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Protocol: Telephone Delivered Behavioral Skills Intervention for Blacks With T2DM

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A: SPECIFIC AIMS

Blacks (African Americans) with Type 2 diabetes (T2DM) have higher prevalence of diabetes, poorer metabolic control, and greater risk for complications and death compared to Whites (NIH2002). Poor outcomes in Blacks with T2DM can be attributed to patient, provider, and health systems level factors (Egede 2005). Provider and health system factors account for <10% of variance in major diabetes outcomes including hemoglobin A1c (HbA1c), lipid control, and resource use (Hofer 1999, Krein 2002). Key differences appear to be at the patient level (Egede 2005). Of the patient level factors, consistent differences between Blacks and Whites with T2DM have been found in diabetes knowledge, self-management skills, empowerment, and perceived control (Egede 2005, Anderson 1991, Harris 1993, Egede 2004, Jack 2004, Egede 2003). This study provides a unique opportunity to address this gap in the literature. Using a 2x2 factorial design, this study will test the efficacy of separate and *combined telephone-delivered, diabetes knowledge/information and motivation/behavioral skills training intervention* in high risk Blacks with poorly controlled T2DM (HbA1c ≥9%).

Primary Objective
To test the separate and combined efficacy of a *telephone-delivered diabetes knowledge/information and motivation/behavioral skills training intervention* in improving HbA1c levels in Blacks with T2DM using a 2x2 factorial design.

Secondary Objectives
1. To determine whether patients randomized to the *telephone-delivered diabetes knowledge/information intervention, the telephone-delivered motivation/behavioral skills training intervention, or the combined intervention* will have greater improvement in physical activity, diet, medication adherence, and self-monitoring of blood glucose at 12 months of follow-up compared to usual care.

2. To determine the cost-effectiveness of each telephone intervention separately, and then in combination.

The primary outcome is HbA1c level at 12 months of follow-up. HbA1c will be measured by obtaining blood specimens, physical activity will be measured by the 7-day physical activity recall, diet will be measured by the Block food frequency questionnaire, medication adherence will be measured by electronic medication event monitoring system, and self-monitoring of blood glucose will be measured by glucometer downloads.

RESEARCH DESIGN AND METHODS
Study Overview: We propose to test the efficacy of a combined telephone-delivered, diabetes knowledge/information and motivation/behavioral skills training intervention in high risk Blacks with poorly controlled T2DM (HbA1c ≥9%). Our aim is to determine whether a separate or combined telephone-delivered diabetes knowledge/information and motivation/behavioral skills training intervention will lead to greater improvements in glycemic control compared to usual care using a 2x2 factorial design. 232 African Americans with T2DM will be randomized to one of four groups: 1) telephone-delivered diabetes knowledge/information; 2) telephone-delivered motivation/behavioral skills training; 3) combined telephone-delivered diabetes knowledge/information and motivation/behavioral skills training; and 4) usual care. The proposed patient-level intervention is based on the information-motivation-behavioral skills model and provides information, motivation, and behavioral skills training. The usual care group will receive weekly telephone-delivered general health education lasting 30 minutes every week for 12 weeks to control for attention. Study assessments will be performed by a blinded research assistant at baseline, 3, 6, and 12 months of follow-up. The primary outcome is HbA1c level at 12 months of follow-up.

Study Population & Recruitment plan:

Study clinics: The study sites for this study are primarily the MUSC general medicine, endocrine, family medicine, and community primary care clinics. The study will be conducted out of the MUSC Center for Health Disparities Research.
Participant Payment: Participants will receive $25 for completion of baseline assessment materials, $25 for the 3-month assessment, $25 for the 6-month assessment, and $25 for completion of the 12-month follow-up assessment.

Attrition and Retention: Based on prior experience with this population, we anticipate a 15% attrition rate in 12 months. To account for this under an intent-to-treat analysis plan, we increased the sample size for 15% attrition. We will enroll 232 patients (n=58 per group). We intend to minimize drop out from the study by providing monetary compensation for completing the study. In addition, at enrollment, following consent, we will request from every participant, the names, addresses, and telephone numbers of a next of kin who would know how to get in touch with the participant, in the event of a missed appointment.

