Sample Size and Power Calculations

Power calculations were based on examinations of the least detectable differences. The first set of calculations assumes that because of random assignment, there is no need to adjust for covariates. Adjustment does not necessarily reduce bias or increase precision if the covariates are measured with error, and it may be better not to adjust.\(^1\)\(^2\) Moreover, the treatment of the baseline value depends on the analytic strategy selected.\(^2\) First examined is the power for unadjusted effects.

Power calculations

Power calculations have been performed treating A1c as both continuous and binary. As noted above, the primary analytic strategy will be to treat A1c as continuous. Thus, shown first are the calculations based on treating the outcome as continuous. Calculations of sample size were based on adjustments for unreliability and clustering. Based on prior experience, the inter-rater reliability of lab values is assumed conservatively to be \(\approx 0.90\). The estimated average cluster size of PCPs in our clinic is 2.5; the intra-cluster correlation is low, about .03, on average.\(^3\) A1c is typically normally distributed.

A1c as a continuous variable

The following analyses examine sample size required to detect differences in A1c between the experimental and enhanced usual care groups. Shown are the power curves, after adjustment for unreliability and clustering (figure 2). Sample
size refers to sample size per group. Data from the IDEATel study were used for estimation;³ the pooled mean and standard deviation for the Northern Manhattan sample with an A1c greater than or equal to eight percent, was 9.53 and 1.36, respectively at baseline. (The experimental group means and standard deviations at baseline, and one year follow-up were 9.37 (1.24) and 7.98 (1.29) respectively; while the comparable values for the control group were 9.70 (1.46) and 8.47 (1.90) respectively.) Based on an analysis of the Northern Manhattan sample, the adjusted group difference was -0.23; however, the effect size could be higher with inclusion of more cases of uncontrolled A1c. These calculations apply to two parallel groups and assume less than perfect reliability of change scores. We assume the following: \( \alpha = .05; 1-\beta = .80 \delta = \mu_1 - \mu_2 = 0.51 \text{ units}; \sigma^2 = (1.36)^2; R \text{ (reliability)} = .90; r \text{ (intracluster correlation)} = .03; g \text{ (average cluster size)} = 2.5. \) 

\[
n^* = \frac{2(\sigma^2_T + \sigma^2_e)(Z_{\alpha/2} + Z_{\beta})^2}{\delta^2}, \text{ adjusting for unreliability: } n = n^*/R\text{ (see Fleiss, pp4-5), and } n^* = 102; n = 108/\text{group}; \text{ adjusting for clustering, using the variance inflation factor, } IF = 1 + (g-1)r = 1.05, \text{ the adjusted } n = 119/\text{group}; \text{ after (30%) attrition, with } n = 170, \text{ an effect size as small as 0.51 could be detected.}^4 \text{ If all subjects are included in the analyses, smaller effect sizes can be detected. Thus, 180 subjects per group is a sufficient sample size for the detection of an effect size as small as a change of 0.5 in A1c. Such a decrease is considered clinically meaningful and represents about a 5% decrease in relative risk for development of microvascular complications. In a pilot study of 31 patients enrolled in Alianza's diabetes CHW programs, a pre-post test difference of 1.3 was observed.}
**A1c as a Binary Variable**

Based on pilot data from the AIM clinic, among those individuals with A1c values \( \geq 8.0 \), 67% are very poorly controlled (A1c \( \geq 9.0 \)). Examined are the minimally detectable changes associated with the proposed sample size. The first calculation was performed without a continuity correction (equation 1, below); and the second with the continuity correction (equation 2, below).

