BMJ open accessible medical research

Protocol for the Northern Manhattan Diabetes Community Outreach Project. A randomised trial of a community health worker intervention to improve diabetes care in Hispanic adults

Walter Palmas,[1] Jeanne A Teresi,[2] Sally Findley,[3] Miriam Mejia,[4] Milagros Batista,[4] Jian Kong,[2] Stephanie Silver,[2] Jose A Luchsinger,[1] Olveen Carrasquillo[5]

To cite: Palmas W, Teresi JA, Findley S, *et al*. Protocol for the Northern Manhattan Diabetes Community Outreach Project. A randomised trial of a community health worker intervention to improve diabetes care in Hispanic adults. *BMJ Open* 2012;**2**: e001051. doi:10.1136/bmjopen-2012-001051

► Prepublication history and additional materials for this paper are available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2012-001051).

Received 20 February 2012
Accepted 27 February 2012

[1]Department of Medicine, Columbia University, New York, New York, USA
[2]Hebrew Home for the Aged, Riverdale, New York, USA
[3]Joseph Mailman School of Public Health, Columbia University, New York, New York, USA
[4]Alianza Dominicana, New York, New York, USA
[5]Department of Medicine, University of Miami, Miami, Florida, USA

Correspondence to
Dr Walter Palmas;
wp56@columbia.edu

ABSTRACT

Objective: Hispanics in the USA are affected by the diabetes epidemic disproportionately, and they consistently have lower access to care, poorer control of the disease and higher risk of complications. This study evaluates whether a community health worker (CHW) intervention may improve clinically relevant markers of diabetes care in adult underserved Hispanics.

Methods and analysis: The Northern Manhattan Diabetes Community Outreach Project (NOCHOP) is a two-armed randomised controlled trial to be performed as a community-based participatory research study performed in a Primary Care Setting in Northern Manhattan (New York City). 360 Hispanic adults with poorly controlled type 2 diabetes mellitus (haemoglobin A1c >8%), aged 35–70 years, will be randomised at a 1:1 ratio, within Primary Care Provider clusters. The two study arms are (1) a 12-month CHW intervention and (2) enhanced usual care (educational materials mailed at 4-month intervals, preceded by phone calls). The end points, assessed after 12 months, are primary = haemoglobin A1c and secondary = blood pressure and low-density lipoprotein-cholesterol levels. In addition, the study will describe the CHW intervention in terms of components and intensity and will assess its effects on (1) medication adherence, (2) medication intensification, (3) diet and (4) physical activity.

Ethics and dissemination: All participants will provide informed consent; the study protocol has been approved by the Institutional Review Board of Columbia University Medical Center. CHW interventions hold great promise in improving the well-being of minority populations who suffer from diabetes mellitus. The NOCHOP study will provide valuable information about the efficacy of those interventions vis-à-vis clinically relevant end points and will inform policy makers through a detailed characterisation of the programme and its effects.

Clinical trial registration number: NCT00787475 at clinicaltrials.gov.

ARTICLE SUMMARY

Article focus

- Randomised controlled trial.
- CHW intervention.
- Diabetes care.

Key messages

- This community-based participatory research study is a collaboration between a community organisation and a university in Northern Manhattan, New York City.
- The goal is to assess whether the CHW worker intervention may improve diabetes care in underserved adult Hispanics from the community.
- The primary outcome of interest is haemoglobin A1c, a marker of diabetes control; secondary outcomes are blood pressure and low-density lipoprotein cholesterol levels.

Strengths and limitations of this study

- This study will examine effects of the CHW intervention after 12 months, a longer time period than in previous studies.
- The CHW intervention protocol was developed in a culturally appropriate manner to address the needs of Hispanics residing in our community.
- If proven efficacious, it will warrant examination in other cultural socioeconomic milieus.

INTRODUCTION

The current diabetes epidemic affects US Hispanics disproportionately, both in prevalence and frequency of complications as compared with Caucasians.[1] Hispanics suffer from less access to care and poorer control of their diabetes.[2 3] On the other hand, there is a great paucity of culturally appropriate models of care that maximise access and enhance healthcare delivery in Hispanics.[4 5] The lack of such models perpetuates the role of language and culture as 'barriers to care'.

Thus, there is great interest in patient-cantered interventions that, instead, embrace the culture and language of our patients. This paradigm shift has the potential to transform those perceived 'barriers' into integral components of the intervention, empowering patients and their families in dealing with diabetes mellitus and helping them navigate the complexities of our medical system.

