completion of the following (+/- 14 days from enrollment) and will be conducted over the phone or in-person at the Eskenazi Health, Fifth Third Building on the Eskenazi Health Hospital Campus. The in-person visit option is entirely optional and is based on the caregiver's expressed preference. COVID-19 safety and cleaning procedures are listed on page 22 of this protocol. Explanations that older adults and individuals with underlying health conditions are at greater risk for contracting COVID-19 and for having more severe health problems from COVID-19 if they contract the illness, including death, are outlined in the consent/assent:**
  1) Single Item Literacy Screener (SILS)
  2) Motivations and Barriers Survey
  3) Dyad Demographics
  4) Neuropsychiatric Inventory Questionnaire (NPI-Q)
  5) Perceived Stress Scale 14 (PSS-14)
  6) Zarit Burden Interview (ZBI)
  7) COVID-19 Physical & Mental Health Questionnaire
  8) Senior Technology Acceptance Form
  9) Caregiver & Environment Assessment of Neuropsychiatric Symptoms (CEAN)
  10) Caregiver Pre-Intervention Semi-Structured Interview
  11) Provision of education on BPSD
  12) Provision of a $10 Kroger gift card to both the patient and caregiver following completion of the baseline visit activities.
  13) Provision of an Eskenazi Health parking voucher (only if the visit takes place in-person).

- The caregiver in the intervention group will be asked to complete a survey on Behavioral and Psychological Symptoms of Dementia (BPSD) for the person with aMCI or AD for 6 months through either the caregiver's smartphone or a loaner smartphone from the study. The survey is a mobile health version of the

Neuropsychiatric Inventory – Questionnaire (NPI-Q) delivered by the Brain CareNotes (BCN) app. The following additional survey question well be asked following delivery of the NPI-Q, *"How burdensome was completion of the prior scale? (Answer options: not at all burdensome, mildly burdensome, moderately burdensome, or extremely burdensome)"*

- Clinically Significant BPSD will be defined as when any NPI-Q severity domain = 3 regardless of caregiver distress, or whenever NPI-Q caregiver distress is marked as "moderate" "severe" or "very severe".

- When Clinically significant BPSD is present at either the baseline visit, 3-month visit, final (6-month) visit or through completion of a BCN app record then the following actions will be triggered:

  1) Automatic free response follow-up questions (via BCN).
  2) Automatic notification of study team.
  3) Automatic notification of SECBCI clinical team.
  4) The research team to contact the caregiver and complete a semi-structured interview and the Caregiver & Environment Assessment for Neuropsychiatric Symptoms.
  5) The study team member documents findings and notifies PI and SECBCI clinical team.

- If the participants choose to complete their assessment in person then the study team will call 24-48 hours before the 3-month visit to make sure that in the past 2 weeks the patient and caregiver have not been in contact with anyone diagnosed with COVID-19, and have not developed any symptoms to suggest that they currently have COVID-19. If they choose to complete their assessment over the telephone, then the study team will not make this call.

- **The 3-month assessment visit occurs 3 months from their baseline completion (+/- 14 days) includes completion of the following, and will be conducted over the phone or in-person at the Eskenazi Health, Fifth Third Building on the Eskenazi Health Hospital Campus. The in-person visit option is entirely optional and is based on the caregiver's expressed preference. COVID-19 safety and cleaning procedures are listed on page 22 of this protocol. Explanations that older adults and individuals with underlying health conditions are at greater risk for contracting COVID-19 and for having more severe health problems from COVID-19 if they contract the illness, including death, are outlined in the consent/assent:**
  1
  2)
  3)
  4) Neuropsychiatric Inventory Questionnaire (NPI-Q)

5) Perceived Stress Scale 14 (PSS-14)
6) Zarit Burden Interview (ZBI)
7) COVID-19 Physical & Mental Health Questionnaire
8) Senior Technology Acceptance Form
9) Caregiver & Environment Assessment of Neuropsychiatric Symptoms (CEAN)
10) System Usability Scale (SUS) – only administered to the intervention group
11) Caregiver Post-Intervention Survey – only administered to the intervention group
12) Caregiver Pre-Intervention Semi-Structured Interview
13) Provision of an Eskenazi Health parking voucher (only if the visit takes place in-person).

- Clinically Significant BPSD will be defined as when any NPI-Q severity domain = 3 regardless of caregiver distress, or whenever NPI-Q caregiver distress is marked as “moderate” “severe” or “very severe”.

