Improving Medication Adherence in Older African Americans with Diabetes

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CHAPTER 1: RESEARCH DESIGN SUMMARY

A. Purpose of Study: This randomized controlled clinical trial (RCT) will test the efficacy of a collaborative **Primary Care-Occupational Therapy (PC-OT)** intervention to lower hemoglobin A1c levels (HbA1c) in older African Americans (AAs) with type 2 diabetes (DM), Mild Cognitive Impairment (MCI), and suboptimal medication adherence and glycemic control. PC-OT aims to lower HbA1c levels by increasing adherence to oral hypoglycemic medications and other diabetes self-management (DSM) practices (e.g., diet, exercise). The control condition is **Enhanced Usual Care (EUC)**, which is usual medical care plus low intensity DSM education, delivered by a community healthcare worker. Participants in both PC-OT and EUC will have 5 initial in-home treatment sessions over 3 months, and then 3 subsequent booster sessions during this 12 month study. The primary outcome is a reduction in HbA1c of 0.5%, which reduces the risk for DM complications and other adverse health outcomes. The primary efficacy analysis will compare the proportion of participants in the 2 treatment groups with a reduction in HbA1c of 0.5% at month 6 (for short term effects) and at month 12 (maintenance effect). We will measure adherence to an oral hypoglycemic medication using a Medication Event Monitoring System (MEMS), self-report, and prescription refill records, and we evaluate the extent to which improving medication adherence mediates PC-OT's impact on HbA1c levels. The main hypothesis is that 55% of PC-OT-treated participants, compared to 25% of EUC controls, will have a reduction in HbA1c of 0.5% at 6 months. The secondary aims are to: (1) test the efficacy of PC-OT to reduce HbA1c level by 0.5% at 12 months (maintenance effect); (2) test the efficacy of PC-OT to increase adherence to an oral hypoglycemic medication at 6 and 12 months; and 3) determine whether increasing adherence to an oral hypoglycemic medication mediates PC-OT's impact on HbA1c levels at 6 and 12 months. Exploratory Aims will: 1) Evaluate if PC-OT over 12 months: a) improves other DSM practices (e.g., diet, exercise); b) prevents DM-related ER visits and hospitalizations; c) prevents declines in cognition, function and mood; and d) improves quality of life; and 2) Evaluate **PC-OT's** costs and net financial benefits.

B. Study Design: This study is a randomized controlled clinical trial in which the unit of randomization is the person. Participants will be randomized 1:1 to PC-OT (the experimental treatment) or EUC (the control treatment). Randomization will be stratified based on baseline HbA1c (7.5% to 9.0% vs. > 9.0%).

C. Sample: Participants will be 100 older persons who meet the following criteria:

Inclusion criteria:
1. African-American race (self-identified)
2. Age ≥ 60 years
3. Type 2 diabetes
4. HbA1c ≥ 7.5% at screening
5. MCI, based on National Institute on Aging/Alzheimer's Association (NIA/AA) criteria
6. ≤ 80% adherence to an oral hypoglycemic medication, as documented during a 2 week run-in phase using MEMS caps

Exclusion Criteria:
1. Treatment with insulin
2. Dementia, based on NIA/AA criteria
3. DSM-V psychiatric disorder other than depression or anxiety
4. End-stage renal disease
6. Hearing or vision impairment that precludes study participation

D. Participant Enrollment: Participants will be recruited from primary care and endocrinology clinics at Thomas Jefferson University.

E. Informed Consent: Informed consent will be obtained in participants' homes by the Outcome Assessor.

F. Participant Follow-Up. Participants will be assessed at baseline and months 6 and 12. Data from the MEMS bottle/caps will be collected monthly in participants' homes.

G. Data Monitoring. Data monitoring will consist of: (1) having research staff check all completed instruments for errors of omission; (2) running frequency distributions on a regular basis to check for out of range values; and (3) carefully documenting all edits made to the data sets.

H. Quality Assurance Procedures: At the study onset, the Outcome Assessor will receive extensive training on administering all assessments. This training will be conducted by the P.I. (Dr. Rovner). Rater drift will be minimized by having Drs. Rovner or Casten review a random sample of 10% of in-home assessments (both baseline and follow-up) throughout the study.

The PC-OT occupational therapists (OT) will undergo training to administer the active intervention. Training will consist of diabetes education (to be administered by Co-Is Drs. White and Jabbour, and Hill-Briggs). Co-I Cathy Piersol, PhD will lead the training on the occupational therapy portion of the intervention. Co-I Robin Casten, PhD will train the OTs on the principles and administration of behavior activation. Drs. Rovner and Casten will hold case review meetings twice a month with the study OTs. The purpose of these meetings is to review current cases, problem solve issues as they arise, and provide ongoing supervision for both study treatments. Drs. Piersol and White will attend the PC-OT case review meetings as well.

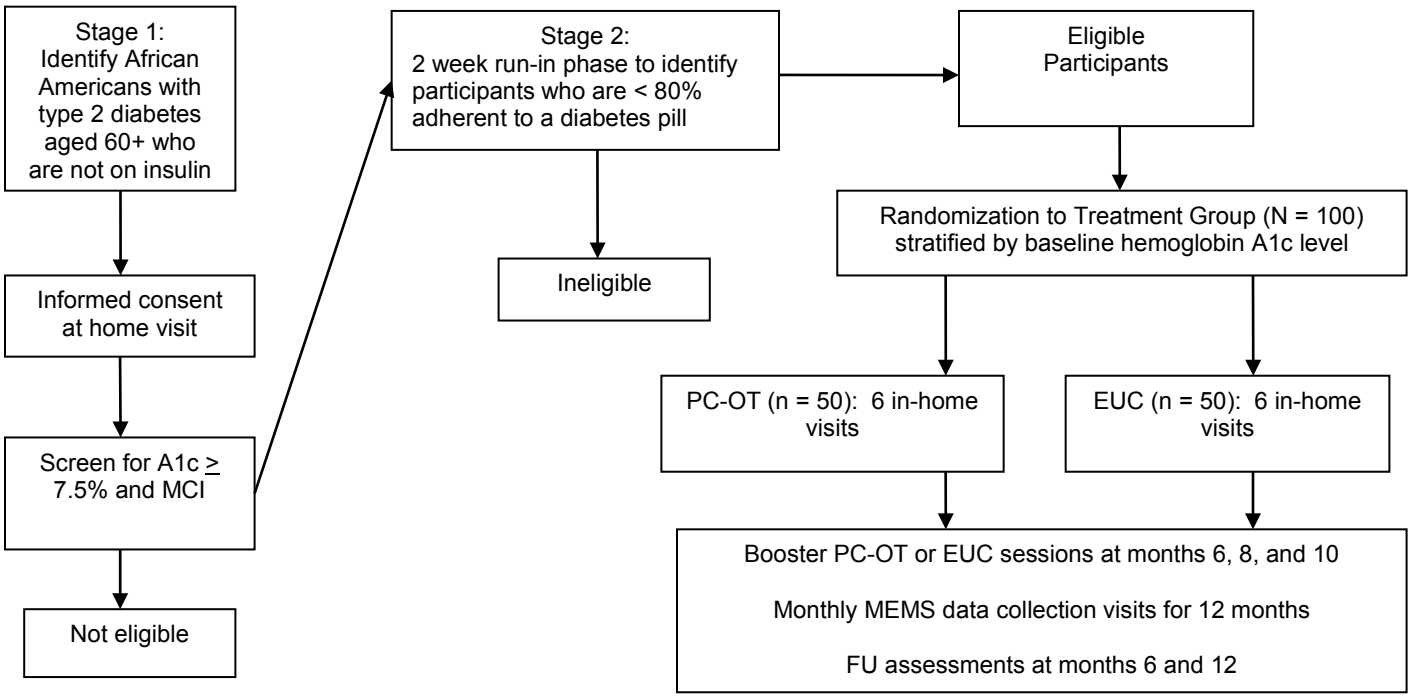
Dr. Casten will train the community health care worker (CHW) to deliver EUC, and Drs. White, Jabbour, and Hill-Briggs will provide diabetes education. Drs. Rovner, Casten, and White will hold twice monthly case review meetings with the EUC interventionist.

Treatment fidelity for both PC-OT and EUC will be maintained by having Drs. Casten, White, and Piersol review a random one-third sample of audio recordings of intervention sessions. This will be followed by telephone supervision sessions with the OTs or the CHW.