Community health workers (CHWs, known as *Promotoras* or *Promotores de Salud* in Spanish) have been shown to be efficacious in improving healthcare delivery around the world, including Latin America and the USA.[6] However, a better characterisation of the efficacy of CHW interventions is needed, particularly in regards to widely accepted clinical end points, such as serum haemoglobin A1c (A1c, a measure of blood glucose levels over the previous weeks), blood pressure and cholesterol levels. Several randomised controlled trials (RCTs) have been performed to assess the potential benefits of CHW interventions in improving the care of minority populations with diabetes. However, those trials recruited relatively small numbers of participants and were carried out for rather short periods of time.[7–13] Indeed, as recently reviewed, data from some of those studies suggest that short-term efficacy achieved in lowering A1c is later lost at 12 months.[14] Systematic reviews and meta-analyses have also highlighted the need for larger and longer term RCTs in Hispanic and other underserved communities.[14–17] In addition to clinically relevant end points (such as A1c lowering), there is a clear need for interventions that are well described both in nature and intensity and that target a well-defined population.[17]

We describe here the protocol of a study designed to address those gaps in knowledge, the Northern Manhattan Diabetes Community Outreach Project (NOCHOP). The NOCHOP is a RCT to evaluate the efficacy of a 12-month CHW intervention to improve the care of Hispanics with poorly controlled type 2 diabetes mellitus. It is a two-arm study with an active control group, designed such that the control group receives enhanced standard care. It is a community-based participatory research enterprise designed and conducted by two partner institutions from Northern Manhattan: Alianza Dominicana, Inc., and Columbia University.

METHODS AND ANALYSIS

Study outcomes

The primary study outcome is glycaemic control, measured by A1c. The secondary outcomes are systolic and diastolic blood pressure and low-density lipoprotein (LDL) cholesterol levels. We also are collecting data, which will allow examination of the putative mechanisms that may account for the hypothesised effects of the intervention in this population. Data are being collected during the intake and 1-year follow-up examination on the following mechanistic end points: (1) medication adherence, (2) medication intensification, (3) diet and (4) physical activity.

Study participants

NOCHOP is an RCT of 360 Hispanic participants with poorly controlled type 2 diabetes, aged 35–70 years and who are currently receiving care at one of our primary care practice sites in Northern Manhattan.[18] Participants are classified as having poorly controlled diabetes if their last A1c measurement (performed in the preceding 12 months) was ≥8.0. Exclusion criteria are (1) type 1 diabetes and/or diabetes with onset before age of 25; (2) subjects who do not self-identify as Hispanic; (3) any life-threatening or extreme medical comorbidity, such as an active cancer or end-stage cardiopulmonary disease; (4) having a diabetes diagnosis for <1 year; (5) planning to move out of the neighbourhood during the next year; (6) enrolment in any other study and (7) arm circumference of >47 cm (due to inability to accurately measure blood pressure using an oscillometric device).

All participants provide informed consent prior to enrolment; the study protocol has been approved by the Institutional Review Board (IRB) of Columbia University Medical Center. Consent is obtained by trained study personnel, following IRB-approved procedures. Recruitment is performed within the Primary Care Clinics at Columbia University Medical Center, and it is centred around Primary Care Physicians (PCP), who approve all contacts with potential participants. This approach has proven successful for our group when recruiting, from the same population, for a recent RCT of innovative diabetes care management.[19] Moreover, the collaboration with Alianza Dominicana, the largest and best-known community organisation in our neighbourhoods, probably enhances recruitment.

Participant attrition is usually a concern in trials enrolling underserved populations, as it may compromise the statistical power of the study. Thus, steps are taken in both arms to maximise retention. In the intervention arm, CHWs regularly stress the importance to all participants of undergoing their 12-month evaluation visit, and they use reminders when approaching the end of the intervention. In the control arm, the study coordinator takes the opportunity provided by the scheduled phone calls (see below) to address this issue. Based on the intention-to-treat principle, all efforts will be made to bring participants back for the 12-month evaluation visit. For those participants who are unable or unwilling to undergo that evaluation, sensitivity analyses will be performed—please see the Statistical analysis methods section, for a description of our analytic approach to missing data. Of note, as described in the supplementary data file, our sample size was determined using a conservative approach to attrition when modelling the statistical power estimates.

Randomisation

After providing informed consent, participants are remotely and blindly randomised (1:1) to either

intervention (CHW intervention for 12 months) or to enhanced usual care (EUC) by the Research Department at the Hebrew Home at Riverdale, NY. Randomisation is clustered within PCP practice; the algorithm accounts for rolling enrolment within PCPs. Balance between the two study arms is checked periodically.