- When Clinically significant BPSD is present at either the baseline visit, 3-month visit, final (6-month) visit or through completion of a BCN app record then the following actions will be triggered:

1) Automatic free response follow-up questions (via BCN).
2) Automatic notification of study team.
3) Automatic notification of SECBCI clinical team.
4) The research team to contact the caregiver and complete a semi-structured interview and the Caregiver & Environment Assessment for Neuropsychiatric Symptoms.
5) The study team member documents findings and notifies PI and SECBCI clinical team.

- The study team will call 24-48 hours before the final / 6-month visit to make sure that in the past 2 weeks the patient and caregiver have not been in contact with anyone diagnosed with COVID-19, and have not developed any symptoms to suggest that they currently have COVID-19.

- **Final / 6-month visit occurs from the completion of their 6 month participation (+/- 14 days) includes completion of the following, and will be conducted over the phone or in-person at the Eskenazi Health, Fifth Third Building on the Eskenazi Health Hospital Campus. The in-person visit option is entirely optional and is based on the caregiver’s expressed preference. COVID-19 safety and cleaning procedures are listed on page 22 of this protocol. Explanations that older adults and individuals with underlying health conditions are at greater risk for contracting COVID-19 and for having more severe health problems from COVID-19 if they contract the illness, including death, are outlined in the consent/assent:**
  1) Caregiver is asked to return the loaner phone or where personal phone is used the Brain CareNotes app will be uninstalled.

2) Neuropsychiatric Inventory Questionnaire (NPI-Q)
3) Perceived Stress Scale 14 (PSS-14)
4) Zarit Burden Interview (ZBI)
5) Caregiver & Environment Assessment of Neuropsychiatric Symptoms (CEAN)
6) COVID-19 Physical & Mental Health Questionnaire
7) Senior Technology Acceptance Form
8) System Usability Scale (SUS) – only administered to the intervention group
9) Caregiver Post-Intervention Survey – only administered to the intervention group
10) Caregiver Post-Intervention Semi-Structured Interview
11) Provision of a $10 Kroeger gift card to the caregiver after completion of final visit activities.
12) Provision of an Eskenazi Health parking voucher (only if the visit takes place in-person).

- Once the final visit has been completed and the caregiver has received the $10-dollar Kroger gift card for their time, participation in the study will be complete.

- All semi-structured interviews will be audio recorded, stored securely, and transcribed. Once transcribed audio recordings will be destroyed.

- For every remote assessment, baseline/ 3-month/ 6-month, the research team will follow the COVID-19 safety precautions, which includes donning proper PPE and cleaning procedures.
    - If the subject requests a remote assessment, the research team member delivers and retrieves the supply box; the team member will don gloves and a mask during the respective transaction.
    - If the team member has retrieved the supply box they will put the supply box into another plastic bin, and load it into the trunk of their car. It will remain there until they have the opportunity to sanitize the plastic supply box and supplies.
    - The research team members will wear gloves and use sanitizing wipes and/or a prepared bleach solution with paper towels.
    - They will dispose of contaminated materials into a plastic bag and throw it away.
    - Once all of the supplies have been sanitized, the research team member will wash their hands thoroughly for a minimum of 20 seconds.

- For every in-person assessment, baseline/ 3-month/ 6-month, the research team will follow the COVID-19 safety precautions, which includes donning proper PPE and cleaning procedures. The research visits as well as the safety procedures have been reviewed and approved by Eskenazi Health.
    - If the subject is comfortable with being seen in person at the Fifth Third Building, the research team member will call the day before and the day of to screen the subject for any COVID-19 related symptoms.
    - If the subject responds “YES” then the assessment will be rescheduled. If the subject responds “NO” then they can proceed with the appointment.

- On the day of the appointment, the research team member will don a mask and wear gloves throughout the assessment. They will also request the subject wear a mask. If the patient/caregiver dyad doesn't bring one with them or isn't provided one upon arrival to Eskenazi Health, the study team will provide the mask for them. The dyad will also receive a parking voucher for their time spent with the research team member.
- If the subject has a cough, that is not COVID-19 related, the research team member will be required to wear a gown and face shield.
- All cleaning procedures remain the same.

8.0 Study Calendar

A detailed table of study activities is listed below.