Table 1. Design Summary

Objective	To test the efficacy of PC-OT to lower hemoglobin A1c levels (HbA1c) in African Americans aged 60+ who have mild cognitive impairment (MCI), type 2 DM, ≤ 80% adherence to an oral hypoglycemic medication, and HbA1c ≥ 7.5%.
Major Eligibility Criteria	1. African-American race 2. Age 60+ 3. Type 2 diabetes 4. HbA1c ≥ 7.5% 5. MCI 6. ≤ 80% adherence to an oral hypoglycemic medication
Randomization Unit	Person
Stratification	Baseline hemoglobin A1c of 7.5% to 9.0% vs. >9.0%
Treatments	PC-OT (n = 50) EUC (n = 50)
Recruitment Site	Primary care and endocrine clinics at Thomas Jefferson University
Enrollment Site	Participants' homes
Outcome Measures	Primary: Hemoglobin A1c level Secondary: Medication Adherence
Sample Size	100
Enrollment Timeline	Months 6 through 26
Masking Procedures	This is a single-masked study in which the outcome assessor will be masked but participants and interventionists will not.
Study Visit Schedule	Assessments: Baseline, 6, and 12 months Interventions: 5 in-home sessions of either PC-OT or EUC, followed by 3 booster sessions at months 6, 8, and 10
Length of Follow-up	12 months

Figure 1. Flow Chart and Study Design



CHAPTER 2: ORGANIZATIONAL STRUCTURE

PI: Barry Rovner, MD. Dr. Rovner will be responsible for the overall conduct of the project. This will include assuring the integrity of the study interventions, supervision of procedures to ascertain the sample, obtain informed consent, train and supervise research staff, ensure the quality of data collection and management, and conduct data analyses. Dr. Rovner will also guide the development and administration of study questionnaires, advise on conventions for scoring neuropsychological instruments when questions arise, and safeguard procedures for patient confidentiality. Dr. Rovner will also hold case review meetings with the PC-OT and EUC interventionists (separately) and the outcome assessor to assure data quality.

Co-I; Christine Arenson, MD. Dr. Arenson is director of Geriatric Medicine and a practicing clinician in the Jefferson's Department of Family and Community Medicine. Her expertise lies in developing educational activities that focus on enhancing the care of older adults and persons with chronic conditions. For this study Dr. Arenson will supervise recruitment procedures at the Family Medicine and Senior Health clinics. She will also train study staff on using Jefferson's Electronic Medical Record (EMR) system.

Co-I: Robin Casten, PhD. Dr. Casten will coordinate the daily operations of data collection, management, and analysis. Her duties will include: 1) coordinate participant recruitment; 2) oversee treatment fidelity for both interventions; 3) participate in the training of research staff and supervise their daily activities; 4) conduct quality control for data collection, entry, and cleaning; 5) assist in preparation and dissemination of research findings; 6) prepare IRB documentation; and 7) attend PC-OT and EUC case review meetings. Dr. Casten will also assist with the interpretation of study results and the dissemination of research findings.

Co-I; Laura Gitlin, PhD. Dr. Gitlin is a nationally recognized expert in designing and conducting clinical trials of in-home behavioral interventions, particularly for older African Americans. She will consult on project design and implementation, and assist with data interpretation and the dissemination of study findings.

Consultant; Felicia Hill-Briggs, PhD. Dr. Hill-Brigs will advise on the delivery of PC-OT and will assist with interventionist training. She will assist with refining the educational materials to be distributed to participants in both the PC-OT and EUC groups. Dr. Hill-Briggs will also help to ensure the cultural relevance of the educational materials and recruitment and retention strategies. The educational components of both interventions will incorporate aspects of the educational materials that Dr. Hill-Brigs developed for Project DECIDE (Decision-making Education for Choices In Diabetes Everyday), which aims to improve glycemic control using problem-based diabetes self-management training that is adapted for low literacy and accessibility.

Co-I: Serge Jabbour, MD. Dr. Jabbour will oversee medical and safety procedures, focusing on training, obtaining, and interpreting the results of hemoglobin A1c testing and other aspects of the medical management of diabetes. As a Co-Investigator he will assist in the interpretation of study results, contribute to training on DM, and prepare manuscripts.

Outcome Assessor: Tammy Johnson. Ms. Johnson will obtain informed consent and will administer all assessments (baseline and follow-up) masked to treatment assignment.

Biostatistician: Benjamin Leiby, PhD. Dr. Leiby will create the randomization schedule, consult on questions of study design and execution, direct the statistical analysis, and assist with manuscript preparation.

Study Coordinator; Megan Mowrer. Ms. Mowrer will be responsible for: 1) assisting with subject recruitment and enrollment; (2) maintaining administrative data bases; 3) assisting with the preparation of IRB documentation; 4) managing the payment of participant incentives; and 5) collecting data regarding medication changes and significant health events from the EMR.

Co-I; Catherine Piersol, PhD. Dr. Piersol will oversee the occupational therapy component of the intervention. In this capacity, she will hire the OT interventionists, develop and provide training on delivering the occupational therapy intervention within the context of a clinical trial, train on administration of OT assessments, oversee treatment documentation procedures, and provide supervision to the OT interventionists. Dr. Piersol will attend the case review meetings and will listen to recordings of treatment sessions for treatment fidelity purposes. Dr. Piersol will assist in the interpretation of study results and the dissemination of study findings.

Co-I; Laura Pizzi, PharmD, MPH. Dr. Pizzi is a Professor at Thomas Jefferson University's School of Pharmacy. As a registered pharmacist and applied health economics researcher, Dr. Pizzi will design and conduct the economic analysis of this clinical trial, consult on medication adherence measurement and medication use, and deliver the interventionists' training module on diabetes medications.

Co-I: Rhea Powell, MD. Dr. Powell will coordinate participant recruitment from the 3 Internal Medicine practices at Jefferson. She will also advise on chronic disease management in the setting of DM and other medical comorbidity.

Co-I: Neva White, DNP. Dr. White will provide diabetes education training to the study OTs, the EUC interventionist, the Outcome Assessor, and the Research Assistant. She will provide ongoing supervision regarding the provision of diabetes self-management education to study participants. She will also be available to study staff to address diabetes-related issues as needed. Dr. White will attend both the PC-OT and EUC case review meetings, and will assist with treatment fidelity for both study interventions as it pertains to diabetes education.

Study Occupational Therapists; To be hired. The OTs will deliver the active intervention to participants randomized to PC-OT. In this capacity they will: (1) adhere to the protocol for administering the active treatment including collaborating with the participants' PCPs; (2) maintain detailed records of participants' progress including compliance with Action Plans; and (3) audio tape intervention sessions for treatment fidelity purposes. The OTs will attend PC-OT case review meetings.

Community Health Care Worker (CHW); To be hired. The CHW will administer the low intensity DM education intervention component of EUC to participants randomized to the control treatment arm. The CHW will be responsible for maintaining treatment notes, adhering to the EUC treatment protocol, and recording treatment sessions for treatment fidelity purposes. The EUC interventionist will have regular case review meetings with Drs. Rovner, Casten, and White for supervision purposes.

Research Assistant; To be hired. The research assistant will go to participants' homes on a monthly basis to download electronic data stored in the MEMS caps. The RA will also conduct the run-in visits.

Research Assistant for Cost Analysis; To be hired. The research assistant will provide ongoing research assistance to Dr. Pizzi on the cost aim. She will be responsible for organization of files pertaining to the cost study, and she will develop a table to inform monetization of staff time. She will also construct the necessary reference tables for monetization of healthcare services, medications, and mileage, and procure receipts for supplies required to deliver the training and intervention. She will also support the biostatistician when he is conducting the analysis, in particular, when he requests clarifications or confirmation of the cost data elements. Finally, she will assist in constructing data tables and figures, as well as preparation and technical review of all resulting publications and presentations pertaining to the cost findings.

CHAPTER 3: STUDY POLICIES

1. Consent

Participants will be required to provide signed informed consent to participate in the study. Written consent will be obtained by the study assessor in participants' homes.

2. Recruitment

Participants will be recruited from primary care and endocrinology clinics at Thomas Jefferson University. Potentially eligible patients will be informed of the study via recruitment letters from their attending physicians. Study staff will follow up with a telephone call to patients to explain the study and to ascertain eligibility criteria. Most participants will be recruited from primary care clinics, but some will be recruited from endocrinology clinics. For participants recruited from endocrinology, the endocrinologist (rather than the PCP) will collaborate with the OT for participants randomized to the active treatment group, and all EMR communications will be with the endocrinologist.

3. Participant costs

All patient costs directly related to study participation will be covered by the trial, and thus there will be no financial burden on study participants. Participants will be responsible for the cost of their diabetes medications.

4. Access to study information

4.1. Study documents

Study documents include: (1) the grant application (excluding the study budget); (2) progress reports to the NIH; (3) materials submitted to the IRB at Thomas Jefferson University; (4) meeting minutes; (5) reporting of adverse events; (6) the Manual of Procedures; (7) treatment manuals; and (8) manuscripts and presentations. The study PI and Co-Is will have access to all study documents. Other study staff will have access to study documents on an as needed basis. The IRB at Thomas Jefferson University is permitted access to all study materials.

4.2. Study data

All data will be de-identified expect for the pharmacy labels for the medication to be put into the MEMS bottle and the pharmacy records used to indicate the number of times participants' prescriptions were filled during the study. The data collected from screening, blood tests, baseline and follow-up assessments, MEMS data downloads, EMR, and intervention sessions will be de-identified.

The identity of individual participants will not be revealed in any public report or presentation. The PI is responsible for assuring that the integrity and confidentiality of study records are maintained. Study data include raw data files, hard copies of completed data collection forms, blood test results, data collected from EMR and pharmacies, and intervention notes and forms. The PI (Barry Rovner, MD), Dr. Casten, Dr. Leiby, Dr. Pizzi, and the study coordinator will have access to identified study data throughout the trial because they will not be involved in the direct administration of the treatments. No other study personnel will have access to raw data or identified data. The IRB at Thomas Jefferson University is permitted full access to de-identified study data.