Procedures

All participants undergo two examination visits: one at baseline and another one at the end of the participation a year later. Personnel performing evaluation visits are blinded to randomisation status. Subjects are instructed to come to examinations fasting, and having held their diabetes medications, but taking their blood pressure medications. Questionnaire data are obtained during examination visits using a computer-assisted telephone interviewing system.[20]

Measures

Height and weight are measured without shoes and wearing lightweight clothes and using a stadiometer and a validated digital scale. All measurements are recorded to the nearest 0.1 cm/0.1 kg. Specimens are analysed in blinded fashion by the Columbia University CRC Core Laboratory. A1c is measured using a latex agglutination assay (Hitachi 912 Polymedco Inc., Cortlandt Manor, New York, USA). Total cholesterol, triglyceride and high-density lipoprotein cholesterol is measured using enzymatic colorimetric methods (Vitros, Johnson & Johnson, New Brunswick, New Jersey, USA). LDL cholesterol is calculated using the Friedewald equation.[21] For subjects with triglyceride level ≥300 mg/dl, LDL cholesterol is measured directly using a homogeneous assay (Polymedco, Cortlandt Manor, New York, USA). Resting blood pressure is measured using a BpTRU automated oscillometric device (VSM Tech Ltd, Coquitlam, BC, Canada). Three measurements are obtained following 5 min of rest. The average of the second and third measurements is recorded as the resting blood pressure. Other constructs measured include medication adherence,[22] dosage and intensity,[23] physical activity,[24] diet[25] and depression.[26]

CHW intervention

Basic features

The CHW intervention is based on (1) existing consensus of successful diabetes interventions in vulnerable populations and (2) its promise as a sustainable generalisable intervention. Two full time CHWs based at Alianza Dominicana, Inc., are delivering a multicomponent intervention that includes home visits, group visits and telephone follow-up, the focus of the home visits is on assessment of existing barriers to healthcare (diabetes and non-diabetes), empowering the patient to overcome these barriers and then developing achievable goals for the upcoming year. The group visits focuses on nutrition and exercise activities. The phone intervention serves as a follow-up mechanism for adherence to the individualised plan and reinforcement. The intervention is summarised in figure 1 of the supplementary data. CHW intervention is flexible and tailored to each participant's needs, but the goal will be to perform at least four home visits, 10 group sessions and 10 follow-up phone calls per subject over a 12-month period.

CHW medical service/patient navigator activities

Self-management is key to the CCM, and fundamental to this is empowering patients to make effective use of the healthcare system.[27 28] This requires a positive and productive relation with the PCP, wherein the patient is comfortable in asking questions and speaking honestly about concerns regarding medications.[29 30] Through individual and group activities, the CHWs help the participants develop communication and self-advocacy skills to be able to take a more active role in their visits. They teach participants how to maximise their time with the provider, how to advocate for themselves and what questions they should ask. Additional patient navigator activities by CHWs during the home visit may include reminding patients of their next appointments and, if needed, setting up home medication reminder systems for patients such as refrigerator charts noting when it is time to get refills.

Referrals

The CHWS also assist the participants in accomplishing their goals by connecting them to needed services. The CHWS make referrals to community-based resources, both for social and healthcare services. One example would be if the participant is facing eviction or experiencing problems such as domestic violence. Alianza has specific programmes for housing and domestic violence and the CHWS facilitate referrals; if not available through Alianza, they are referred to other community partners where such services would be available.

Informatics support for CHWs

The CHWs have remote real-time access to participant data, in a HIPAA-compliant manner,[31] through secure access to a dedicated database.

EUC arm of the study

Patients randomised to the control group receive usual care from their PCP. This includes routine monitoring and care from the PCP and the possibility of referral to several existing diabetes management resources, among them the multidisciplinary comprehensive Naomi Berrie Diabetes Center at Columbia University Medical Center. The N. Berrie Center resources comprise a multidisciplinary team of endocrinologists, certified diabetes educators and nurse case managers who provide intensive diabetes case management requiring very involved patient participation. Providers can also refer patients to the Visiting Nurse Service of New York. The Visiting Nurse Service programme includes nurses, nutritionists and diabetes educators who can deliver home-based diabetes care and education to patients. This service is ideal for those older patients who are home-bound. In addition, our primary care clinic has a certified diabetes

health educator nurse who provides on site individual diabetes education, group diabetes classes and, if requested, can assist providers with case management. In NOCHOP, PCPs remain free to use any of these existing resources for their patients, at their discretion. The usual care received will be enhanced by providing patients with three sets of Spanish language educational materials published by the National Institutes of Health. These materials include information on communication between physician and patient, diabetes management, mental health and a diabetes cookbook. During the 12-month period, a project coordinator calls EUC patients four times. The goals of the phone calls are to (1) ensure that the participants have received the mailed brochures and that they find those brochures appropriate for their own literacy and (2) maximise retention in the study, aiming to reduce attrition in this group.

STATISTICAL ANALYSIS METHODS

Sample size and power

The sample size was chosen to ensure sufficient power to detect clinically meaningful effects associated with a change in A1c as a continuous outcome. The calculations performed indicate that the proposed sample size of 360 (180 per arm) will provide sufficient power for the main study hypotheses, under a variety of assumptions. The power calculations, including a detailed description of assumptions and scenarios, are described in detail in the supplementary file.