Table 4. Schedule of Study Activities

Schedule of Study Activities	**Baseline Visit** *Within 14 days of enrollment*	**3-mo** *Within 14 days of scheduled* target date	**Final Visit** (6-mo) *Within 14 days of scheduled end*
Provision of Study Information	X		
Completion of Informed Consent and HIPAA Consent	X		
Installation of BCN on loaner or caregiver phone	X		
Provision of BCN instructions	X		
Provision of Education on BPSD	X	X	X
COVID-19 Symptom Screener	X	X	X
Collect/Administer the following:			
COVID-19 Physical & Mental Health Questionnaire	X	X	X
Single Item Literacy Screener (SILS)	X		
Dyad Demographics	X		
NPI-Q	X	X	X
PSS-14	X	X	X
ZBI	X	X	X
Motivators and Barriers Survey	X		
Caregiver Pre-Intervention and Phone Semi-Structured Interview*	X	X	X
Caregiver & Environment Assessment of Neuropsychiatric Symptoms (CEAN)*	X	X	X
BCN app - Task Completion Burden Questions*	X	X	X
BCN app - Free Response Follow-Up Questions*	X	X	X
Data from EMR	X	X	X
Senior Technology Acceptance Scale	X	X	X

System Usability Scale (SUS)		X Intervention group only	X Intervention group only
Caregiver Post-intervention Survey		X Intervention group only	X Intervention group only
Caregiver Post-Intervention Semi-Structured Interview			X
Loaner phone retrieved or BCN app uninstalled from the caregiver phone			X
Provision of a $10 Kroeger gift card to Caregiver	X		X
Provision of a $10 Kroeger gift card to Caregiver	X		
Provision of a parking voucher, only if visit is conducted in-person	X	X	X

* Triggered by Clinically Significant BPSD

9.0 Collection and Reporting of Adverse Events and Serious Adverse Events

The PI will comply with Indiana University IRB and the NIA guidelines for defining, collecting, and reporting serious adverse events (SAE), adverse events (AE), and unanticipated problems.

9.1 AE/SAE Definitions

9.1.1 Classification of Severity, Expectedness and Study Relatedness

Severity

- ***Mild -*** Awareness of signs or symptoms, but easily tolerated and are of minor irritant type causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.
- ***Moderate -*** Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning
- ***Severe -*** Events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating

Expectedness

AEs will be assessed as to whether they were expected to occur or unexpected, meaning not anticipated based on current knowledge found in the protocol, investigator brochure, product insert, or label.

Categories

- ***Unexpected*** *- nature or severity of the event is not consistent with information about the condition under study or intervention in the protocol, consent form, product brochure, or investigator brochure.*

- ***Expected*** *- event is known to be associated with the intervention or condition under study.*

Relatedness

The potential event relationship to the study intervention and/or participation is assessed by the PI with input from the study research coordinator.

Categories

- ***Definitely Related*** *- The adverse event is clearly related to the investigational agent/procedure – i.e. an event that follows a reasonable temporal sequence from administration of the study intervention, follows a known or expected response pattern to the suspected intervention, that is confirmed by improvement on stopping and reappearance of the event on repeated exposure and that could not be reasonably explained by the known characteristics of the subject's clinical state.*

- ***Possibly Related****: - An adverse event that follows a reasonable temporal sequence from administration of the study intervention follows a known or expected response pattern to the suspected intervention, but that could readily have been produced by a number of other factors.*

- ***Not Related****: - The adverse event is clearly not related to the investigational agent/procedure - i.e. another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the onset of the event and the study intervention and/or a causal relationship is considered biologically implausible.*

9.2 Protocol for AE/SAE Data Collection and Reporting

All adverse events, unanticipated problems and potential risks will be monitored and collected ongoing and throughout the study by the study PI, research coordinator and research assistants. Events related to any patient and caregiver loss of privacy or confidentiality or discomfort, anxiety or distress related to completing the intervention or the outcome questionnaires will be assessed by the research assistant via monitoring of the BPSD and caregiver distress data reported by the caregiver via smartphone, by phone or face-to-face interactions and by patient and caregiver reports.

For all participants, ***adverse events*** will be collected starting at enrollment and continue until after the participant has completed the study. If an adverse event occurs, it will be documented on the NIA adverse event and serious adverse event forms found at: https://www.nia.nih.gov/research/dgcg/clinical-research-study-investigators-toolbox/adverse-events.

Unanticipated problems that do not meet the definition of an adverse event, will be documented in a study log that will be stored in a secure electronic folder behind the IU fire wall. Details in the log may include participant study ID, date that the problem was reported or discovered by the study, a description of the problem, and a corrective plan and measures to prevent reoccurrence.