CHAPTER 4: PARTICIPANT ENROLLMENT AND RANDOMIZATION

1. Participant recruitment

This study will enroll 100 participants, at a rate of 5 subjects per month. A participant will be considered to be enrolled in the study after they sign the informed consent form. Randomization will occur once it is established that participants meet all inclusion criteria (after the 2 week run-in phase).

We will invite patients who meet the following eligibility criteria to be screened for study participation:

1) African-American race
2) Age ≥ 60 years
3) Type 2 DM
4) HbA1c ≥ 7.5%
5) MCI, based on National Institute on Aging/Alzheimer's Association (NIA/AA) criteria
6) ≤ 80% adherence to an oral hypoglycemic medication, as documented during a Run-in Phase using MEMS caps.

Exclusion criteria are as follows:

1) Treatment with insulin
2) Dementia, based on NIA/AA criteria
3) DSM-V psychiatric disorder other than depression or anxiety
4) End-stage renal disease
5) Hearing or vision impairment that precludes study participation

Potential participants will be recruited as follows. Billing records from TJUH clinics will be reviewed to identify AAs aged 60+ who have type 2 diabetes. We will obtain the attending physician's permission to contact these patients. We will then mail an introductory letter signed by the PCP (or endocrinologist for patients recruited from the endocrinology clinic) that describes the study and includes a telephone number to call if the patient wishes to participate or opt out. We will also place study brochures and posters in the waiting rooms of the medical recruitment sites.

The letters will be followed by recruitment calls (to patients who did not opt out) from study staff to ascertain study interest. If the patient is interested, study staff will explain the study details and confirm eligibility criteria (e.g., self-report of memory problems). Study staff will administer a brief memory test to screen out patients who are unlikely to have MCI. The memory test will consist of asking patients to recall a list of 12 words. Participants who recall fewer than 5 words will be considered to have possible memory impairment, and will be invited to enroll in the study. The Outcome Assessor will then schedule an in-home visit to obtain informed consent, administer the baseline assessment, and test the participant's A1c level. Within 1 week of this in-home visit, the PI will review the participant's neuropsychological test profile to determine if the participant has MCI, and will confirm that the participant meets all other eligibility criteria.

For participants who meet cognitive and diabetes criteria, the research assistant will contact the participant to discuss the Run-in Phase. Participants will be informed that they will be paid $10 for each of the two run-in visits. During this call, the RA will review the participants' current oral hypoglycemic medications, and will ask them to identify the one that is prescribed at the highest dosing frequency (this will be referred to as the Target Medication). The Target Medication is the diabetes drug that is selected to be put in the MEMS bottle/cap. The RA will instruct the participant to contact their pharmacy to request 2 copies of the label for the Target Medication. The RA will offer to

call the pharmacy on the participant's behalf if the participant prefers. The RA will then pick up the labels from the pharmacy (or have the labels faxed if possible). The RA will bring a signed letter from the PI to the pharmacy that explains that the participant is in a research study, and that the labels are needed for study participation. The purpose of the study will not be revealed in the letter. Once the RA has the labels, he/she will schedule an appointment to go to the participant's home. At this visit, the RA will demonstrate the use of the MEMS bottle/cap and will place one of the pharmacy-provided labels on the bottle (the second label will be stored in the participant's research chart). The RA will ensure that participants can correctly use the cap/bottle; those who cannot will be dropped from the study. Based on a pilot study of MEMS bottles/caps with patients who have MCI, the anticipated rate of participants who will be dropped for this reason is very low. The RA will give participants a hotline number to call if they have difficulties with the MEMS bottle/cap, will call all participants in 2 days to identify problems, and will meet with participants to provide additional instruction if needed.

After 2 weeks, the RA will return to the participant's home with an electronic reader to download the data from the participant's run-in phase and to determine the run-in adherence rate. The adherence rate will be determined at this visit while the RA is in the participant's home. If the adherence rate is less than 80%, the RA will review again the outline and procedures of the clinical trial, including a description of the 2 study interventions, randomization, and the outcome assessment schedule, and will confirm the participant's willingness to proceed. The RA will leave the MEMS bottle/cap with the participant and will instruct them to continue to take the Target Medication using the MEMS bottle/cap. The participant will be told that the RA will visit monthly to download the MEMS data, and that they will be paid $10 for each MEMS reading visit. Participants will be instructed to call the study coordinator if the dose of the Target Medication is ever changed or stopped.

The adherence rate will be determined by the percent of pills that were taken on time. The instructions on the pharmacy label will be used to determine the number and timing of pills to be taken each day. If a participant only takes 1 dose daily, and no time is specified on the label, the RA will ask the participant what time they typically take the pill. This time will be designated as the Target Time. If the label indicates that multiple daily doses should be taken (and no time is listed), the participant will be asked for the times that they usually take each dose to determine the Target Time of each dose. If the label specifies specific times, these times will be the Target Times. To be considered as "on time", a pill must be taken within 4 hours of the Target Time. Days in which the participant did not open the MEMS bottle due to out of the ordinary circumstances (e.g., hospitalization) will not be counted when computing the adherence rate. All participants will be given a MEMS log to write down such situations. In addition, at the second run-in visit, the RA will ask participants if there were any unusual circumstances that interfered with medication taking. At each MEMS reading visit, participants will be asked if the time(s) that they take their Target Medication have changed, and if so, the adherence rate for that particular reading will be adjusted accordingly.

Once it is established that the run-in adherence rate is <80% and the participant agrees, the RA will inform Dr. Casten that the participant should be randomized. Randomized participants will be instructed to put any refills for the Target Medication in the MEMS bottle.

2. Assignment of study identification numbers

Study identification numbers will be assigned immediately after enrollment. The identification number will consist of a 3 digit number chosen from a consecutive list. All data forms will also contain the participant's 3 initials (the first letter of the first, middle, and last names). If the participant has no middle name, an X will be used. Identification numbers and initials will be used to cross reference

participants in the data bases. Participant names, corresponding identification numbers, address, and phone numbers are then entered into the participant log.

3. Baseline Assessment

The following will occur at the baseline assessment. The Outcome Assessor will: 1) explain the details of the study to the participant; 2) obtain informed consent in writing; and 3) administer the baseline assessment.

4. Randomization to study group

Randomization will occur after: (1) the PI confirms that the participant has MCI; (2) the PI confirms that the participant's A1c is $\geq$ 7.5%; and (3) the run-in adherence rate is determined to be < 80%. Once all 3 criteria are confirmed, the RA will contact Dr. Casten, who will randomize the participant. Ben Leiby, PhD, the study statistician, will develop the randomize schedule.

Prior to beginning participant recruitment, Dr. Leiby will record the group assignments on a sheet of paper, which will then be placed in a sequentially numbered opaque envelope by stratification group. The envelopes will be stacked in the order in which they will be opened. The resulting stack of envelopes will be given to Dr. Casten, who in turn will store them in a locked box.

After the randomization is performed for a given participant, the study coordinator will send through inter-departmental mail a photocopy of the randomization sheets to Dr. Leiby, who will store them in a locked file. The original will be stored in the participant's chart.

Figure 2. Sample Randomization Notice:

Treatment Assignment

Stratification group: Baseline HbA1c level 7.5% to 9.0%

Sequence # 1

Date of Randomization: ____/____/____
month / day / year

Participant Initials: _____

Study ID #_____

ASSIGNMENT: Treatment Group: PC-OT

Completed by: _____

CHAPTER 5: SCHEDULE AND OVERVIEW OF DATA COLLECTION

1. Overview

The Outcome Assessor will conduct assessments at baseline, and 6 and 12 months post-baseline masked to treatment assignment in participants' homes. Below we describe all of the study instruments. Table 2 describes how each measure will be used to assess the study aims.

2. Description of Study Measures

Personal/Demographic Characteristics: At baseline we will collect data on age, sex, education, duration of DM, marital status, living arrangements, family responsibilities, socioeconomic status, alcohol use, and access to healthy foods.

Uniform Data Set (UDS) Neuropsychological Battery**:** We will administer the UDS at baseline to diagnose MCI and at months 6 and 12 to detect cognitive change. The UDS assesses multiple cognitive domains and distinguishes normal cognition, MCI subtypes, and dementia. Most tests have age- and education-adjusted norms for AAs. We will enroll participants who meet criteria for amnestic or nonamnestic MCI based on: 1) self-reported cognitive decline (to be ascertained during the screening call); 2) preserved general cognition (i.e., Mini-Mental State Exam > 24); 3) minimal functional disability (i.e., scores ≥ 50.0 on the University of California Performance-based Skills Assessment (UPSA); and 4) scores ≤ 7th percentile or ≤ 1.5 SD on a test of memory, executive function, language, processing speed, or visual-spatial function.

Function: We will administer the University of California Performance-based Skills Assessment **(**UPSA) which, as a performance-based test, avoids self-report bias. The UPSA evaluates financial (i.e., writing checks, counting change) and communication skills (e.g., using telephone), takes 10–15 minutes to administer, has good psychometric properties, correlates with neuropsychological test scores, and distinguishes older persons with intact cognition, MCI, and dementia. We will also administer the Activities of Daily Living–Prevention Instrument, a self-rating scale of ability to carry out multiple complex activities (e.g., shopping, preparing meals).