Patient eligibility criteria: The study inclusion and exclusion criteria are as follows

Inclusion Criteria: 1) Age ≥18 years; 2) Clinical diagnosis of T2DM and HbA1c ≥9% at the screening visit; 3) Self-identified as Black or African American; 4) Subject must be taking at least one oral medication for diabetes, hypertension, or hyperlipidemia and must be willing to use the MEMS cap and bottle for 12 months; 5) Subjects must be able to communicate in English; and 6) Subjects must have access to a telephone (landline or cell phone) for the 12 week intervention period.

Exclusion Criteria: 1) Mental confusion on interview suggesting significant dementia; 2) Participation in other diabetes clinical trials; 3) Alcohol or drug abuse/dependency; 5) Active psychosis or acute mental disorder; and 5) Life expectancy <6 months.

Description of Intervention: The proposed separate and combined diabetes education and behavioral skills training intervention are based on the information-motivation-behavioral skills model and provide information, motivation, and behavioral skills training. The interventions will be delivered via weekly telephone calls over a 12-week period by trained diabetes educators. Two full-time diabetes educators will deliver the interventions. Each full-time educator will only be responsible for providing care to subjects in all the four study arms (i.e. knowledge/information, motivation/behavioral skills, combined, or usual care). Diabetes educators will be trained in behavioral skills counseling by study consultant.

Baseline Visit & follow-up visits: At the baseline visit, the RA will give detailed explanation of the study, the reimbursement schedule, and obtain consent. Subjects will get their blood pressure measured and provide blood specimen to measure HbA1c. In addition, subjects will complete a questionnaire that captures demographics, medical history, HRQOL, physical activity, home blood glucose monitoring, resource utilization, and medication adherence. After the baseline assessment, follow-up assessments will be conducted at 3-, 6-, and 12 months. As much as possible, research visits will be scheduled on the same day as their clinic visit.

Primary Outcome Measure:

HbA1c/Fasting Lipid Profile: Blood specimens will be obtained at baseline, 3-, 6- and 12-months visits by trained phlebotomists. About 10cc of blood will be drawn and sent to the laboratory for HbA1c. Fasting lipids will also be measured at baseline, 3-, 6-, and 12 months.

Patient Randomization Procedures: All subjects who sign an informed consent for the study, meet eligibility requirements and are randomized will be entered into the study database. The research coordinator will collect the pre-specified eligibility information (written informed consent, demographics, eligibility criteria) and enter the information into the study database via the secured study website. Personal health information (PHI), e.g., name, medical record number, social security number, will not be entered into the study database. When all pre-specified information is entered for the patient, the project-specific computer program will confirm the eligibility of that patient. Once confirmed, the computer will generate the intervention assignment based on a pre-programmed randomization scheme. A confirmation report will be generated by the computer and will include the subject's study ID number, assigned treatment date of randomization, basic demographics (age, gender) and eligibility criteria compliance. This report will be filed at the primary center in the confidential study specific files. All registered patients who are screened yet do not get randomized will have specific screening information entered into the study database.

Sample Size and Power

The proposed sample size calculations are based on the premise that we will test three hypotheses in this 2x2 factorial design: 1) the overall effect of diabetes knowledge/information versus no diabetes knowledge/information, 2) the overall effect of motivation/behavioral skills versus no motivation/behavioral skills, and 3) the effect of the combined interventions. The primary endpoint for testing these hypotheses is the 12 month HbA1c value. Power calculations are based on the comparison of group means when accounting for