**Equation 1:**

\[
n' = \frac{z_{a/2} \sqrt{2pq} + z_{\beta} \sqrt{p_1q_1 + p_2q_2}}{(P_2 - P_1)^2}
\]

**Equation 2:**

\[
n = n' \left( 1 + \frac{4}{n' \sqrt{n' |P_2 - P_1|}} \right)^2
\]

**Equation 3:**

\[
z = \frac{P_2 - P_1}{\sqrt{2pq/n'}}
\]

It has been shown that without the continuity correction, the sample sizes may be too small. The use of the continuity correction in the test statistic (Equation 3), where \( p = \frac{1}{2} (p_1 + p_2) \) and \( q = 1-p \), results in the derivation of the second formula above which yields a sample size for each group that provides the desired significance level and power. Shown in figure 3 are the sample sizes per group and power associated with different effect sizes (after adjustment for clustering, and unreliability). Using the formula without the continuity correction, a sample size of 180 (assuming intent-to-treat analyses with no missing data) would allow detection of an endpoint difference of 15.6%. After applying the continuity
correction, the value is 16.3%. Based on data from AIM, this would be a reduction from 67% to 51% in the proportion of patients who remained in poor A1c control assuming no changes were to occur in the control group.

**Expected Attrition**

It is anticipated that attrition will be primarily due to drop-out (mortality will be rare in this age group). Other types of missing data, such as unanswered questions will be handled by pro-rating algorithms. Assumptions about attrition are based on the experience in IDEATel.$^3$ In that study (an older cohort, the majority 65 and over), the downstate 12 month attrition (including dropout and mortality) was about 12%; at 24 months of follow-up, the attrition was 20%. Given that the sample will be under the age of 65, and only followed for 12 months, a conservative estimate of attrition is 20%; however, a very conservative rate of 30% was used in some power calculations. Thus, it is expected that under the most conservative scenario, at least 252 (126 per treatment group) respondents will continue in the study. However, more will be analyzed because intent-to-treat is the analytic strategy proposed, and all subjects will be encouraged to return for the follow-up interview even if they were randomized to the CHW group but did not complete the 12 month intervention. Moreover, under full information likelihood estimation, assuming missing at random, all participants with at least one wave of data may be included in the analyses.
REFERENCES


FIGURES (see next)
<table>
<thead>
<tr>
<th>INITIAL HOME VISIT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention:</strong> Assessment</td>
</tr>
<tr>
<td><strong>Objective:</strong> Help participant develop a list of issues that affect his/her overall health and well-being</td>
</tr>
<tr>
<td><strong>Type:</strong> Home visit</td>
</tr>
<tr>
<td><strong>Number:</strong> 1st of 4 enactment phase visits</td>
</tr>
<tr>
<td><strong>When:</strong> Within 1st month &amp; prior to &quot;goal setting&quot; visits</td>
</tr>
<tr>
<td><strong>CHW will address participant's:</strong> (1) social context, (2) current knowledge about diabetes and its management, (3) current medications, (4) views on medication adherence, including perceptions of barriers or facilitators to adherence, (5) pertinent lifestyle and health behaviors, and (6) barriers to communicating and doing business with the healthcare system</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SECOND TO FOURTH HOME VISITS, MONTHS 1 &amp; 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention:</strong> Goal Setting &amp; Dealing with Barriers</td>
</tr>
<tr>
<td><strong>Objective:</strong> Assist participant in developing an individualized plan to advance his/her overall health and well-being</td>
</tr>
<tr>
<td><strong>Type:</strong> Home visits</td>
</tr>
<tr>
<td><strong>Number:</strong> 2nd, 3rd, and 4th enactment phase visits</td>
</tr>
<tr>
<td><strong>When:</strong> Within months 1 &amp; 2 after initial visit</td>
</tr>
<tr>
<td><strong>CHW efforts include:</strong> (1) stimulate self-management by teaching problem-solving skills (setting priorities, making goals, developing a plan, reviewing results, and revising the plan), (2) facilitate navigation of the healthcare system, (3) provide referrals to or assistance in accessing both social and medical community-based resources, and (4) give counseling &amp; coaching aimed at the improving lifestyle behaviors</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GROUP VISITS, MONTHS 3-12</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention:</strong> Group Interactive Discussions</td>
</tr>
<tr>
<td><strong>Type:</strong> Culturally tailored &amp; interactive sessions lead by CHW (60 min. duration, 1 session/week, &amp; 20 person max/cohort)</td>
</tr>
<tr>
<td><strong>Number:</strong> 10 (6 nutrition &amp; 4 physical activity sessions)</td>
</tr>
<tr>
<td><strong>When:</strong> Within initial part of maintenance phase (months 3-12)</td>
</tr>
<tr>
<td><strong>Objective:</strong> Stimulate lifestyle change by increasing knowledge and practice of healthy eating and physically active behaviors CHW may organize additional sessions such as: (1) knowledge building workshops addressing diabetes or health system navigation, (2) exercise excursions (i.e. participation in a walking club), or (3) nutritionally educational activities (i.e. healthy food festivals or farmers market field trips)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TELEPHONE FOLLOW-UP, MONTHS 3-12</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention:</strong> Telephone Consultations</td>
</tr>
<tr>
<td><strong>Type:</strong> Phone call (CHW may also utilize home visits)</td>
</tr>
<tr>
<td><strong>Number:</strong> Minimum of 1 call/contact per month</td>
</tr>
<tr>
<td><strong>When:</strong> Throughout maintenance phase (months 3-12)</td>
</tr>
<tr>
<td><strong>Objectives:</strong> (1) help facilitate participant's health goals by checking on progress of intended plan of action and addressing new problems (i.e., CHW may follow-up on adherence to medications), and (2) continue healthcare system navigation assistance (i.e. providing appointment reminders, bridging communication with PCP regarding prescription)</td>
</tr>
</tbody>
</table>