Medical Comorbidity: The Health-Related Quality of Life Comorbidity Index (H-RQLCI) assesses 20 medical conditions and yields a reliable and valid index of medical comorbidity. The study coordinator will review the EMR to complete the H-RQLCI and also track changes in blood pressure and lipids. Although the latter contribute to health outcomes and may respond to better medication adherence, they are not the primary focus of the intervention. We will also ask participants to identify functional limitations due to physical problems (e.g., vision loss, mobility problems, and peripheral neuropathy) and will track weight over time.

Medications: The OA will record all participants' medications (including over-the-counter medications) at baseline and months 6 and 12, will record the names, doses, dosing schedule, and aids/procedures currently used to take them, and ascertain reported reasons for nonadherence to any prescribed medication.

Beliefs about Medicines Questionnaire (BMQ): The BMQ assesses beliefs about the necessity of prescribed medications and concern about adverse effects (e.g., "It's better to do without medicines"; "Natural remedies are safer than medicines."). Its reliability and validity have been established in older AAs with DM. Responses are rated on a 5-point Likert scale, ranging from "strongly disagree" to "strongly agree"; higher scores indicate stronger beliefs.

Diabetes Self-Care Inventory-Revised (DSCI-R): This self-report instrument measures adherence to 12 DSM care behaviors (e.g., glucose monitoring, exercise, diet) over the previous 1–2 months. It is

a reliable and valid instrument that correlates with HbA1c levels and is sensitive to treatment effects over time. Individuals rate adherence to the 12 items (written on 6th grade reading level) on a 5-point Likert scale (i.e., 1 = "never do this" to 5 = "always do this as recommended"). Higher scores indicate better adherence.

Patient Health Questionnaire-9 (PHQ-9): Depression is associated with medication nonadherence in DM. We will use the Patient Health Questionnaire-9 (PHQ-9) to measure depressive symptoms (as a continuous variable) over time to assess PC-OT's impact on depression. The PHQ-9 has known reliability and validity in older AAs.

Diabetes Distress Scale (DDS): The DDS is a valid diabetes-specific Quality-of-Life (QoL) measure that assesses emotional distress and functioning in persons with DM. It yields subjective appraisals of health and well-being and has been used as a QoL measure in other studies of older AAs with DM.

Hemoglobin A1c (HbA1c): HbA1c level reflects blood glucose concentration over the preceding 2–3 months and predicts DM complications, health care utilization, and costs. Although levels ≥ 7.0% indicate uncontrolled DM for most older persons, levels of 7.5-8.0% are acceptable in older persons with long-standing DM, extensive medical comorbidity, or a history of severe hypoglycemia. These patients nevertheless require adequate glycemic control to prevent dehydration, electrolyte abnormalities, incontinence, falls, and hyperglycemic hyperosmolar coma. We will measure HbA1c from blood obtained by venipuncture and analyzed with high performance liquid chromatography. Because these HbA1c levels constitute the primary outcome measure and need to remain masked to treatment assignment, they will not be available to PCPs. However, if we detect HbA1c levels ≤ 6.5 , ≥ 10.0, or a change ≥ 1.5 over 6 months, we will notify PCPs.

Blood samples will be obtained by the Outcome Assessor. The Assessor will be instructed to store the blood sample in a portable cooler during transport. She will be required to drop the blood off at the lab within 4 hours of collection. The samples will be de-identified; they will only be labeled with the participant's initials and study identification number. Results of the blood tests will be sent to the PI.

Some participants may start insulin during the study, which may have a substantial effect on HbA1c independent of adherence to oral agents alone. For this reason we will consider these participants as having not had meaningful reduction, regardless of the actual HbA1c at 6 months. We anticipate this will occur in ≤ 5 % of participants and we will recruit additional participants to account for this effect.

Medication Adherence: We will assess adherence to the Target Medication with Medication Event Monitoring System (MEMS). MEMS are electronic monitoring caps that electronically record the date and time of medication bottle openings. Research studies indicate that MEMS use does not influence adherence. Because MEMS caps are costly, we will measure adherence to one oral hypoglycemic medication, which participants will identify as the one they are prescribed at the highest dosing frequency. We will also ask participants to keep a MEMS log to report unintended or missed openings (e.g. early pill removal to be taken later in the day) or prolonged non-usage (e.g., if hospitalized). MEMS adherence to a single medication correlates highly with adherence to other medications. For randomized participants, we will download MEMS data every month for 12 months. Prior to each monthly MEMS data download visit, the study coordinator will logon to EMR to see if the participant's Target Medication dose was changed. If she detects a medication change, she will ask the RA to visit the participant at home to ensure that he/she makes the appropriate adjustment. For example, if the MEMS-monitored drug is discontinued, the RA will ensure that the newly prescribed drug is placed in the MEMS bottle. We will also ask participants to call the study coordinator if the PCP makes any medication changes.

We will assess self-reported adherence with the Morisky Medication Adherence Scale (MMAS). The MMAS is a widely used, validated self-report medication adherence instrument. Scores range from 0 to 4, with higher scores indicating better adherence. In adults with DM (37% AA), Morisky scores ≥ 3 were associated with a 10% lower HbA1c level. Although self-reports often overestimate actual adherence and are biased by memory problems, self-reports are commonly used in clinical practice and will provide a useful comparison to MEMS data.

We will also assess Pharmacy Refill Prescription Data. At 3, 6, 9, and 12 months, we will fax a release form (signed by the participant) to the pharmacy(cies) where s/he obtained their medications. The release will ask the pharmacist(s) to fax a printout of all medication fills over the study period to the Study Coordinator. These are available as standardized reports in pharmacy computer systems. The reports show the medication name, dose, frequency, quantity, and date filled. Our experience obtaining medication labels for MEMS bottles during our pilot study suggests that pharmacies will cooperate with this data request. Our team pharmacist (Dr. Pizzi) will identify all oral DM medications and calculate the Proportion of Days Covered (PDC), an established measure of prescription-based adherence developed by the Pharmacy Quality Alliance and endorsed for DM medications by the National Quality Forum. We will define PDC-adherence as having adequate supply of hypoglycemic medication for ≥ 80% of days from baseline to 6 months, and from 6 to 12 months.

Health Care Utilization: The Study Coordinator will review the EMR every 6 months to record incident medical events and track number of physician visits, screening eye and foot examinations, acute hospitalizations, ER visits, and deaths. We will specifically look for medical events due to adverse drug reactions. We will also record any changes to the diabetes medication regimen. We will supplement these data by asking participants if they received any medical care outside of the TJU health system.

Social Supports: We will assess receipt of tangible assistance with medications and other daily living activities when we complete the Activities of Daily Living–Prevention Instrument. Asking participants if someone helps them with each activity will identify different sources of support for different tasks. This will yield several quantitative measures of tangible assistance including number and relation of different helpers (e.g. family vs. friends vs. paid assistants); number and nature of tasks for which assistance is routinely provided, and unmet needs (i. e., tasks for which assistance is needed but none is routinely available).

Table 2. Conceptualization of Study Measures

Variable	Name of Measure	Occasion
Primary Outcome:		
Glycemic Control	Hemoglobin A1c	Baseline, 6, 12
Secondary Outcomes:		
Medication Adherence: Objective	- Medication Event Monitoring System (MEMS) - Pharmacy refill records	Monthly 3,6,9,12
Medication Adherence: Subjective	- Morisky Medication Adherence Scale	Baseline, 6, 12
Exploratory Outcomes:		
Cognition (cognition will be assessed at baseline to ascertain if the participant has MCI, and will be assessed at 6 and 12 months to explore the impact of PC-OT on change in cognition)	Uniform Data Set (UDS) Neuropsychological Battery: 1) General cognition: Mini Mental State Exam (MMSE) 2) Verbal episodic memory: Wechsler Memory Scale 1A Immediate (WMS-R) 3) Attention: Digit Span Forward and Backward 4) Semantic Memory/Language: Category Fluency; Boston Naming Test 5) Psychomotor Speed: Wechsler Adult Intelligence Scale (WAIS-R) Digit Symbol; Trailmaking Test Part A 6) Executive Function: Trailmaking Test Part B 7) Delayed Verbal Episodic Memory: WMS-R Logical Memory IIA—Delayed	Baseline, 6, 12
Functional Abilities	- University of California Performance-based Skills Assessment UPSA) - Activities of Daily Living–Prevention Instrument (ADL-PI)	Baseline, 6, 12
Diabetes Self-Management	Diabetes Self-Care Inventory-Revised (DSCI-R)	Baseline, 6, 12
Depressive Symptoms	Patient Health Questionnaire-9 (PHQ-9)	Baseline, 6, 12
Quality of Life	Diabetes Distress Scale (DDS):	Baseline, 6, 12
Potential Covariates		
Demographic and Background Characteristics	- age, sex, education, duration of DM, marital status, living arrangements, family responsibilities - Alcohol use: Alcohol Use Disorders Identification Test (AUDIT) - Food access: Nutrition Environment Measures Survey in Stores (NEMS-S) - WRAT	Baseline
Medical Comorbidity	- - Health-Related Quality of Life Comorbidity Index (HRQL-CI)Change in weight - Change in blood pressure - Change in lipids - Current medications	Baseline, 6, 12
Beliefs about Medication	- Beliefs about Medicines Questionnaire (BMQ)	Baseline, 6, 12
Interim medical events and treatment	- EMR - Participant Report	Baseline, 6, 12
Social Support	- Receipt of tangible assistance with daily living activities on the Activities of Daily Living–Prevention Instrument (ADL-PI)	Baseline, 6, 12
Process Variables (to be collected by the interventionists)		
Characteristics of each treatment session (both PC-OT and EUC interventionists)	- Number of treatment sessions - Length of each treatment session - Family/friend involvement	Intervention visits
Treatment Goals (PC-OT interventionist only)	- Description of each goal worked on during the course of the intervention - Plan for achieving goal - Goal Satisfaction Form - Strategies recommended (including devices/aids dispensed) - Referral made by OT - Extent of family/friend involvement for each recommended strategy	Intervention Visits