Unit of analysis and clustering

The patient will constitute the unit of analysis for the study. Patients will be randomised within PCP; therefore, sample sizes must be larger to account for unreliability of measures and for design features.[32–34] Both correlation among repeated measures over time on the same subject and correlation due to clustering of patients within providers (characteristics of the providers or practice which may influence outcomes among their patients) will be taken into account. This dependency among members of the cluster will inflate the variance of the effect of the intervention.[35]

Adjustment for multiple comparisons

Adjustment for multiple comparisons is an area of controversy.[36–40] Following recent guidelines for clinical trials,[41] we propose to treat primary and secondary outcomes as separate clusters, setting a 0.05 level of significance to the primary outcome within each cluster. A Bonferroni or Benjamini–Hochberg correction would be applied to secondary treatment outcomes. Thus, a 0.05 level will be assigned to the A1c outcome and a 0.01 level to the three secondary outcomes (LDL, diastolic blood pressure and systolic blood pressure).

Analyses

A parallel group design with equivalent baseline values as a result of randomisation is proposed. Calculations are provided for the primary outcome treated as continuous and as binary. The main analyses will be performed using continuous data. Analyses of A1c treated as binary assumes intent-to-treat and that all dropout and missing data are considered as failures. Thus, the proportion of successes is based on the entire sample randomised. However, in the context of cost limitations, large samples are required to examine small effects when continuous data are treated as binary because of the severe loss of power associated with dichotomising a normally distributed dependent variable such as A1c. Dichotomisation of skewed variables leads to even greater loss of power.[42] Additionally, there are theoretical considerations that include the fact that in health disparities research, stringent goals, for example, complete glycaemic control, may not be realised and one may consider smaller average reductions in outcomes as clinically meaningful.

The general approach to the analyses is guided by our own experience in the analyses of such data[43 44] and by recent reviews of best methods for analyses of longitudinal data from clinical trials.[45] Because the design is to randomise individuals to groups within PCP strata, some baseline imbalance in the outcome might occur; in this case, the basic analytic approach will be analysis of covariance (ANCOVA) model that adjusts for baseline values of the outcome, as well as for the design feature of clustering. In order to determine the best approach, two basic models could be examined. One is a basic t test or ANCOVA approach, with inclusion of a random effect for PCP to model the clustered data. The second is a repeated measures approach that examines time as continuous. The latter allows inclusion of more subjects, however, with only two waves of data (and if 90% of the subjects are interviewed within ±2 months of the 12-month mark), it is not clear that there will be sufficient benefits associated with the approach. The post-treatment values of continuous outcomes will be modelled as functions of baseline values, treatment and the interaction of baseline and treatment. A general longitudinal mixed effects model, using SAS PROC MIXED, will be used to allow for the correlation between subjects within a PCP. Additionally, the group heterogeneity in cluster and residual variances may require modelling to satisfy model assumptions and improve model fit. (There may be violations of the more rigid assumptions involved in ANCOVA, such as homoscedasticity, so that modelling the group heterogeneity in cluster and residual variances will be necessary.) Based on prior analytic experience with the outcome variables, the need to transform them is not anticipated. Although the primary analysis is to examine A1c as a continuous measure, it is also proposed to treat A1c as a binary outcome defining those with poor glycaemic control as A1c ≥9.0. In this case, dichotomous outcome measures will be analysed using generalised estimating equations to account for potentially correlated outcomes of subjects with the same PCP (PROC GLIMMIX in SAS). Prior to analyses,

baseline values of all variables from each arm will be examined; however, no p values will be provided, and covariates (other than baseline values) are not proposed for inclusion in the main analyses of treatment effects. Examination of baseline differences on key variables between subjects remaining and those lost to follow-up will also be conducted. The first set of analyses will not adjust for dropout. Only cases with complete data will be included; however, as stated, these analyses will include those who did not complete the CHW intervention but who returned to provide the follow-up interview, under an intent-to-treat design. The intent-to-treat analyses of the total group could be repeated using baseline values carried forward to account for cases lost to follow-up (using SAS PROC MIXED). However, baseline values carried forward is not optimal, depending on the type of variable studied.[46] For example, blood pressure may increase over time due to ageing. Thus, other methods of examining missing data, for example, propensity scores, EM algorithm and multiple imputation sensitivity analyses, will be considered.

ETHICS AND DISSEMINATION

Data and Safety Monitoring Board

The Data and safety monitoring board (DSMB, also known as a Data Monitoring Committee) is an independent four-member multidisciplinary group consisting of biostatisticians and clinicians that collectively have experience in the management of patients and in the conduct and monitoring of randomised clinical trials. It is 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. A detailed description of the NOCHOP DSMB and its duties can be found in the DSMB Charter, in the supplementary data file.

Protection of participant privacy

The NOCHOP study adheres to the privacy rules instituted by the Health Insurance Portability and Accountability Act of 1996 (HIPAA). All examination data are electronically transmitted using encryption software at the end of the visit, and all data are stored in firewall-protected servers. Data analysis will be performed in de-identified data sets (ie, sets that contain no participant identifiers, as defined by HIPAA). Moreover, only de-identified data sets will be shared using IRB-authorised procedures or (upon request) with the National Institutes of Health.