Figure 1. Summary of CHW Intervention.
Figure 2. Power to detect changes in A1c (0.4-0.7), as a continuous variable.
Figure 3. Power to detect changes in A1c, as binary variable.
The Data and Safety Monitoring

Board Charter

TITLE OF PROTOCOL: Northern Manhattan Diabetes Community
Health Worker Outreach Project—Columbia Center for Health of
Urban Minorities

PROTOCOL NUMBER: Columbia IRB-AAAD1689; NIH-NCMHHD 2
P60 MD000206-6
TABLE OF CONTENTS

1. INTRODUCTION

2. PRIMARY RESPONSIBILITIES OF THE DSMB

3. MEMBERSHIP OF THE DSMB
   3.1 Members
   3.2 Conflicts of Interest
   3.3 Compensation

4. TIMING AND PURPOSE OF THE DSMB MEETINGS
   4.1 Organizational Meeting/Conference Call
   4.2 Annual Meeting/Conference Call
   4.3 Ad Hoc Adverse Event Meetings

5. PROCEDURES TO ENSURE CONFIDENTIALITY & PROPER COMMUNICATION
5.1 DSMB Sessions

5.2 Reports

5.3 Minutes of the DSMB Meeting

5.4 Recommendations to the Clinical Trial Leadership Group

5.5 Study Termination
1. INTRODUCTION

This Charter is for the Data and Safety Monitoring Board (DSMB) for the Protocol entitled **Northern Manhattan Diabetes Community Health Worker Outreach Project, IRB-AAAD1689; NIH-NCMHHD 2 P60 MD000206-6**.

The Charter defines the primary responsibilities of the DSMB, its relationship with other trial components, its membership, and the purpose and timing of its meetings. The Charter also provides the procedures for ensuring confidentiality and proper communication, and an outline of the content of the Reports that will be provided to the DSMB.