3. Follow up assessments

Follow-up assessments will be conducted by the OA. Monthly, the study coordinator will generate a computerized list of participants who are due for their follow-up assessments within the upcoming month. Included on the list will be the date of the last assessment for each participant as well as the ideal date that the assessment should take place. The date of the baseline in-home assessment will determine when the follow-up assessments should occur. For example, if the baseline assessment date was 7/31/14, ideally the 6-month assessment should take place on 1/31/15. Follow-up assessments should be timed so as to take place within 5 days of the ideal assessment date. For instance, in the above example, the 6-month assessment needs to occur anywhere from 1/26/15 through 2/5/15. If unforeseeable events prevent the follow-up assessment from occurring on time, an "Out of Window" form will be completed by the study coordinator and stored in the participant's research chart.

4. Out of window policy

For any of the above described events that occur outside of the time window, an "Out of Window" form will be completed. The following information will be recorded on this form: Participant's name and ID, the event that is out of window, the ideal date of the event as well as the actual date of the event, and the reason that the event is out of window.

Our goal is to have 80% of the assessment and treatment visits occur within the ideal time frame as specified above. We will produce monthly reports that delineate the percent of assessments and treatments that are occurring within the desired range. We will closely monitor these figures and develop corrective strategies as needed.

CHAPTER 6: QUALITY ASSURANCE AND MONITORING PROCEDURES

In conducting an RCT with older people that involves multiple follow-up assessments, several issues can compromise the integrity of the data. These include: (1) unmasking; (2) treatments not being delivered as intended; (3) data not being obtained in a standardized manner; (4) attrition and missing data; and (5) malfunctioning or misuse of MEMS caps. Plans for addressing each of these issues are discussed below.

1. Preservation of masking

An unavoidable aspect of behavioral intervention research is that participants are aware of their treatment assignments. To minimize unmasking, only persons masked to treatment assignment will manage central data collection and measurement; only the PI, project director, statistician, study coordinator, and the interventionists will be aware of treatment assignment. Ben Leiby, PhD, the study statistician, will develop the randomize schedule and Co-Investigator Robin Casten, PhD will perform the randomizations.

Several measures will be undertaken to preserve the integrity of masking. First, the outcomes assessor, who assesses all outcomes, will have no knowledge regarding anyone's treatment assignment. Second, prior to performing any assessment, the OA will emphasize to all participants the importance of not revealing their treatment assignment. They will be instructed to call the study coordinator should they have any questions about this. Third, the OA and the study interventionists will be instructed to never discuss any of the participants with each other, either generally or specifically. Individual staff meetings will be held with the respective interventionists to maintain separation of the study treatments and treatment expectations. Fourth, for quality control purposes, after each follow up assessment, the outcome assessor will be asked to indicate her best guess of which study group the participant is in, as well as her reasons for this estimate. If at anytime the outcome assessor learns of a participant's treatment group, she will notify the study coordinator immediately. The study coordinator will record this information in a data base so that statistical analyses can be adjusted accordingly. We will closely monitor unmasking and make revisions if rates exceed 10%. We will specifically examine whether unmasking leads to the introduction of treatment-related biases in all reporting of study results.

2. Treatment fidelity:

To assess treatment fidelity during the study, staff will record all PC-OT and EUC treatment sessions and all assessment visits. Thirty percent of participants will be randomly selected for treatment fidelity evaluation. For the PC-OT sessions, Dr. Casten (to evaluate the behavioral activation component), Dr. White (to evaluate the diabetes education component), and Dr. Piersol (to evaluate the OT component) will rate 2 recordings (of the 5 initial sessions) and 2 of the 3 booster sessions. Dr. Casten (to evaluate overall session delivery) and Dr. White (to evaluate the quality of the diabetes education) will review a random selection of recordings of EUC sessions.

To determine which participants and intervention sessions will be selected for treatment fidelity review, Dr. Leiby will create a randomization schedule. The schedule will determine: (1) which participants will be selected for treatment fidelity; and (2) which sessions from those participants will be reviewed. After reviewing each tape, the reviewers will provide feedback to the

interventionist. The PI will regularly review each interventionist's progress to insure that each is meeting the standard of performance.

3. Assessments

Inter-rater reliability for the in-home assessments will be evaluated by having the PI review 10% of these assessments. For these assessments, the study assessor will conduct the assessment as usual, except that it will be audio recorded. Dr. Rovner will review the recordings and discrepancies in the interpretation of participant responses will be discussed and reconciled. The study assessor may be referred for additional training at the PI's discretion if there are many discrepancies.

4. Attrition

We will use the following strategies to maximize retention. 1) All participants will receive a meaningful intervention that supports ongoing participation; 2) Our established relationships with PCPs convey credibility to participants; 3) All participants receive $10 monthly for visits to retrieve MEMS data, and $20 and certificates of completion for assessments at months 6 and 12; 4) We will mail birthday cards and a quarterly "Question-and-Answers" newsletter to maintain positive, personalized contact; 5) We make reminder calls the day before in-home appointments, and maintain flexibility when scheduling follow-up appointments; and 6) We will have a dedicated telephone line for participants to call research staff for study-related questions. These strategies are known to be effective.

5. Malfunctioning MEMS caps

We will run a test on all MEMS caps before distributing them to participants to insure that they are functioning correctly. Participants will be instructed to be sure that the MEMS bottle/cap does not get wet, and to be sure that the cap is tightly closed after each opening. Participants will also be given a log to record "curiosity openings", episodes of "pill pocketing", episodes of not being in control of medication management (e.g., hospitalization), and any other event that may bias adherence rates. All adherence rates will be adjusted for such circumstances.

CHAPTER 7: CERTIFICATION PROCEDURES

1. Certification in the Protection of Human Subjects

As per the regulations of the Institutional Review Board (IRB) at Jefferson, all study staff are required to be trained and certified in the practices of human subjects research. The training is done through the Collaborative Institutional Training Initiative (CITI).

2. PC-OT interventionist training

The OT will receive 15 hours of core didactic training on the pathophysiology and treatment of DM (Drs. White and Jabbour). The OTs will be trained to deliver occupational therapy in accord with the study protocol and to provide DSM education using the BA treatment paradigm. To accomplish this, Drs. Casten, While, and Piersol will jointly train the OTs, emphasizing skill development and providing supervised training with the goal of integrating DSM and occupational therapy within the BA treatment paradigm. This aspect of the training will consist of a day long workshop, which will include readings, didactic and experiential sessions, and conducting supervised role-play treatment sessions. Dr. Casten will provide didactic instruction in BA theory, review the PC-OT treatment manual, and session procedures. Dr. White will continue DSM education and skills training, including review of core DM knowledge/skills training (i.e., monitoring of blood glucose and implementing intervention protocols) and community resources to assist the PC-OT interventionists in developing Action Plans to enable participants to achieve DSM goals. Dr. Piersol will review the major strategies/skills employed by OTs for improving medication management. She will also provide education on MCI and will review techniques for overcoming barriers related to impaired memory. Dr. Piersol will also train the OTs to conduct the OT assessments to be administered to determine current ability to manage medication [Allen Cognitive Level Screen, Allen Diagnostic Module, Performance Assessment of Self-care Skills (PASS)-Medication Management Task, Safety Assessment of Function & the Environment for Rehabilitation Tool (SAFER)].

Dr. Casten will also review procedures to maintain treatment fidelity, treatment documentation (e.g., specifics of Action Plans, strategies imparted to participants, devices/aids dispensed), and maintenance of treatment records and adherence to protocols. Dr. Hill-Briggs will discuss the realities of delivering DSM education and training in the community (i.e., logistical and social barriers encountered in conducting home visits).

Following these formal training experiences, we will assign each OT 5 training cases to be treated consecutively for 5 sessions. Drs. Casten, Piersol, and White will supervise the training cases by reviewing and rating recordings of the first, third and sixth sessions and use standardized monitoring checklists developed for this study (see Appendix). Then each supervisor will provide feedback following each of these rated sessions. The OT interventionist must meet satisfactory levels of competence on his/her training cases before starting the clinical trial. The OTs (along with the outcome assessor and the research assistant) will also receive training on Jefferson's Electronic Medical Records (EMR) system (to be conducted by Dr. Arenson).