Measurement and Reporting of Adverse Events - Adverse events associated with monitoring of BPSD or caregiver distress related to AD are infrequent. Therefore, adverse event rates are expected to vary little between the two screening groups and control group. Adverse events will be monitored by the research coordinator on an ongoing basis. All adverse events and unanticipated problems will be reported to the study PI within 24 hours. We plan to present adverse events data to the DSMP safety officer when requested and at scheduled meetings. The NIA adverse event form will be used by the study staff to report all adverse events caused by the intervention.

In the case of a participant death related to the intervention, the NIA Program Officer, the IU IRB and the Safety Officer will be notified within 24 hours using NIA standardized forms for reporting serious adverse events (noted above). If unanticipated, serious adverse events occur (i.e., not listed in the Data and Safety Monitoring Plan) and that are related to the intervention, they will be reported to NIA Program Officer, the IU IRB, and to the study Safety Officer within 48 hours of study's knowledge of the event using NIA standardized forms for reporting serious adverse events. In cases where there is any question regarding the level of an adverse event or attributable cause, or areas of uncertainty, the study team and PI will consult with the Safety Officer and IU IRB. The summary of all other adverse events and unanticipated problems should be reported to NIA Program Officer and to the Safety Officer **semi-annually**, unless otherwise requested.

10.0 Data Safety Monitoring

The data safety monitoring plan (DSMP) for this trial will be monitored by the PI and a Safety Officer from an outside institution. The Safety Officer will act in an advisory capacity to the IU IRB and NIA Program Officer to monitor participant safety, evaluate the progress of the study, to review procedures for maintaining the confidentiality of data, the quality of data collection, management, and analyses.

10.1 Frequency of Data and Safety Monitoring

The Safety Officer and the PI will meet by teleconference initially to review and approve the study protocol and DSMP. Following that initial meeting, the Safety Officer and the PI will meet twice annually, either in person or by teleconference, to review study progress, data quality, and participants' safety. The first DSMP review will occur six months after approval to begin recruitment. Reporting will include subject accrual, adverse event rates, subject complaints, compliance to interventions, and protocol violations/noncompliance. Thereafter, the PI and Safety Officer review will occur every six months and review of adverse events reports will occur as summarized in table 5.

Table 5. Safety Officer Reporting

Frequency of Review			
	Each Occurrence	Quarterly	Semi-Annually
Subject accrual (adherence to inclusion/exclusion); drop-out rates; randomization		X	X
Serious adverse events (e.g. death)	X	X	X
Adverse events		X	X
Subject Complaints		X	X
Compliance with Intervention		X	X
Protocol Violation/Non-compliance		X	X
Stopping rules report	X		X

The PI is responsible for collecting and recording all study data and ensuring participants safety on a daily basis. Adverse events, will be monitored on an ongoing basis by the study research assistant and PI. All adverse events and unanticipated problems will be reported to the study PI within 24 hours. In the case of a participant death related to the intervention, the NIA Program Officer, the IU IRB and the Safety Officer will be notified within 24 hours. If unanticipated, serious adverse events occur (i.e., not listed in the Data and Safety Monitoring Plan) and that are related to the intervention, they will be reported to NIA Program Officer, the IU IRB, and to the Safety Officer within 48 hours of study's knowledge of the unanticipated serious adverse event. In cases where there is any question regarding the level of an adverse event or attributable cause, or areas of uncertainty, the study team will consult with the Safety Officer and IU IRB. The summary of all other serious adverse events should be reported to NIA Program Officer and to the Safety Officer semi-annually, unless otherwise requested by the Safety Officer.

10.2 Content of Data and Safety Monitoring Report

The research coordinator and study biostatistician will generate data and safety monitoring reports for PI and the Safety Officer that will contain:

a) Summary of adverse events and an explanation of how each event was handled,
b) Summary of complaints and how each complaint was handled,
c) Subject retention, including the number and reasons of participant withdrawals, and study quality
d) Intervention compliance (session attendance), and
e) Summary of protocol violations and how each was handled. All reports will be submitted to IU IRB at time of continuing review.

10.3 Safety Officer Affiliation

The Safety Officer will be determined after the NIA review of the proposed study DSMP. The Safety Officer will be reviewed and approved by the NIA. Should there be any questions regarding the independence of the Safety Officer, they will be addressed and corrected if necessary at that time.

10.4 Conflict of Interest for Safety Officer

The Safety Officer will not have a direct involvement with the study or conflict of interest with the investigators or institutions conducting the study. The Safety Officer will complete COI forms that report all financial interests such as salary, consulting and / or speaker fees, honoraria, research support, equity interests (e.g., stocks, stock options, or other ownership interests), and intellectual property rights (e.g., patents, copyright and royalties from such rights).