Relevance and dissemination

Our project seeks to examine the efficacy of a CHW intervention to improve the care of adult Hispanics with type 2 diabetes in Northern Manhattan. CHW interventions are rooted in over 30 years of culturally tailored public health service delivery in Hispanic communities. The acceptability of this approach to enhance healthcare delivery has been shown in Hispanic populations in numerous studies. An additional strength of the community-based design is that it will not further tax the already limited resources of health providers caring for low-income minority populations, such as inner-city clinics. In addition, this project will help characterise the specific components of a CHW intervention that lead to an improvement in clinically and socially relevant outcomes in this high-risk population. In doing so, NOCHOP is expected to make a substantial contribution to the ongoing national debate about the sustainability and optimal design of CHW programmes.

Contributors All authors edited the draft and contributed substantially to the manuscript; they all approved this submission. WP, JAT, SF, MM, MB and OC conceived of and designed the study. MM, JAT, JAL and SS participated in the design of the study. SF, MM and MB designed the community health workers intervention protocol, with input from WP, JAL and OC. MM and MB supervise the community health workers intervention, with assistance from WP and SF. JAT supervised the power analyses and wrote the data analyses section. SS and JK created the data entry system, under the supervision of JT; they will be responsible for performing the statistical analysis. JK programmed the Macros for power analyses. WP, OC and JAL designed and planned the evaluation visits. WP bears overall responsibility for the design, ethical conduct and publication of the study.

Funding This study was funded by the National Institute on Minority Health and Health Disparities and the National Institutes of Health, grant number P60 MD00020606.

Competing interests None.

Ethics approval Ethics approval was provided by the Columbia University Medical Center Institutional Review Board.

Provenance and peer review Not commissioned; internally peer reviewed.

REFERENCES

1. Mainous AG 3rd, Baker R, Koopman RJ, *et al*. Impact of the population at risk of diabetes on projections of diabetes burden in the United States: an epidemic on the way. *Diabetologia* 2007;50:934–40.
2. Harris MI, Eastman RC, Cowie CC, *et al*. Racial and ethnic differences in glycemic control of adults with type 2 diabetes. *Diabetes Care* 1999;22:403–8.
3. Harris MI. Racial and ethnic differences in health care access and health outcomes for adults with type 2 diabetes. *Diabetes Care* 2001;24:454–9.
4. Anon. Policy statements adopted by the Governing Council of the American Public Health Association, November 18, 1998. *Am J Public Health* 1999;89:428–50.
5. Mieres JH, Phillips LM. The interdisciplinary approach to culturally tailored medical care: "Social networking" for decreasing risk: comment on "The effects of a nurse case manager and a community health worker team on diabetic control, emergency department visits, and hospitalizations among urban African Americans with type 2 diabetes mellitus: a randomized controlled trial" and "Trial of family and friend support for weight loss in African American adults". *Arch Intern Med* 2009;169:1804–5.
6. Perez LM, Martinez J. Community health workers: social justice and policy advocates for community health and well-being. *Am J Public Health* 2008;98:11–14.
7. Babamoto KS, Sey KA, Camilleri AJ, *et al*. Improving diabetes care and health measures among hispanics using community health workers: results from a randomized controlled trial. *Health Educ Behav* 2009;36:113–26.
8. Brown SA, Garcia AA, Kouzekanani K, *et al*. Culturally competent diabetes self-management education for Mexican Americans: the Starr County border health initiative. *Diabetes Care* 2002;25:259–68.
9. Gary TL, Batts-Turner M, Bone LR, *et al*. A randomized controlled trial of the effects of nurse case manager and community health worker team interventions in urban African-Americans with type 2 diabetes. *Control Clin Trials* 2004;25:53–66.
10. Gary TL, Batts-Turner M, Yeh HC, *et al*. The effects of a nurse case manager and a community health worker team on diabetic control, emergency department visits, and hospitalizations among urban African Americans with type 2 diabetes mellitus: a randomized controlled trial. *Arch Intern Med* 2009;169:1788–94.