the baseline value (ANCOVA) with normally distributed data. The model will have an intercept plus three coefficients: beta1 for the effect of diabetes knowledge/information, beta2 for the effect of motivation/behavioral skills and beta3 for the interaction effect. .The study has 85% power (2-sided type I error rate of 0.05) to detect a clinically relevant difference of 1 percentage point in the 12-month HbA1c (assuming a common standard deviation of 1.5). The clinically relevant difference in HbA1c at 12 months is based upon the findings of a previous RCT of telephone-delivered diabetes intervention (Piette et. al., 2001) and our pilot study. Sample size estimation is based on a 2x2 factorial design and takes into account the potential interaction between the diabetes knowledge/information and motivation/behavioral skills intervention. A total of 42 subjects per arm is required to achieve 85% power (type I error rate of 0.05) to detect a clinically relevant difference of 1 percentage point in the 12-month HbA1c (assuming a common standard deviation of 1.5). Because testing for an interaction can greatly increase the sample size and since interaction is not our specific interest, we chose to ensure that we have adequate power to detect main effects in the presence of an interaction. Thus the total number of subjects required for randomization is 168 subjects (42 per treatment arm). The total sample size is inflated by a factor of 1.38 to account for an anticipated 15% attrition rate in an intent-to-treat analysis (Friedman et al, 2003). Thus a total of 232 subjects will be randomized into this study.

Data Analysis
Primary and secondary data analyses will be conducted using the intent-to-treat population. This population is defined as all randomized subjects. Sensitivity analyses will be conducted by repeating the proposed analyses using the per protocol population which is defined as all randomized subjects who complete 12 months of follow up. **Primary Objective**: To test the separate and combined efficacy of a *telephone-delivered diabetes knowledge/information and motivation/behavioral skills training intervention* in improving HbA1c levels in Blacks with T2DM using a 2x2 factorial design. Preliminary analyses will be conducted to assess the similarity of the treatment arms based on collected variables. Univariate descriptive statistics and frequency distributions will be calculated, as appropriate for all variables along with two-sided 95% confidence intervals when appropriate. Study discontinuation (attrition) rates will be estimated for each group. The primary framework for analysis is analysis of covariance. Twelve-month HbA1c measurements (dependent variable) will be compared between treatment arms using a model-based approach with telephone-delivered *diabetes knowledge/information*, telephone-delivered *motivation/behavioral skills training* and the interaction of the two factors in the model along with baseline HbA1c as a covariate. A global test approach will be implemented in order to preserve the type I error rate *(Green, Liu and O'Sullivan, 2002)*. A mixed model repeated measures analysis of covariance will be conducted as a secondary analysis to assess the difference in HbA1c levels over time. The model will include telephone-delivered *diabetes knowledge/information* and telephone-delivered *motivation/behavioral skills training* and the interaction of the two as factors in the model along with baseline HbA1c as a covariate. A similar analysis plan using a global test approach as describe above will be implemented. If the interaction is not significant, it will be dropped from the model. Covariance structures will be assessed during the model-fitting process using SAS PROC MIXED.

Project Timeline: We will randomize 232 patients in 4 cohorts of 58 patients every 6 months for 24 months, with an average of 10 patients randomized per month. Activities in Year 1 will include staff recruitment and training; establishing patient safety procedures; and purchase of study equipment and supplies. Recruitment of Cohort 1 will begin in month 7 of Year 1; while Cohort 4 will be recruited in month 1 of Year 3. Follow-up data collection for the Cohort 4 will be completed in month 6 of Year 4. Data cleaning and final data analyses will be take place in months 7-12 of Year 4. Manuscripts will be prepared and submitted for publication in months 7-12 of Year 3 and months 1-12 of Year 4. We plan to publish an initial paper within the first 24 months to describe the study design and expected outcomes.

HUMAN SUBJECTS RESEARCH

PROTECTION OF HUMAN SUBJECTS

<u>**RISKS TO THE SUBJECTS**</u>

<u>**Human Subjects Involvement and Characteristics**</u>
We will recruit 232 male and female African American patients with T2DM from MUSC general medicine, endocrine, and family medicine clinics. We will use two complementary approaches to identify eligible study subjects. The first method will consist of systematic identification of patients with type 2 diabetes. The second method will consist of referrals from primary care providers, other clinic staff such as nurses, or patients themselves in response to recruitment flyers for the study.