10.5 Protection of Confidentiality

Data presented at the PI and the Safety Officer semiannual meeting, the Safety Officer Reports, and discussions at the meeting will be kept confidential. Participant identities will not be known to the Safety Officer

10.6 Safety Officer Responsibilities

In summary, the Safety Officer will meet with the PI by teleconference or in person, initially to review and approve the protocol and DSMP, and then will meet semi-annually to review study progress, data quality, and participants' safety. Reporting will include subject accrual, adverse event rates, subject complaints, compliance to interventions, and protocol violations/noncompliance. Other Safety Officer responsibilities include:

- Review the research protocol, informed consent documents, plans for data safety and monitoring, and Manual of Procedures;
- Recommend subject recruitment be initiated after receipt of a satisfactory protocol;
- Evaluate the progress of the trial, including periodic assessments of data quality and timeliness, recruitment, accrual and retention, participant risk versus benefit, performance of the trial sites, and other factors that can affect study outcome;
- Consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the trial;
- Review study performance, make recommendations and assist in the resolution of problems reported by the Principal Investigator;
- Protect the safety of the study participants;
- Report to NIA on the safety and progress of the trial;
- Make recommendations to the NIA and the Principal Investigator concerning continuation, termination or other modifications of the trial based on the observed beneficial or adverse effects of the treatment under study;
- If appropriate, review data in accordance with stopping rules, which are clearly defined in advance of data analysis.
- Ensure the confidentiality of the study data and the results of monitoring; and,
- Assist the NIA by commenting on any problems with study conduct, enrollment, sample size, and/or data collection.

10.7 Stopping Rules

To ensure the integrity of the data, our study biostatistician will perform monthly cross tabulations of the data to confirm that each data field is being filled properly. It is unlikely that the study would be stopped early due to important favorable differences in the intervention group compared to control group because of the nature of the intervention and outcome measures. However, the study could be stopped early due to adverse events. Some events of particular concern would be a high number of study withdrawals due to discontent with the study procedures. The IU IRB and/or NIA Program Officer will make the final decision on whether or not to accept the Safety Officer's recommendation about discontinuation of any component of the study.

10.8 Limits of Assumptions

It is possible that baseline differences between the groups, excessive study dropouts and/or missing data by the interim measurement time point (midway point to targeted enrollment) will limit the value of data analysis of measurements. Baseline differences will be evaluated after the first measurement time point and effects on the power to detect differences in the primary outcome will be evaluated and communicated by the study biostatistician to the PI and Safety Officer. Given the monitoring plans outlined, it is exceedingly unlikely that there will be baseline differences between groups of any magnitude to threaten the validity of the study.

11.0 Study Withdrawal/Discontinuation

Participants can decide to withdraw from the study at any time. The study team will help the participant safely withdraw from the study.

To withdraw from the study the participant must either contact the principal investigator Dr. Daniel Bateman, MD by phone (317) 963-7326 (voicemail) or in writing darbate@iupui.edu (email) or address: Daniel Bateman, MD, IU Department of Psychiatry, Suite 2800, 355 West 16th Street, Indianapolis, IN 46202

If they cannot reach Dr. Bateman during his regular business hours (i.e. 8:00AM-5:00PM), they can call the IU Human Subjects Office at (317) 278-3458 or (800) 696-2949.

There are no expected risks for early withdrawal from the study.

12.0 Statistical Considerations and Analysis

12.1 AIM 1: Quantitatively and qualitatively, determine the feasibility of collecting responses on an EMA version of the Neuropsychiatric Inventory Questionnaire (NPIQ-EMA) from caregivers using smartphone technology at differing frequency intervals weekly or monthly, or a control group with data collected without the mobile health version and only at baseline and 6 month).

H1: Caregivers in the intervention groups will complete the assessments via smartphone and report an acceptable response burden. We anticipate that the response burden will be comparable to data collected in routine office visits.

Analysis H1: The primary outcomes for AIM 1 are feasibility and usability.
Feasibility will be measured 5 different ways:

1) Completion rate of the NPIQ-EMA over 6 months
2) Answers to the NPIQ-EMA response burden question every time the NPIQ-EMA is completed: "How burdensome was completion of the prior scale (Answer options: not at all burdensome, mildly burdensome, moderately burdensome, or extremely burdensome)"
3) Completion rate of the semi-structured phone interviews triggered by "clinically significant" symptoms
4) Post-intervention survey (quantitative)
5) Post-intervention semi-structured interview (qualitative) occurring immediately at the end of 6 months.