11. Gary TL, Bone LR, Hill MN, *et al*. Randomized controlled trial of the effects of nurse case manager and community health worker interventions on risk factors for diabetes-related complications in urban African Americans. *Prev Med* 2003;37:23–32.
12. Lujan J, Ostwald SK, Ortiz M. Promotora diabetes intervention for Mexican Americans. *Diabetes Educ* 2007;33:660–70.
13. Lorig K, Ritter PL, Villa FJ, *et al*. Community-based peer-led diabetes self-management: a randomized trial. *Diabetes Educ* 2009;35:641–51.
14. Hawthorne K, Robles Y, Cannings-John R, *et al*. Culturally appropriate health education for type 2 diabetes mellitus in ethnic minority groups. *Cochrane Database Syst Rev* 2008;(3):CD006424.
15. Sarkisian CA, Brown AF, Norris KC, *et al*. A systematic review of diabetes self-care interventions for older, African American, or Latino adults. *Diabetes Educ* 2003;29:467–79.
16. Lewin SA, Dick J, Pond P, *et al*. Lay health workers in primary and community health care. *Cochrane Database Syst Rev* 2005;(1): CD004015.
17. Swider SM. Outcome effectiveness of community health workers: an integrative literature review. *Public Health Nurs* 2002;19:11–20.
18. Bakken S, Lantigua RA, Busacca LV, *et al*. Barriers, enablers, and incentives for research participation: a report from the Ambulatory Care Research Network (ACRN). *J Am Board Fam Med* 2009;22:436–45.
19. Shea S, Weinstock RS, Teresi JA, *et al*. A randomized trial comparing telemedicine case management with usual care in older, ethnically diverse, medically underserved patients with diabetes mellitus: 5 year results of the IDEATel study. *J Am Med Inform Assoc* 2009;16:446–56.
20. White MJ, Stark JR, Luckmann R, *et al*. Implementing a computer-assisted telephone interview (CATI) system to increase colorectal cancer screening: a process evaluation. *Patient Educ Couns* 2006;61:419–28.
21. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972;18:499–502.
22. MacLaughlin EJ, Raehl CL, Treadway AK, *et al*. Assessing medication adherence in the elderly: which tools to use in clinical practice? *Drugs Aging* 2005;22:231–55.
23. Winston GJ, Barr RG, Carrasquillo O, *et al*. Sex and racial/ethnic differences in cardiovascular disease risk factor treatment and control among individuals with diabetes in the Multi-Ethnic Study of Atherosclerosis (MESA). *Diabetes Care* 2009;32:1467–9.
24. Blair SN, Haskell WL, Ho P, *et al*. Assessment of habitual physical activity by a seven-day recall in a community survey and controlled experiments. *Am J Epidemiol* 1985;122:794–804.
25. Thompson FE, Kipnis V, Subar AF, *et al*. Evaluation of 2 brief instruments and a food-frequency questionnaire to estimate daily number of servings of fruit and vegetables. *Am J Clin Nutr* 2000;71:1503–10.
26. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001;16:606–13.
27. Findley SE, Irigoyen M, See D, *et al*. Community-provider partnerships to reduce immunization disparities: field report from northern Manhattan. *Am J Public Health* 2003;93:1041–4.
28. Bar-Yam Y. Improving the effectiveness of health care and public health: a multiscale complex systems analysis. *Am J Public Health* 2006;96:459–66.
29. Whetten K, Leserman J, Whetten R, *et al*. Exploring lack of trust in care providers and the government as a barrier to health service use. *Am J Public Health* 2006;96:716–21.
30. Konrad TR, Howard DL, Edwards LJ, *et al*. Physician-patient racial concordance, continuity of care, and patterns of care for hypertension. *Am J Public Health* 2005;95:2186–90.
31. Gunn PP, Fremont AM, Bottrell M, *et al*. The Health Insurance Portability and Accountability Act Privacy Rule: a practical guide for researchers. *Med Care* 2004;42:321–7.
32. Donner A. Approaches to sample size estimation in the design of clinical trials—a review. *Stat Med* 1984;3:199–214.
33. Sullivan LM, D'Agostino RB. Robustness and power of analysis of covariance applied to data distorted from normality by floor effects: homogeneous regression slopes. *Stat Med* 1996;15:477–96.
34. Hsieh FY. Sample size formulae for intervention studies with the cluster as unit of randomization. *Stat Med* 1988;7:1195–201.
35. Klar N, Donner A. The merits of matching in community intervention trials: a cautionary tale. *Stat Med* 1997;16:1753–64.
36. D'Agostino RB Sr. Controlling alpha in a clinical trial: the case for secondary endpoints. *Stat Med* 2000;19:763–6.
37. Koch GG. Discussion for 'Alpha calculus in clinical trials: considerations and commentary for the new millennium'. *Stat Med* 2000;19:781–4.
38. Moye LA. Alpha calculus in clinical trials: considerations and commentary for the new millennium. *Stat Med* 2000;19:767–79.
39. Moye LA. Response to commentaries on 'Alpha calculus in clinical trials: considerations for the new millennium'. *Stat Med* 2000;19:795–9.
40. O'Neill RT. Commentary on 'Alpha calculus in clinical trials: considerations and commentary for the new millennium'. *Stat Med* 2000;19:785–99.
41. Proschan MA, Waclawiw MA. Practical guidelines for multiplicity adjustment in clinical trials. *Control Clin Trials* 2000;21:527–39.
42. Taylor A, West S, Aiken L. Loss of power in logistic, ordinal logistic and probit regression when an outcome variable is coarsely categorized. *Educ Psychol Meas* 2006;66:228–39.
43. Petkova E, Teresi J. Some statistical issues in the analyses of data from longitudinal studies of elderly chronic care populations. *Psychosom Med* 2002;64:531–47.
44. Liu X, Teresi JA, Waternaux C. Modelling the decline pattern in functional measures from a prevalent cohort study. *Stat Med* 2000;19:1593–606.
45. Gardiner JC, Luo Z, Roman LA. Fixed effects, random effects and GEE: what are the differences? *Stat Med* 2009;28:221–39.
46. Petkova E, Teresi J. Some statistical issues in the analyses of data from longitudinal studies of elderly chronic care populations. *Psychosom Med* 2002;64:531–47.