3. Community Health Worker (CHW) training

The CHW will deliver all EUC sessions to participants randomized to the control group. To develop the CHW's knowledge-based and skills-based competencies, we will provide core

didactic and experiential training, including reviewing the pathophysiology and treatment of DM (Drs. White and Jabbour), management of DM in the community (Drs. White and Hill-Briggs), and the treatment protocol (Drs. Rovner and Casten). Dr. Casten will also train the CHW in the principles and delivery of supportive therapy to control for the effects of attention.. The CHW will be required to deliver EUC to 3 training cases, which will be reviewed by Drs. Casten and White.

4. Outcome Assessor training

Drs. Casten and Rovner will review general interviewing techniques (e.g., establishing rapport, maintaining structure, completing paperwork, and managing time), and procedures for obtaining informed consent. Dr. Rovner will review each study instrument to ensure that the assessor understands all items and measurement intent. The assessor will administer assessments in-person (i.e., with the participant) and will enter all data directly onto a laptop. Prior to entering the field, the Assessor will conduct 5 practice baseline assessments that will be audio recorded. Dr. Rovner will review the recordings and provide feedback to the assessor on her performance and protocol adherence. Thereafter, we will hold 2 meetings per month to review recent cases, test administration procedures, and coding decisions to ensure accuracy and minimize assessor drift. Dr. Rovner will review procedures for collecting blood samples, including safety issues, proper storage, labeling samples, and transporting samples to the lab.

5. Research assistant (RA) training

The RA will be responsible for conducting the run-in visits and monthly MEMS data collection. Dr. Casten will provide training on conducting these visits and using the MEMS bottles/caps and electronic reader. The RA will be trained on how to calculate the run-in adherence rate.

CHAPTER 8. DESCRIPTION OF INTERVENTIONS

PC-OT:

PC-OT aims to improve glycemic control by increasing medication adherence and improving other DSM practices. Treatment addresses medication adherence first, and then moves onto other aspects of DSM. PC-OT consists of 4 major elements: 1) PCP-OT collaboration; 2) DSM education tailored to cognitive impairment; 3) standard OT cognitive-functional assessment; and 4) OT-delivered Behavior Activation (BA) to develop and reinforce treatment plans. Treatment plans are designed to compensate for cognitive and physical deficits, anchor drug administration to daily routines (e.g., mealtimes, personal hygiene), incorporate personal values and beliefs, recognize social realities (e.g., competing caregiving responsibilities), and capitalize on procedural memory, which refers to learning behaviors that are enacted automatically. Procedural memory remains intact relative to episodic memory (i.e., delayed recall) in MCI, as the 2 memory systems have different neural substrates. The OT builds on this retained capacity when developing medication adherence (e.g., linking medication-taking to daily routines) and other DSM adherence plans.

1. PC-OT Collaboration: The OT and the PCP will have a minimum of 4 EMR communications. They begin by reviewing a participant's medications and when they should be taken, identify evidence of polypharmacy, and discuss a participant's target HbA1c, given his/her current HbA1c ≥ 7.5 and ≤ 80% adherence. The PCP will decide if: 1) the OT will increase adherence to the current regimen (likely if the participant takes metformin); or 2) the PCP will change the regimen (e.g., reduce sulfonylurea dose) to avoid hypoglycemia, anticipating that better adherence will lower blood glucose. The PCP will also inform the OT of relevant medical factors (e.g., comorbidities, exercise limitations) that may influence DSM. The OT will then begin in-home evaluation and treatment. After the 3rd session, the OT will inform the PCP via the EMR of the medication adherence Action Plans (e.g., linking medication-taking to morning routines, organizing medications), and convey any question a participant has about their medications (e.g., possible side effects). The PCP will respond, approve, or modify the plan via the EMR. In subsequent contacts, the OT and PCP will discuss treatment progress and Action Plans to improve diet and exercise. The PCP will reinforce Action Plans with participants during office visits (about every 3 months). The OT will update the PCP after the 5th session, and after each of the 3 booster sessions. The OT will inform the PCP of clinical (e.g., persistent depression) or treatment information (needs prescription refill). The PCP will respond and post incident health events and needed health screens for the OT to include in future Action Plans

2. DM Education: The OT will provide DM education throughout the intervention to build knowledge and skills (e.g., blood sugar monitoring) according to national standards. The OT will review the NIH publication, *"4 Steps to Control your Diabetes for Life"* and "*Project DECIDE"* (Decision-making Education for Choices In Diabetes Everyday) educational materials. Previous studies have demonstrated the value of the latter materials in older AAs with DM and cognitive impairment. The OTs will tailor the education to participants' cognitive strengths and deficits. They will respect participants' learning pace as they introduce new information and use repetition and "reflecting back" (i.e., asking participants to state what they understand in their own words) to ensure adequate understanding.

3. Cognitive-Functional Assessment: Medication adherence involves participant (e.g., cognition, beliefs), environmental (e.g., disorganization), and contextual (e.g., competing social demands)

factors. The OTs will assess these factors, drawing from baseline data (i.e., health beliefs, cognitive tests, current DSM practices) and their formal evaluations, to tailor the treatment plan. For example, the OT may identify environmental barriers (e.g., medications stored in different rooms) that inhibit medication adherence, and then suggest strategies to mitigate their impact. Or the OT might identify health perceptions that compromise adherence. For example, the OT might say, "At the baseline interview, you said you take metformin only when you feel whoozy. You might feel less whoozy if you take it every day. Are there reasons you prefer not to? Let's talk about them and see if we can help you take your medications the way your doctor thinks is best for you." In this way the OT identifies perceived obstacles [e.g., costs, side effects, beliefs, depression, transportation, and distractions (e.g., visiting family) that can be addressed in the treatment plan.

The OT then administers the Allen Cognitive Assessment battery, which is a standardized performance-based assessment that grades information processing and visuo-motor abilities (e.g., following directions, problem-solving, learning potential, cueing needs) and links activity demands to performance skills. The OT uses the Allen to identify participants' cognitive-functional capacities in order to select strategies that build on the participant's best abilities. The OT also administers the Performance Assessment of Self-care Skills-Medication Management Task to evaluate specific physical (e.g., upper extremity motor/sensory function, dexterity) and cognitive aspects of medication-taking (e.g., efficiency, safety awareness, and performance quality). Based on these assessments, the OT will determine if participants are intentionally nonadherent (due to side effects, costs, or misperceptions about their medications), occasionally but not intentionally miss doses, or lack cognitive or motor capacity to adhere adequately. This determination will guide the selection and tailoring of intervention strategies (e.g., environmental cues to help sequence a task). As needed, the OT will suggest referral to the Area Agency on Aging to ensure that basic needs are met to support effective DSM.

4. OT-delivered Behavior Activation (BA):

a) Medication Adherence: The OT and participant begin by reviewing all medications, their purpose, and dosing instructions. They devise a plan to integrate medication-taking into daily routines (e.g., take metformin after making coffee), involve caregivers if available, and use environment adaptations and memory aids to increase adherence. The OT draws from 3 broad rehabilitative strategies: 1) activity simplification (e.g., break down complex activities into component tasks; 2) environmental modification (e.g., visual cues like reminder cards, strategic placement of medications, reduce clutter, improve lighting); and 3) device use (e.g., pill organizers, magnifiers, talking watch with reminders). For example, visual cues (e.g., placing morning medications by coffee maker) might be linked to the verbal messages (e.g., "I turn on the coffee maker, take my pills, and mark the check sheet on the refrigerator."). Once the OT is sure the plan is feasible, the OT uses BA to reinforce and routinize the plan. BA involves: 1) developing Action Plans that define the plan goal and the steps to achieve it; and 2) recording completion of the steps on a checklist. The steps need to be observable, quantifiable, and easy enough to succeed to provide positive reinforcement. In subsequent sessions, the OT evaluates the success of the Action Plan and modifies it if necessary.

The OT does not manage medication dosing or put medications in pill organizers. Instead, they help the participant establish a routine for medication management that is supported by the home environment and accounts for personal, cultural, and social influences. If there are problems with medications (e.g., confusion about dosing schedule), the OT works with the PCP to resolve them, and then works with the participant to determine the best adherence strategy. If pills need to be

transferred from one container to another, the OT provides the needed structure and supervision based on the prescription and communication with the PCP, which reinforces the skills necessary to adhere to medication regimen. To prevent the intervention from confounding MEMS measurement, the OT strictly avoids any instruction on or assistance with MEMS. Although OTs may incorporate the MEMS medication into a general adherence plan (e.g., place all medications in the kitchen), they provide no specific instruction/assistance with MEMS beyond that.

b) Other DSM Practices: In subsequent sessions the OT develops BA Action Plans to improve other DSM practices. Action Plans for diet might include reducing soft drink consumption, eating 3 vegetables/day, eliminating table salt, reading food labels, and using the plate method to balance food portion by food group. For exercise, Action Plans might include using a pedometer to monitor/increase physical activity, doing chair exercises 3 times/day, walking to church). Glucose monitoring plans might include finger sticks linked to meals, or keeping glucose tablets in purse to treat hypoglycemia. The OT will provide skills training as needed (e.g., using a glucometer, plate method to organize meals).