Usability will be measured in 3 different ways post-intervention:

1) System usability scale (SUS) total score
2) Post-intervention survey (quantitative)
3) Semi-structured phone interview (qualitative).

Quantitative Analysis: For quantitative analyses, there scores are continuous scale scores. Therefore, the intervention group feasibility scores will be compared to the control group's feasibility (response burden question) relative using ANCOVA to adjust for baseline characteristics including baseline demographics. The adjustment for baseline will increase precision and will statistically ensure comparability of the baseline level symptoms, even though random assignment should generally provide approximate comparability across a host of baseline characteristics.

Qualitative Analysis: We will interpret the post-intervention semi-structured interview feasibility and usability questions with the thematic analysis methodology developed by Braun and Clarke[44]. We will take an inductive approach searching for observed patterns and working to develop theories for these findings[44]. Reflexivity journals, subjective reflections of the investigators interpretation of emerging findings, will be used to help account for differences in investigator biases, values and judgments[45,46]. Expected outcomes regarding feasibility and usability will inform app development for AD caregivers in the future.

12.2 AIM 2: Determine whether more frequent surveillance of BPSD yields more actionable data.

H2: We expect there to be more occurrences of actionable data in the groups (i.e., intervention vs control) or conditions within a group (i.e., weekly vs monthly condition within the intervention group) that have more frequent monitoring.

Analysis H2: We define actionable data as data that could lead to a change in care plan. This was operationalized by setting “clinically significant” thresholds for NPI-Q symptoms and caregiver distress (see research design and methodology overview) that when reached led to contact and interval assessment between the research team and the caregiver. We will compare groups and conditions on the percentage of participants in each group or each condition that met at least one “clinically significant” threshold per month.

A between-group test, using mixed nonlinear models to adjust for baseline covariates, will be used to compare the intervention group to the control group. A within-group test, using mixed *nonlinear* models to adjust for baseline covariates as well as the period effect (i.e., months 1-6) and the randomized condition (i.e., assigned to start with weekly vs monthly surveillance frequency), will be used to compare the two surveillance conditions (measured weekly or monthly depending on the month period) within the intervention group in a 2 x 6 cross-over analysis.

12.3 AIM 3: Explore whether different surveillance intervals are associated with greater improvement in BPSD and CG distress.

H3: Groups or conditions within a group that receive more frequent surveillance paired with response to “clinically significant” symptoms will have greater improvement in BPSD and in caregiver distress.

Analysis H3: The change in rating of BPSD calculated by the difference in NPI-Q total scores and caregiver distress calculated by the difference in NPI-Q caregiver distress total scores at time of baseline assessment, 3 months and 6 months of the intervention group will be compared to the control group during the same time intervals. For this comparison we will use a between-group test, using mixed linear models to adjust for baseline covariates and to adjust for the baseline measure of the response variable (i.e., baseline NPI-Q total score or NPI-Q caregiver distress total score), will be used to compare the intervention group and control group on the repeated measured follow-up response variables (i.e., follow-up NPI-Q total score or NPI-Q caregiver distress total score). Separate models will be run for the NPI-Q total score and NPI-Q caregiver distress total score. A within-group test, using mixed *linear* models to adjust for baseline covariates and to adjust for the baseline measure of the response variable (i.e., baseline NPI-Q total score or NPI-Q caregiver distress total score) as well as the period effect (i.e., months 1-6) and the randomized condition (i.e., assigned to start with weekly vs monthly surveillance frequency), will be used to compare the two surveillance conditions (measured weekly or monthly depending on the month period) within the intervention group in a 2 x 6 cross-over analysis. We will also use these *linear* mixed models to perform the same type of between-group and within-group analyses in which the dependent variables are the following secondary variables: Perceived Stress Scale-14, and Zarit Burden Interview.

12.4 Power Justification and Analysis: The study was designed to have a power of 80% for two-tailed tests with a significance of 5%.