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 ≈ 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: $\alpha = .05$; $1-\beta = .80$ $\delta=\mu_1-\mu_2 = 0.51$ units; $\sigma^2 = (1.36)^2$; R (reliability) = .90; r (intracluster correlation) = .03; g (average cluster size) = 2.5. $n^* = [2(\sigma^2_T + \sigma^2_e)(Z_{\alpha/2} + Z_\beta)^2]/\delta^2$, adjusting for unreliability: $n=n^*/R$ (see Fleiss, pp4-5), and $n^*=102$; n=108/group; adjusting for clustering, using the variance inflation factor, $IF = 1 + (g-1)r = 1.05$, the adjusted n = 119/group; after (30%) attrition, with n=170, an effect size as small as 0.51 could be detected.[4] 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 >=8.0, 67% are very poorly controlled (A1c >=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: $$n' = \frac{\left(z_{\alpha/2}\sqrt{2\overline{PQ}} + z_{\beta}\sqrt{P_1Q_1 + P_2Q_2}\right)^2}{\left(P_2 - P_1\right)^2}$$

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

Equation 3: $$z = \frac{p_2 - p_1}{\sqrt{2\overline{pq}/n'}}$$

It has been shown that without the continuity correction, the sample sizes may be too small.[5] The use of the continuity correction in the test statistic (Equation 3), where p = ½ (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.[6] 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

1. Beach ML, Meier P. Choosing covariates in the analysis of clinical trials. *Control Clin Trials* 1989;10(4 Suppl):161S-75S.
2. Liu GF, Lu K, Mogg R, Mallick M, Mehrotra DV. Should baseline be a covariate or dependent variable in analyses of change from baseline in clinical trials? *Stat Med* 2009;28(20):2509-30.
3. Shea S, Weinstock RS, Teresi JA, Palmas W, Starren J, Cimino JJ, et al. A randomized trial comparing telemedicine case management with usual care in older, ethnically diverse, medically underserved patients with diabetes mellitus: 5 year results of the IDEATel study. *J Am Med Inform Assoc* 2009;16(4):446-56.
4. Fleiss J. *Design and Analysis of Clinical Experiments*. New York: John Wiley and Sons, 1999.
5. Fleiss J, Levin B, Paik M. *Statistical Methods for Rates and Proportions* 3rd ed. New York: John Wiley and Sons, 2003.
6. Casagrande JT, Pike MC. An improved approximate formula for calculating sample sizes for comparing two binomial distributions. *Biometrics* 1978;34(3):483-6.

FIGURES (see next)

INITIAL HOME VISIT
Intervention: Assessment
Objective: Help participant develop a list of issues that affect his/her overall health and well-being
Type: Home visit
Number: 1st of 4 enactment phase visits
When: Within 1st month & prior to "goal setting" visits
CHW will address participant's: (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

SECOND TO FOURTH HOME VISITS, MONTHS 1 & 2
Intervention: Goal Setting & Dealing with Barriers
Objective: Assist participant in developing an individualized plan to advance his/her overall health and well-being
Type: Home visits
Number: 2nd, 3rd, and 4th enactment phase visits
When: Within months 1 & 2 after initial visit
CHW efforts include: (I) 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 & coaching aimed at the improving lifestyle behaviors

GROUP VISITS, MONTHS 3-12
Intervention: Group Interactive Discussions
Type: Culturally tailored & interactive sessions lead by CHW (60 min. duration, 1 session/week, & 20 person max/cohort)
Number: 10 (6 nutrition & 4 physical activity sessions)
When: Within initial part of maintenance phase (months 3-12)
Objective: 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)

TELEPHONE FOLLOW-UP, MONTHS 3-12
Intervention: Telephone Consultations
Type: Phone call (CHW may also utilize home visits)
Number: Minimum of 1 call/contact per month
When: Throughout maintenance phase (months 3-12)
Objectives: (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.

Figure 1. Summary of CHW Intervention.