5. Booster Sessions (Months 6, 8, and 10): Scheduling booster sessions will sustain the therapeutic relationship and treatment gains and reduce attrition. The OT will administer 3 in-home booster sessions to reinforce medication adherence and other DSM activities. Prior to each session, the OT will review the EMR to identify changes in a participant's health or medications. If a participant starts insulin, the OT will address that in the treatment plan. The OT and participant will review Action Plans from previous sessions, identify obstacles, and modify Action Plans to accommodate changes in cognition, health, medications, or social circumstances. The OT also provides information on resources to address future needs.

Enhanced Usual Care (EUC):

The control treatment is EUC, which is comprised of "Usual Care" (i.e., routine PCP-delivered medical care) that is "Enhanced" with in-home, low-intensity education and support delivered by a bachelor's level Community Health Worker (CHW). The education component aims to increase DM knowledge and controls for the nonspecific effects of the in-home OT visits. Similar interventions, delivered by lay educators, lead to modest increases in glycemic control in ethnic minorities and are congruent with the American Association of Diabetes Educators' position statement on the role of CHWs in community care of persons with DM. In this RCT, EUC exceeds usual care in its individual attention to participants and use of DM educational materials specifically designed for older AAs with cognitive impairment. The CHWs will meet with participants in their homes at the same frequency and intensity (including booster sessions) and use the same educational materials as the OTs but the CHWs will not interact with PCPs, access the EMR, or develop Action Plans to increase medication adherence or other DSM practices. During each treatment session, the CHW will review core aspects of DM using the written materials to structure the sessions. The CHWs will also facilitate participants' personal expression about the impact of memory loss, DM, and aging on their lives.

CHAPTER 9. ADVERSE EVENTS AND ALERTS

1. Serious adverse events

In providing oversight to human subject safety we distinguish between an Alert and a Serious Adverse Event. We consider an Alert to be a dangerous situation discovered to exist by a member of the research team that is not related to the conduct of the research study. Alerts are not specific to or consequences of the study but represent situations that may be encountered in any interaction with a participant in a home. An example of an Alert may be a hazardous home condition (e.g., no fan or air conditioning and windows unable to open in summer where the home reaches temperatures over 100 degrees).

As per the IRB at TJU, we will report Serious Adverse Events (SAE) (study related or otherwise) to the IRB within 48 hours of learning of an event. Examples of SAEs include in-patient hospitalization, emergency room visits, or any other event that significantly impacts a patient's health status.

2. Documentation

For an alert, documentation involves notifying designated members of the research team (PI and project director) and completing an Alert Event Reporting Form within 24 hours of occurrence of the event. The reporting of alerts to the IRB of TJU is not required.

For a serious adverse event, documentation involves notifying the PI and project director immediately, completing the TJU IRB Serious Adverse Event form, and notifying the TJU IRB within 48 hours of occurrence. Although this is a minimal risk study, all study personal will be trained in these alert and serious adverse event procedures.

The PI will be informed of alerts, actions taken, and resolution. For a serious adverse event, the PI will be notified as soon as the event occurs, either by telephone from the participant's home or immediately there after.

CHAPTER 10: DATA MANAGEMENT

1. General issues

All assessment forms will be created in Teleform, which is a tool whereby data collected in the field are entered directly into a computer. This will be accomplished as follows. The OA will take a laptop computer to all in-home assessments. The computer will prompt the OA to ask each question and enter the participant's response directly into the computer. Immediately after the assessment, the OA will back up the completed assessment on a memory stick. Weekly, the OA will meet with the project director to turn over electronic copies of assessments that were completed the previous week. The electronic copy will be stored on the project director's hard drive, and added to the ongoing database of all participants' completed assessments. The advantages of this method are: (1) it eliminates the need for a data entry person; (2) that skip patterns are built into the program, minimizing this type of data entry error; and (3) the computer signals the OA when questions are skipped or out-of-range values are entered. The OA will bring a back-up computer battery to all assessments. Further, the OA will also bring a blank hard copy of the assessment should the computer malfunction. All computers used for data collection and storage will be encrypted and password protected. The following data will be collected with written forms which will be entered by hand: (1) intervention notes; (2) intervention forms; and (3) data collected from the EMR.

Data management and cleaning will be ongoing throughout the study. Inconsistencies and missing data will be reconciled (e.g. call participant or check EMR for missing data). We will create a separate database for each time wave. Participant identification numbers will be used to link data from multiple time points for longitudinal analyses. On a monthly basis, the project director will run frequency distributions for all variables to check for accuracy. We will perform weekly back-ups of all databases in triplicate.

Although we will take careful efforts to minimize missing data, we will handle missing data in the following way: at each time point, participants who complete that assessment will be compared to those lost to attrition on all baseline variables as well as those from previous time points if appropriate. Any variable(s) that emerge as significantly different will be controlled statistically.

2. Description of computing environment

2.1. Hardware

Computers will be purchased for project staff, and they will be password protected and encrypted. All computers will be serviced by the IT department at Thomas Jefferson University.

2.2. Software

All data will be managed and analyzed with SAS, SPSS, or Mplus. Teleform will be used to create all data forms. It will also be used for direct data entry and scanning hard copies of data. Both the project director and the OA will have individual licenses. We purchase annual support contracts for Teleform.

3. Distribution of blank forms

All assessment data will be entered directly onto the OA's laptop, eliminating the need for blank forms. The OA will, however, bring blank hard copies of assessment forms to all assessment visits should the laptop malfunction. Electronic copies of all forms will be stored on the study network (which it maintained by Jefferson). Intervention forms will be distributed to the interventionists as they are needed.

4. Participant identification and confidentiality

Participant identifiers will be assigned immediately after enrollment, and will be used on all data forms. Neither participant names, nor any other identifying information other than the identifiers, will ever be on the data forms. All hard copies of participant information (data forms, contact information, signed informed consents, randomization sheets, etc.) will be stored in locked file cabinets stored in the PI's lab. Each participant will have 2 charts, and each will be stored in separate file drawers. The following will be stored in the participant identification chart: the participant's contact information, data collected at screening, the signed consent forms, the randomization sheet, copies of medication labels, pharmacy refill records, and serious adverse event/alert documentation. The following will be stored in the participant data chart: all hard copies of assessment forms, intervention forms, notes, withdrawal forms, and out of window forms. None of the documents contained in the data chart will have the participant's name. A master list linking participant name with identifier will be stored in an encrypted password protected file on the project director's computer.

5. Linking participant records

The only data base that will contain both participant names and identifiers is the tracking list which will accessible to the PI, the project director, and the study coordinator. All other data bases will identify individual participants by their unique identifiers. Assessments completed at different time points will be stored in separate data bases. Unique identifiers will be used to link data obtained from participants at different time points.

6. Procedures for data checking and editing

Data forms (screens, all assessment batteries, intervention notes) will be reviewed within 1 week of completion. This review is performed to check that all information is accurate, check marks or circled answers are clearly demarcated (if completed on a hard copy), and that each item is completed. Staff also checks to assure that each page of the IRB participant consent form is initialed and the participant's signature is obtained on the final page of the consent.

All changes to data are submitted via a data edit request form for review and signature by the PI. Data edits are entered directly into the respective data bases. The data edit request form will be stored in the participant's chart. A data base will be maintained that documents each data edit, including the date of the edit as well as the type of change that was made.

7. Description of data edits

Each month the project director will generate a report documenting the number and type of data edits performed for the previous month. We expect few data edits as data entry errors will be minimal due to direct entry. Most edits will consist of changes in participant contact information.

8. Internal data quality monitoring

Data quality monitoring will be minimal, owing to the use of Teleform. Since all data will be entered directly into the computer or scanned, there will be no data entry errors. To insure data integrity, weekly, the project director will produce frequency distributions on all assessment data. This will highlight out of range values. In the event that this occurs, the project director will inform the OA, and a data edit request form will be completed accordingly.

9. Communication related to data collection

Weekly, the study coordinator will generate assessment schedules for the study assessor that will indicate which participants are due for follow-up assessments, MEMS data downloads, or booster intervention sessions in the upcoming 2 weeks. On a monthly basis, the study coordinator will produce reports that will indicate the number of participants who: (1) were approached for study participation; (2) were screened for study eligibility; (3) were enrolled in the study; (4) had an assessment at each time point; and (5) withdrew from the study (and the reason for withdrawal). This report will also indicate the number of assessments that occurred out of window, the number and type of protocol deviations, the number of participants who became unmasked, and the percent of missing data.

10. Missing data

Missing data are entered according to the following established coding scheme: (1) NA = 99; and (2) refused = 88.

11. Data back up

Data files are entered and stored on a secure network maintained by TJU. An additional full-drive backup is completed monthly.

12. Data collection and transition

All in-home assessments will be entered directly on a laptop computer. The OA will always bring an extra laptop battery as well as a blank hard copy of the assessment form to the participants' homes. This will enable all data to be collected should the computer malfunction. It is very important that all fields on all assessment forms are filled in (unless otherwise noted). If the participant is unable to respond to a particular item, or if it is not applicable, the OA will check NA for forced choice questions, or write "NA" for open-ended questions. Immediately after completing the in-home assessment, the OA will check the assessment forms to insure that all

information is complete. If there is any missing data, the OA will call the participant in order to obtain complete information.

