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Adapting the Diabetes Prevention Program for low and middle-income countries: Protocol for a cluster randomized trial to evaluate "Lifestyle Africa"

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Abstract

Introduction: Low and middle-income countries like South Africa are experiencing major increases in burden of non-communicable diseases such as diabetes and cardiovascular conditions. However, evidence-based interventions to address behavioral factors related to these diseases are lacking. Our study aims to adapt the CDC's National Diabetes Prevention Program (DPP) within the context of an under-resourced urban community in Cape Town, South Africa.

Methods/analysis: The new intervention (*Lifestyle Africa*) consists of 17 weekly sessions delivered by trained community health workers (CHW). In additional to educational and cultural adaptations of DPP content, the program adds novel components of text messaging and CHW training in motivational interviewing. We will recruit participants who are members of 28 existing community health clubs served by CHWs. In a two-year cluster randomized control trial, clubs will be randomly allocated to receive the intervention or usual care. After Year 1, usual care participants will also receive the intervention and both groups will be followed for another year. The primary outcome analysis will compare percentage of baseline weight loss at Year 1. Secondary outcomes will include diabetes and cardiovascular risk indicators (blood pressure, hemoglobin A1C, lipids), changes in self-reported medication use, diet (fat and fruit and vegetable intake), physical activity, and health-related quality of life. We will also assess potential psychosocial mediators/moderators as well as cost-effectiveness of the program.

Ethics/dissemination: Ethical approval was obtained from the University of Cape Town and Children's Mercy. Results will be submitted for publication in peer-reviewed journals and training curricula will be disseminated to local stakeholders.

Trial registration: NCT03342274

Strengths and Limitations

- Community-engaged development ensures the intervention fits the cultural context and existing models of care.
- Broad participant inclusion criteria will help produce relevant, more generalizable findings.
- Cluster-randomized design will lead to a rigorous evaluation of the intervention.
- Biometric and biologic measures are rigorous outcome indicators.
- Low resource environment will make delivering the intervention reliably and with fidelity challenging.

Introduction

The World Health Organization estimates that of the 56.4 million global deaths in 2015, almost 40 million (70%) were due to non-communicable diseases (NCDs)[1]. The leading causes were cardiovascular diseases (CVD) with a substantial number also coming from diabetes mellitus (DM). Over three-quarters of deaths attributed to NCDs in 2015 occurred in low and middle-income countries, where the disproportionate burden of NCDs is expected to continue to increase [1,2].

As a result of globalization and economic advancement, countries like South Africa are experiencing an "epidemiological transition" in which disease prevalence is shifting from primarily infectious disease and under-nutrition to primarily non-communicable diseases and over-nutrition [2]. These trends have been attributed to rising incomes and urbanization in low and middle-income countries which leads to a shift from eating unrefined carbohydrates to a greater intake of fats, sweeteners and animal source foods, as well as highly-processed foods, sometimes referred to as a "nutrition transition"[3,4]. The negative effects of this dietary change are compounded by reductions in physical activity, which are associated with urban lifestyles [5]. Contributing factors include the limited availability of affordable, healthy food in poorer areas, combined with the increased availability of fast foods and cheap snacks that are high in fats and sugar [6], sedentary employment [4,5], limited outdoor space and high rates of street violence [7–9]. Cultural beliefs and practices may also contribute. For example, obesity is less stigmatized, and even valued, in many African cultures because it is associated with dignity, wealth, and being treated well by one's husband; whereas weight loss is regarded as a source of stigma and a sign of disease, in particular of HIV/AIDS [10].

Although signs of epidemiological transition have been observed in many low and middle income countries, studies suggest that the speed at which this transition appears to be occurring in South Africa is particularly striking [8,11–16]. Fifty-four percent of South African adults are overweight and 28.3% are obese—a statistic that has risen from 17.6% in 1996 and 22.9% in 2006 [17]. South African women have the highest prevalence of obesity in sub-Saharan Africa at 40% [18]. Furthermore, hypertension affects 46% of women and 44% of men nationally [19].