2. PRIMARY RESPONSIBILITIES OF THE DSMB

The DSMB will be responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the clinical trial. The DSMB will provide recommendations about stopping or continuing the trial. To contribute to enhancing the integrity of the trial, the DSMB may also formulate recommendations relating to the selection/recruitment/retention of participants, their management, improving adherence to protocol-specified regimens and retention of participants, and the procedures for data management and quality control.
The DSMB will be advisory to the clinical trial leadership group. The clinical trial leadership group will be responsible for promptly reviewing the DSMB recommendations, to decide whether to continue or terminate the trial, and to determine whether amendments to the protocol or changes in study conduct are required.

3. MEMBERS OF THE DSMB

3.1 Members

The DSMB is an independent multidisciplinary group consisting of biostatisticians and clinicians that collectively have experience in the management of patients, and in the conduct and monitoring of randomized clinical trials.

DSMB Chair: Ruth Weinstock, M.D., Ph.D.
weinstor@upstate.edu

DSMB Biostatistician: Michael Parides, Ph.D.
michael.parides@mssm.edu

DSMB Clinical Investigators: William Chaplin, Ph.D.
chaplinw@stjobs.edu
Roberto Izquierdo, M.D.
IZQUIERR@upstate.edu

3.2 Conflicts of Interest
The DSMB membership has been restricted to individuals free of apparent significant conflicts of interest. The source of these conflicts may be financial, scientific or regulatory in nature. Thus, neither study investigators nor individuals employed by the sponsor, nor individuals who might have regulatory responsibilities related to the trial, are members of the DSMB.

The DSMB members do not own stock in any companies having products or services related to the study hypotheses. The DSMB members will disclose to fellow members any consulting agreements or financial interest they have with the sponsor of the trial (Columbia University) or with any other sponsors whose products are related to the study hypotheses. The DSMB will be responsible for deciding whether these consulting agreements or financial interest materially impact their objectivity.

The DSMB members will be responsible for advising fellow members of any changes in these consulting agreements and financial interest that occur during the course of the trial. Any DSMB members who develop significant conflicts of interest during the course of the trial should resign from the DSMB.

DSMB membership is to be for the duration of the clinical trial. If any members leave the DSMB during the course of the trial, the sponsor, in consultations with the clinical trial leadership group, will promptly appoint their replacements.

3.3 Compensation

All DSMB members will be compensated $1000 per year.
4. TIMING AND PURPOSE OF THE DSMB MEETINGS

4.1 Annual Meeting/Conference Call

The NOCHOP study will test the hypothesis that a behavioral intervention by Community Health Workers (CHWs) will result in an improvement in Hemoglobin A1c, blood pressure, and serum cholesterol levels, as compared to usual care, in Hispanic adults with diabetes. CHWs will attempt to facilitate access to medical care, but will not exert any changes to the care itself. No devices, drugs, or treatments are being evaluated in this project. Therefore, an annual meeting, with ad-hoc meetings if necessary (see below), is appropriate.

The first annual meeting (either in person or via conference call) will be held by the DSMB after at least 10 months after the onset of participant enrollment. At that meeting the DSMB will review safety information, factors relating to quality of trial conduct, and will ensure proper implementation of procedures described in the protocol. The initial meeting or conference call of the DSMB will also be an Organizational Meeting. It will be held to provide advisory review of scientific and ethical issues relating to study conduct, to discuss the standard operating procedures for the role and functioning of the DSMB, and to discuss the format and content of the reports they receive from the Data Coordinating Center.

Subsequent meetings will take place at yearly intervals. To enhance the integrity and credibility of the trial, procedures will be implemented to ensure the DSMB has full
ongoing access to evolving information from the clinical trial, in particular regarding safety data, aggregated by treatment arm.

A designated statistician from the Data Coordinating Center, the Research Division of the Hebrew Home at Riverdale (HHAR), will serve as a liaison between the Coordinating Center and the DSMB.

Procedures will also be implemented to ensure proper communication is achieved between the DSMB and the trial investigators. The Data Coordinating Center will issue a report and recommendations to the investigators after every meeting. In addition, to provide a forum for exchange of information among various parties who share responsibility for the successful conduct of the trial, the DSMB can convene, at their discretion, meetings/conference calls with the study investigators at any point during the trial (see next item).