13. Equipment protection

All study computers will be maintained by the Technical Assistance Center at Thomas Jefferson University. The Technical Assistance Center assumes responsibility for the installation and repairs of all computers. All data are backed up in triplicate every day, so in the event of a malfunction, all data will be preserved.

All MEMS caps and bottles, as well as the software to read the data from the MEMS caps, will be supplied by the Aardex group. The Aardex group has a full support system available should the caps or software malfunction.

CHAPTER 11: DATA ANALYSIS

We will use descriptive statistics and bivariate comparisons of participants by treatment group to characterize the sample, assess randomization success and the impact of attrition, and check data quality. We will use an intent-to-treat approach for all analyses in that we will include all participants with follow-up data regardless of the extent to which they received treatment. For longitudinal analyses we will include all available data from all participants. We account for attrition by assuming that any missing data are missing at random, and apply models that yield valid estimates under this assumption. For analysis of continuous outcomes, we will check assumptions of normality and homoskedasticity of errors using model residuals. If necessary, we will transform outcomes as appropriate prior to analysis. We will present all model-derived estimates with 95% confidence intervals, and will use SPSS, SAS, and Mplus software as appropriate.

Aims 1 and 2: Test the efficacy of PC-OT to reduce HbA1c level by 0.5% at 6 months (Aim 1) and at 12 months (Aim 2).

Hypotheses: 55% of PC-OT-treated participants, compared to 25% of EUC controls, will have a reduction in HbA1c of 0.5% at 6 months (short term effect) and 12 months (maintenance effect).

Analyses: At each outcome measurement (6 and 12 months), we will categorize participants as having achieved this outcome or not. We will jointly model this dichotomous outcome at 6 and 12 months using Poisson regression within a generalized estimating equation (GEE) framework. The model will include time (6 months, 12 months), randomization assignment, time by randomization interaction, the stratification variable (baseline HbA1c), age, and baseline MEMS adherence (from the Run-in Phase). This model allows for direct estimation of the relative risk at each follow-up time while accounting for correlation among repeated measures from the same participant. We will consider participants who start insulin during the trial as not having a meaningful reduction in HbA1c, regardless of the actual level at 6 and 12 months. From the model, we will calculate model-adjusted estimates for incidence of HbA1c reduction in each arm at 6 months, as well as the adjusted estimate of the relative risk. We will evaluate the primary hypothesis by testing the null hypothesis that the relative risk at 6 months = 1. For Aim 2, we will calculate the relative risk at 12 months from the same model, and evaluate the hypothesis by testing the null hypothesis that the relative risk at 12 months = 1.

We will also model HbA1c level as a continuous outcome to estimate the average change over time in each treatment group. We will use mixed effects linear regression to jointly model HbA1c at baseline, 6 months, and 12 months. Fixed effects will be time (baseline, 6 months, 12 months), randomization assignment, time by randomization interaction, age at randomization, and baseline MEMS-adherence from the run-in phase. A random intercept term and an appropriate covariance structure will be used to account for correlation among repeated measurements. Within this model we will estimate the average change in HbA1c by group from baseline to 6 months, and from 6 months to 12 months. We will compare groups with respect to average change over these two time periods as an additional estimate of the effect of PC-OT compared with EUC.

Aim 3: Test the efficacy of PC-OT to increase MEMS-measured adherence to an oral DM medication at 6 and 12 months.

Hypothesis: PC-OT will increase MEMS-measured adherence to a greater extent than EUC at 6 and 12 months.

Analyses: MEMS adherence data will be summarized as "percentage adherence" during each month. We will model the longitudinal trajectory of post-randomization adherence data using mixed effects linear regression. Fixed effects will be time, randomization assignment, time by randomization interaction, run-in phase adherence, age at randomization, and baseline HbA1c. Random intercept and time effects and an appropriate residual error covariance structure will be assumed to account for within-subject correlation. For purposes of this analysis, we will treat time categorically as a 4 level variable (months 1-3, months 4-6, months 7-9, and months 10-12). Thus, we will have 3 repeated measurements of adherence for each time period. Within this model, we will estimate the average adherence by randomization group during months 4-6 and months 10-12 and test for differences between groups. Supplemental adherence measures (i.e., Morisky Self-Report, Proportion of Days Covered) will be analyzed using a mixed effects model similar to that used for the continuous HbA1c analysis above.

Aim 4: Determine if increasing MEMS-adherence to an oral DM medication mediates PC-OT's impact on HbA1c levels at 6 and 12 months.

Hypothesis: PC-OT will reduce HbA1c level to the extent that it increases MEMS-adherence to an oral DM medication at 6 and 12 months.

Analysis: We will use structural equation modeling (SEM) to evaluate this aim. We will simultaneously model the dichotomous HbA1c reduction variable at 6 and 12 months, and adherence data at months 4-6 and 9-12. Adherence at months 4-6 (and 9-12) will be reduced to a latent variable representing the average adherence over the three month period. HbA1c will be modeled using a probit link. The model we will fit has paths from treatment to HbA1c reduction at 6 and 12 months (direct effects), treatment to adherence at 6 and 12 months, adherence at 6 months to HbA1c reduction at 6 months, and adherence at 12 months to HbA1c reduction at 12 months. Using MPlus software, we will fit the SEM model and follow the strategy outlined in Muthén (2011) to calculate the total indirect effect for adherence at 6 months and at 12 months. Adherence is considered a mediator of the effect of treatment on reduced HbA1c if there is a significant path from treatment through adherence to HbA1c (i.e., an indirect effect). Standard errors and confidence intervals will be calculated using bootstrapping. We will perform a similar analysis to explore whether changes in Diabetes Self-Care Inventory-Revised scores [a measure of diabetes self-management (e.g., diet, exercise)] also mediate the effect of treatment on HbA1c reduction.

Exploratory Aims:

1) Evaluate if PC-OT over 12 months: a) improves other DSM practices (e.g., diet, exercise); b) reduces emergency room visits and hospitalizations; c) prevents declines in cognition, function, and depression; and d) improves quality of life.

Analyses: We will evaluate continuous outcomes using the mixed effect model outlined for HbA1c. Count outcomes (e.g., number of ER visits) will be evaluated using repeated measures Poisson regression using GEE.

2) Evaluate PC-OT's costs and net financial benefits: This economic analysis will consist of an exploratory cost-benefit analysis (CBA) based on cost and outcome data. We will calculate the

cost-benefit of PC-OT vs. EUC based on best practices in applied health economic methods. The CBA will employ the payer perspective since its main purpose is to explore whether PC-OT results in a cost-offset to health insurers and plan sponsors. Specifically, the CBA will inform whether the net financial benefit of PC-OT vs. EUC is ≥ $0, i.e., that the *cost* of PC-OT i is equal to or exceeded by its *financial benefits* at 6 and 12 months. Costs will include intervention costs (using the framework for behavioral intervention costs published by Drs. Gitlin and Pizzi) and net financial benefits (e.g., healthcare utilization related to DM. This exploratory cost analysis will help to develop more formal and comprehensive economic analyses if PC-OT proves effective.

CHAPTER 12: STUDY TIMELINE

We anticipate conducting 500 baseline assessments to identify and recruit 100 participants. Recruitment will take 20 months. We will conduct 25 assessments per month, and expect to enroll about 7 to 8 participants per month into the run-in phase. Of these, we will randomize 5 participants per month. Study start-up will take place during the first 6 months of the trial. During the start-up phase we will: (1) refine the educational materials to be distributed to all randomized subjects using components from NIH's "4 Steps to Manage your Diabetes for Life" and Dr. Hill-Brigg's "Project DECIDE" workbook; (2) hire and train study staff; (3) refine and implement procedures for study recruitment; (4) create study data bases; (5) create the randomization schedules; (6) develop the final version of study instruments and protocols; and (7) develop a comprehensive referral list for study interventionists.

The run-in phase will begin immediately after enrollment, and should be completed by month 28. For the 100 randomized participants, we will download MEMS data monthly for 12 months. We expect the collection of MEMS data to be completed by month 40. The 5 initial sessions of study treatment for both PC-OT and EUC participants will be completed by month 30. The 3 booster sessions will begin in month 13 and will continue through month 36. Six month follow-up assessments will take place month 13 through month 33. The 12 month follow-up assessments will begin in month 20 and will be completed by month 40. Months 41 through 48 will be devoted to data cleaning and analysis, and dissemination of study findings.

Year 1 (7/1/14 – 6/30/15)						Year 2 (7/1/15 – 6/30/16)						Year 3 (7/1/16 – 6/30/17)						Year 4 (7/1/17 – 6/30/18)					
2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48
START UP																							
			BASELINE ASSESSMENTS (N = 500)																				
			RUN IN PHASE FOR PARTICIPANTS WITH MCI AND HbA1C ≥ 7.5 (N = 150)																				
			RANDOMIZATION (N = 100)																				
			MONTHLY COLLECTION OF MEMS DATA FOR RANDOMIZED PARTICIPANTS (N = 100)																				
				5 INITIAL SESSIONS OF PC-OT OR EUC																			
						6 MONTH FU ASSESSSMENTS																	
						3 BOOSTER SESSIONS OF PC-OT OR EUC AT MONTHS 6, 8, 10																	
									12 MONTH FU ASSESSMENTS											DATA ANALYSIS			