<u>Patient eligibility criteria</u>: The study inclusion and exclusion criteria are as follows

<u>Inclusion Criteria</u>: 1) Age ≥18 years; 2) Clinical diagnosis of T2DM and HbA1c ≥9% at the screening visit; 3) Self-identified as Black or African American; 4) Subject must be taking at least one oral medication for diabetes, hypertension, or hyperlipidemia and must be willing to use the MEMS cap and bottle for 12 months; 5) Subjects must be able to communicate in English; and 6) Subjects must have access to a telephone (landline or cell phone) for the 12 week intervention period.

<u>Exclusion Criteria</u>: 1) Mental confusion on interview suggesting significant dementia; 2) Participation in other diabetes clinical trials; 3) Alcohol or drug abuse/dependency; 5) Active psychosis or acute mental disorder; and 5) Life expectancy <6 months.

<u>**Sources of Materials**</u>

1. Research Material & Data: Sources of research material include medical history, research questionnaires, blood pressure readings, and blood specimens. The questionnaires will obtain information about demographics, clinical history, diabetes self-care, resource use, depression, and quality of life. Patients will provide ~10cc of blood for laboratory testing.

2. Linkages to Subjects: Subjects will provide identifying information in addition to research data. Paper documents pertaining to this study will be stored in locked file cabinets in both the clinical center and the data management center, and data will be entered into secure, password-protected databases developed for this study. A database of name, contact address, telephone number, and other research identification numbers will be stored separate from the study database, for purposes of audit by the sponsor (NIH) and MUSC IRB, if necessary. Access to study data will be limited to research personnel.

3. Collection of Data and Specimens:
Participants will be randomized to one of four groups: 1) telephone-delivered diabetes knowledge/information; 2) telephone-delivered motivation/behavioral skills training; 3) combined telephone-delivered diabetes knowledge/information and motivation/behavioral skills training; and 4) usual care.

c. <u>Potential Risks</u>
Potential risks to the patient include possible violation of the patient's privacy, discomfort with questions on the research questionnaire, discomfort and bleeding from blood draws, discomfort with BP measurement, and psychological distress. Details on how these risks will be minimized are discussed under adequacy of protection against risks below.

<u>**ADEQUACY OF PROTECTION AGAINST RISKS**</u>

<u>**Recruitment and Informed Consent**</u>
We will use two complementary approaches to identify eligible study subjects. The first method will consist of systematic identification of patients with type 2 diabetes. The second method will consist of referrals

from primary care providers, other clinic staff such as nurses, or patients themselves in response to recruitment flyers for the study.

Protection against Risk
A. Patients will be protected against potential risks as follows:
1. Psychological Distress: Because we will be administering a questionnaire that measures the presence of depression, we will take several steps to ensure the safety of all research participants. RAs will be trained by the PI to identify patients who meet criteria for depression on the PHQ-9. Subjects' who screen positive for depression will be notified during the visit and verbally instructed to seek care from their primary health care provider (PCP). They will also be given the 24-hour MUSC crisis psychiatry telephone service and told to call if they experience acute worsening of symptoms before they can be seen by their PCP.
2. Venipuncture (blood drawing): To reduce the risks of discomfort and bruising, venipuncture will be performed by trained personnel. To reduce the risk of fainting, blood will be drawn while subjects are in a seated position. The amount of blood that will be drawn, approximately 10cc, is not considered to pose a health risk for most adults. .
3. Blood Pressure Measurement: To lessen any associated risks, blood pressure measurements will be performed only by trained personnel utilizing a standardized protocol. Subjects with elevated blood pressure will be advised to contact their primary care provider. Those with potentially life threatening blood pressure readings will be sent to a local emergency room for treatment.
4. Administration of Research Questionnaires: Some participants might be offended by detailed questions about emotional or physical health status and impairment, and healthcare utilization. All participants will be informed at the outset that they may terminate participation at any point. Our past research suggests that data collection using these measures can be conducted without undue psychological distress or exacerbation of symptoms among study participants.
5. Unknown risks: Subject participation in research may have other unknown risks. The researchers will advise subjects if they learn of emerging information that might alter subjects' decisions to participate in this study.