4.2 *Ad Hoc* Adverse Event Meetings

The responsibilities of the study’s research staff and Principal Investigator include reporting on an ongoing basis all patient-specific information on serious adverse events to satisfy the standard requirement for prompt reporting to the regulatory authorities. The Columbia University IRB and the project’s DSMB will be notified.

In the event of an unexpected adverse event that appears to be, as per the Columbia University IRB, related to the project, the DSMB will be convened to review such event. All DSMB members are expected to attend. Reportable adverse events are defined according to criteria defined by the Columbia University IRB.
5.1 Confidentiality of DSMB Meetings

Any information discussed during DSMB meetings will be considered confidential, involving only DSMB membership and the DSMB biostatistician. The DSMB meetings will allow discussion of confidential data from the clinical trial, including information about the safety of interventions. In order to ensure that the DSMB will be fully informed in its primary mission of safeguarding the interest of participating patients, the DSMB will have full access to unblinded study data. At the end of each meeting, the DSMB will develop a consensus on its list of recommendations to the project investigators.

5.2 Open DSMB Meeting with Investigators

In order to allow the DSMB to have adequate access to information provided by the study investigators, a joint session between the investigators and DSMB members (called an Open Session), will be convened by the DSMB, to be followed by a Closed Session, as needed. This session gives the DSMB an opportunity to query the investigators about issues that have arisen during their review. With this format,
important interactions are facilitated through which problems affecting trial integrity can be identified and resolved.

5.3 DSMB Reports

For each DSMB meeting, Reports will be provided by the project Data Coordinating Center. These reports, available to all who attend the DSMB meeting, will include data on recruitment and retention, pooled data on eligibility violations, data completeness, and compliance with the study protocol.

The reports should provide information that is accurate, with follow-up that is complete to within two months of the date of the DSMB meeting. The Reports should be provided to DSMB members at least three days prior to the date of the meeting.

5.4 Minutes of the DSMB Meeting

The DSMB will prepare minutes of their meetings. Two sets may be prepared: the Open Minutes and Closed Minutes, if needed.

The Open Minutes will describe the proceedings in the Open Session of the DSMB meeting, and will summarize all recommendations by the DSMB. Because these minutes will be circulated immediately to the lead study investigators, it is necessary that these minutes do not unblind the efficacy and safety data if the DSMB is not recommending early termination.

If deemed necessary by the DSMB, particularly if un-blinded study data must be included, Closed Minutes will be prepared. It is important that they are not made
available to anyone outside the DSMB. Rather, copies will be archived by the
independent statistician preparing the interim reports, for the distribution to the lead
investigator and regulatory authorities at the time of study closure.

5.5  **Recommendations to the Clinical Trial Leadership Group**

At each meeting of the DSMB during the conduct of the trial, the DSMB will
make recommendations it deems appropriate to the clinical trial leadership group to
ensure the ethical conduct of the project.

The clinical trial leadership group is jointly responsible with the DSMB for
safeguarding the interest of participating patients and for the conduct of the trial.
Recommendations to amend the protocol or conduct of the study made by the DSMB will
be considered and accepted or rejected by the clinical trial leadership group.

The DSMB will be notified of all changes to the protocol or to the study conduct.
The DSMB concurrence will be sought on all substantive recommendations or changes to
the protocol or study conduct prior to their implementation.

5.6  **Study Termination**

Given that the intervention arm of this study does not change participant’s
medical treatment in any way, and is limited to a behavioral intervention, there is no
provision for interim analyses of the outcomes of interest with stopping rules.
The DSMB may recommend stopping the study due to the occurrence of a severe unexpected adverse event that is:

1) Directly caused by the intervention, and

2) In the view of the DSMB cannot be prevented from occurring again through a protocol modification/personnel re-training/etc.