In the original power justification, we used a Cohen's d effect size of 0.65, which is between a medium (0.50) and a large (0.80) effect size. This was done primarily because of budgetary constraints associated with the K23 funding mechanism, which limited our ability to detect effect sizes smaller than 0.65 by enrolling beyond the proposed 96 dyads. However, with additional institutional funding support for 40% RA effort over 30 months we are now able to accommodate an enrollment sample size of 154 dyads (77 in each group), resulting in a projected 64 analyzable participants in each arm (control and intervention) after accounting for an attrition rate of 17% seen in the previously noted in the protocol trial (Callahan et al., 2006; Calculation = (64 X 2)/0.83 = 154). The analyzable sample of 64 per arm for two-tailed tests of two independent populations will provide 80% power (using alpha = 0.05) to detect a medium effect size of 0.50, which is a common effect size chosen in both R01 and K-series proposals. The power for paired within-group tests between weekly vs monthly conditions for the 64 analyzable intervention participants will be slightly greater than 80% power. Selecting a medium effect size of 0.50 matches the effect size seen in the aforementioned non-pharmacologic protocol trial, where effect sizes for total NPI score and NPI caregiver distress score improvements at 12 months were 0.502 and 0.568, respectively (Callahan et al., 2006). We expect that this would require approaching 12 dyads per month and consenting and enrolling 6 dyads per month (1-2 dyads per week) over a span of 30 months.

The SECBCI practice employs 6 physicians each with a half day clinic where they see between 4 and 9 patients on any given half day. Meaning that a range of 24 – 54 total patients are seen per week, with over one third of patients carrying a diagnosis of AD, leading to projections of between 8 – 18 eligible patients per week. Our prior work has consistently shown a recruitment rate of 50% for eligible patients, meaning that it would be reasonable to expect a maximal consent and enrollment rate of 4 – 9 subjects per week, a number much greater than the required study recruitment number of 1 – 2 subjects per week.

12.5 Interim Analysis

The interim analysis will be conducted following completion of the study by 77 patient-caregiver dyads (half-way point) for safety and efficacy monitoring. At this time, adverse events, drop-out rates, and missing data will be reviewed in entirety. Stopping rules will be applied when appropriate. The interim analysis will take place with the involvement of the Research Coordinator, Study Biostatistician, Safety Officer, and PI. The decision to continue the study must be unanimous among these 4 parties.

13.0 Data Management

The Regenstrief Institute has the capacity to safety collect and secure research and clinical data, and a long track record of doing so. To minimize the risk of breach of confidentiality, all study materials will be regarded as strictly confidential. Paper study documents will be stored in a locked filing cabinet in a secure office at the Regenstrief Institute, IU Center for Aging Research. Data will be extracted into a pre-designed

REDCap database stored behind the IU firewall. The study team will not collect any additional data without the consent of the participant and the Indiana University IRB. Computerized data entry and data storage systems are password protected and will be accessible only to study personnel.

Additionally, each participant will be given a unique identifier. Their data will be stored only using the unique identifier. A key that matches the unique identifier with identifiable data (name, dob, mrn) will be stored securely behind the IU firewall. All research study personnel have completed training in Human Subjects Research and HIPAA standards.

Screening data obtained from EMR and phone calls will be collected on paper, stored in a secure office and locked file cabinet in the Regenstrief Institute, Inc. In the instance a potential participant refuses enrollment, the paper document with screening data will be destroyed.

Participant data entered by the participant into the mobile application (BCN intervention) will be stored on an Amazon Web Services, HIPAA secure server and transferred into a secure REDCap database located behind the Indiana University Firewall.

Participants will be asked to give consent to have their interviews recorded. Audio recordings will be transcribed into an electronic word document form. Both the audio recordings and word document will be stored on a secure Regenstrief Institute. Once transcribed audio recordings will be destroyed.

13.1 Protection Against Study Risks

We will only approach potentially eligible patients and caregivers. Both members of the dyad or a legally authorized representative (LAR) need to consent to participate in the study. The PI will be available to clarify any questions and offer any needed consultation during the consent process or data collection process. Participants will be informed that representatives of the IRB or other regulatory bodies may inspect their study records to verify the information collected and that all information will be handled in strictest confidence. All analyses from the study will be performed and reported in aggregate and will exclude any personally identifying information.

To minimize potential anxiety on the part of patients or their family members, we will emphasize that participation is completely voluntary, that all information will be regarded as confidential, and that the subjects do not have to answer any questions they are uncomfortable answering. To minimize the risks that our intervention would have any negative impact on the dyad, we will monitor caregiver reporting of BPSD and caregiver stress, and burden of answering questions.

Additionally, if the patient's SECBCI treating physician objects to any patient's participation in the study because they believe it may have a negative impact on care may refuse to allow us to contact the subject to participate.

13.2 Rigor and Reproducibility: will be maintained through: 1) testing of the REDCap

database by study team prior to moving to production mode, 2) monthly audits of data entry into the REDCap database while the study is active and strict adherence to the proposed study protocol confirmed by audits of study team assessments.