B. Subjects requiring medical or other professional intervention for study-related events will be provided with appropriate and timely medical guidance by the PI. If adverse events occur during the conduct of this study, they will be reported to the IRB in accordance with the MUSC IRB Adverse Event Reporting Policy. The results of subjects' clinical assessments will be available within a few weeks of their study visit. The principal investigator will review and advise subjects of these results by phone and, at their request; he will also advise their personal physician of the results.

C. To protect against the potential risk of loss of confidentiality and/or breach of privacy, data will be compiled using codes in lieu of personal identifiers. Access to study data will be limited to research personnel. Development of and security oversight for the electronic database for this study will be performed by the study statistician. Paper documents pertaining to this study will be stored in locked file cabinets and electronic data will be entered into secure, password-protected databases developed for this study by the research assistants. The PI will perform periodic review of the data entry process to ensure accuracy of recording. When study results are published or presented, only aggregate reports of the results will be used and participants' identity will not be revealed. A file of name, contact address, telephone number, and other research identification numbers will be stored separately on paper and on computer, for purposes of audit by the sponsor (NIH) and MUSC IRB, if necessary.

3. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS
 The intervention is expected to benefit patients, by increasing their knowledge of diabetes, activating and empowering them to better care for their diabetes, improving blood glucose and blood pressure control, and reducing their risk developing complications of diabetes. Patients in the usual care group will benefit by increasing their general health knowledge.

4. IMPORTANCE OF KNOWLEDGE TO BE GAINED

The findings of this study, if successful, will lead to the implementation of this feasible, evidence-based intervention for high risk minority patients with T2DM. The study will provide new information on how to improve quality of care for diabetes in ethnic minorities and reduce the disproportionate burden of diabetes complications and deaths in ethnic minority groups with T2DM.

5. DATA AND SAFETY MONITORING PLAN

The data and safety monitoring plan will include an internal Data Safety Monitoring Committee (DSMC) and the institutional IRB. The purpose of the DSMC and IRB are to ensure the safety of participants and the validity and integrity of the data. Summaries of adverse events reports or patient safety concerns raised by the IRB will be made to NIH in the yearly progress unless the nature of a particular event is such that it bears reporting to NIH immediately.

DSMC: The internal DSMC will consist of the PI, biostatistician, co-investigators/consultants on the proposal, and a designated medical monitor The functions of the DSMC will include: 1) provide scientific oversight; 2) review all adverse effects or complications related to the study; 3) monitor accrual; 4) review summary reports relating to compliance with protocol requirements; and 5) provide advice on resource allocation. The DSMC will meet quarterly and as necessary by telephone. The recommendations of the DSMC will be reviewed and the PI will take appropriate corrective actions as needed.

Institutional IRB: The IRB will review and approve the funded protocol, review patient and provider consent forms, ensure protection of patient privacy and safety, and monitor the study on an ongoing basis. Adverse events will be reported to the IRB as they occur. Annual reports to the IRB will indicate accrual rate, adverse events, new findings that may influence continuation of the study, and reports of the DSMB.

INCLUSION OF CHILDREN

Children (ages 18-21) are included in this study. Children under the age of 18 years are excluded because type 2 diabetes is not common in younger aged children. Based on our study clinic demographics, we estimate that children 18-21 years will comprise ~5% of the sample.

INCLUSION OF WOMEN

Both men and women will be included in this study. Based on our study clinic demographics, we estimate that women will constitute 50% of the sample.

INCLUSION OF MINORITY GROUPS

Only minority adults (African Americans) are included in this study. This is justified because of the high burden of diabetes and its complication in African Americans, and the paucity of data on effective interventions in this population.

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