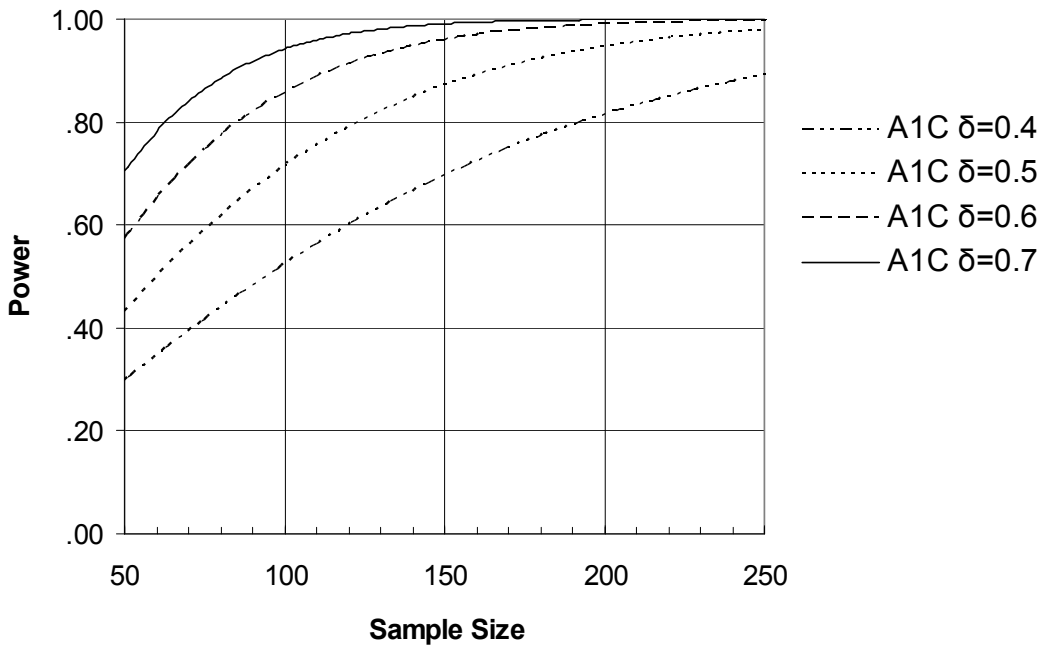

Figure 2. Power to detect changes in A1c (0.4-0.7), as a continuous variable.

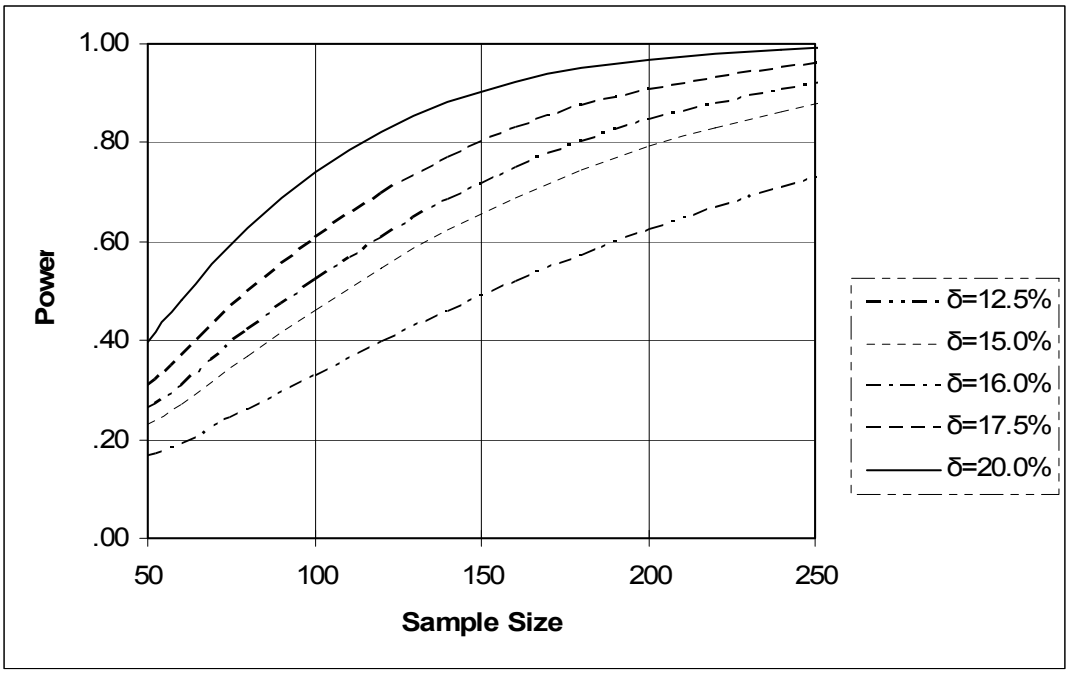

Figure 3. Power to detect changes in A1c, as binary variable.

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

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@stjohns.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 will be held 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 PROCEDURES TO ENSURE CONFIDENTIALITY & PROPER COMMUNICATION

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.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	Title Page
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	Abstract
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	2, 3
	2b	Specific objectives or hypotheses	3
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	4
	4b	Settings and locations where the data were collected	4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	5-8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	5
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	Suppl Data
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	4
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	4
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	4
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	4

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	5
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	8-12
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	10-12
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	
	13b	For each group, losses and exclusions after randomisation, together with reasons	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry	
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.