14.0 Privacy/Confidentiality Issues

A recruitment waiver has been requested, for several reasons: (1) the eligibility criteria for participation is specific enough that any other recruitment method would result in inadequate recruitment, (2) bringing an individual with aMCI/AD to a medical or research appointment can be stressful for both the patient and the caregiver and calling the patient-caregiver dyad prior to their SECBCI appointment to gauge their interest in research has the potential to reduce stress, by reducing unexpected events and planning, 3) by allowing a recruitment waiver we will be able to receive the patient's most recent mini-mental status exam (MMSE) score, a measure of dementia severity that will be used in part to judge whether the patient has capacity to consent to research, and (4) this will allow the research team to seek the patient's SECBCI physician input to on whether or not he or she believes the patient to have capacity to consent to research.

Without access to MMSE scores and physician input, there would need to be more extensive testing burdensome to the patient and caregiver to determine if the patient has capacity to consent for research. Screening data will be destroyed immediately after learning that the patient-caregiver dyad declines interest in the study or declines study enrollment and for those who consent to the study screening data will be destroyed immediately following enrollment.

With the exception of screening information that will be destroyed if the patient-caregiver declines interest in the study, no data included in the study will be recorded without the consent of the patient-caregiver dyad. During the baseline research visit (point of consent), throughout the 6-month study, including the 3-month visit and the final visit, the caregiver will be asked questions about dementia, stress, coping and about difficult behaviors and psychiatric symptoms of dementia. It is possible that some of these questions could cause anxiety or discomfort. To minimize risk the caregiver is made aware that these types of questions will be asked ahead of time. The caregiver is also given the option to not answer the questions or to stop at any time.

As a part of the informed consent the caregiver-dyad will be asked to give consent for investigators to look at the patient's SECBCI medical records. There is the possibility that there could be a loss of confidentiality. We will minimize this risk by following the Regenstrief Institute, Indiana University Center for Aging Research data management and quality assurance practices as a method to mitigate risk for loss of confidentiality.

Additionally, each participant will be given a unique identifier. Their data will be stored only using the unique identifier. A key that matches the unique identifier with identifiable data (name, dob, mrn) will be stored securely behind the IU firewall. All research study personnel have completed training in Human Subjects Research and HIPAA standards.

15.0 Follow-up and Record Retention

The duration of the study will last for 5 years (6 months per each subject) or when enrollment and study activities of 154 patient-caregiver dyads is complete, whichever happens first. Paper data and electronic data will be kept for 5 years, at which point paper-based data will be securely destroyed in line with standard Regenstrief Institute procedures.

16.0 Other

16.1 Essential Equipment: We will use the Android Pixel phone by Google as a loaner phone for study subjects (caregivers) who do not have their own smartphone. The phone will be pre-loaded with the EMA version of the NPI-Q delivered by mobile app.

16.2 Potential Problems and Alternative Strategies:

16.2.1 Worsening caregiver burden: One concern of this proposal, is whether EMA monitoring of BPSD creates too much of a burden on the already burdened caregiver. Participants in our 28-day R01 study and in our pilot have not found the EMA pinging of the smartphone to be burdensome. The R01 study population demographics overlap significantly with our anticipated patient-caregiver population. As a safeguard, we will use usability and burden questions from the semi-structured interview from the initial 10 aMCI/AD caregiver-dyads to determine if the burden of answering EMA questions for the caregivers is too great. If that does turn out to be the case we will consider lengthening the surveillance interval or shortening the assessment battery.

16.2.2 Drop off in participation during the monthly response interval: It is possible that participation in the EMA BPSD surveillance might drop off during the two-month block, where BPSD surveillance takes place monthly instead of weekly. To address the potential, drop off in participation during the monthly surveillance block we will observe attrition rates for our first 10 dyads. If attrition rates exceed that of 17% we will make an adjustment to surveillance frequencies dropping the monthly surveillance block and instead continuing with weekly surveillance.

16.3 Summary and Future Directions: The following study looks to improve the care of aMCI/AD patient-caregiver dyads through the study of a BPSD surveillance intervention. Our choice of a weekly/monthly frequency, was a conservative approach in this early work to manage caregiver and provider burden but should evidence indicate high feasibility and value of weekly intervals, a future project could test higher frequencies to identify a frequency of diminishing return. Findings from this study will be used to develop a BPSD surveillance EMA intervention for a future R01 proposal that will improve the access to care and health of AD patient-caregiver dyads. This work will help my maturation into an independently funded investigator.

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