Considering the public health and economic impacts of NCDs, national and provincial health departments in South Africa have declared promotion of healthy lifestyles a public health priority [20]. Despite the need for effective and affordable interventions for combating DM and CVD, there is a dearth of research devoted to developing and evaluating NCD interventions in low and middle income settings, particularly in Africa. Globally, one of the most notable examples of effective interventions based on lifestyle change is the Diabetes Prevention Program (DPP) which the Centers for Disease Control has adopted and disseminated in the United States as the National DPP [21]. Through 16 core sessions delivered by "lifestyle coaches", the original DPP aimed for its participants to engage in at least 150 minutes of moderate physical activity per week and to reduce initial body weight by 7% over 6 months. Its original randomized control trial (RCT) among individuals with impaired glucose tolerance reported a 58% reduction in DM incidence [22]. A more recent RCT examining long-term effects of a group-based version of the DPP among 5,000 overweight and obese individuals with Type-2 DM (the Look AHEAD trial) showed an average loss of 8.6% of initial body weight in the lifestyle intervention group (compared to 0.7% for controls) and 4.7% at the 4-year follow-up [23–25]. In addition, there were significant improvements in glucose control as well as reductions in blood pressure, triglycerides, HDL cholesterol and medication use.

With evidence of its effectiveness among adults with pre-diabetes as well as adults with diabetes, the DPP has also been adapted for several real-world settings within the U.S. including YMCAs [26,27], African American Churches [28], community hospitals [29], community health-care facilities [30], as well as through online social networks and mobile phone platforms [31]. Adaptions of the DPP designed to be delivered by lay community health workers (CHWs) have also been successful [32,33]—some achieving weight loss in the range of 6-7% [27,33], comparable to the 8.6% observed in the original trial [23] and consistent with recommended weight loss goals for diabetes risk reduction [34].

Although the DPP has been shown to have strong outcomes when adapted for community settings in the U.S., this adaptation has not yet been extended to low and middle-income settings. For example, the mode of delivery in the United States has been through trained health or allied health professionals

with post-graduate training and backgrounds in nutrition or behavior change [22]. This is not feasible in most low-resource environments due to costs and/or the lack of trained public-health professionals. Delivering services at medical facilities may also hinder attendance because of the time loss and cost of local travel. Furthermore, the content of sessions also needs to be adapted to be suitable for the prevailing literacy and numeracy levels of both providers and recipients of the program, and to take into account the unique food preferences, cooking and shopping patterns of the region. Cultural norms that affect food preferences or attitudes about body weight or weight loss, as well as environmental barriers that affect access to food or ability to exercise, need to be addressed. For example, many individuals in South Africa live in crowded informal (shack) settlements that may lack reliable electricity, space, access to affordable produce, cold storage of fresh food, and places that are safe to exercise. In addition to barriers, there may be unique facilitators that can support intervention delivery in low and middle-income countries. For example, many countries provide community-based care using CHWs offering opportunities to tap existing social support networks and a community-based health infrastructure [35]. Also, cell phone use is high offering the opportunity to deliver supportive text messages which have been shown to enhance the effectiveness of behavior change interventions [36,37].

The purpose of our study is to use a community-engaged adaption process to develop and test a new version of the DPP ("*Lifestyle Africa*") tailored to overweight and obese adults in low-income, urban areas of sub-Saharan Africa. The key adaption is to design the program so that it can be delivered by CHWs. In South Africa CHWs are typically drawn from the local community and have similar levels of education as the target population. Evaluation of Lifestyle Africa is based on a community-based cluster randomized controlled trial (RCT) conducted in partnership with two NGOs that provide chronic disease care to individuals with DM and/or CVD using CHWs. CHWs are used to provide medication delivery and health monitoring to individuals who are members of "support groups" or "health clubs". Care is provided from approximately February through November each calendar year due to the year-end holiday season during which most community members travel to their rural homes for an extended period. CHWs and their associated support groups are randomized to receive *Lifestyle Africa* or to serve as a treatment-

as-usual control. The primary outcome analysis will compare percentage weight loss from baseline to follow-up at the end of the year between *Lifestyle Africa* and usual care participants. Secondary outcomes are DM and cardiovascular risk indicators (blood pressure, hemoglobin A1C, lipids), changes in medication use, diet (fat, fruit and vegetable intake), physical activity, and health related quality of life (HRQOL).

Methods and Analysis

Setting:

This study is being conducted in the area of Khayelitsha, a fast-growing urban township of Cape Town, South Africa. Khayelitsha residents are 99% Black African and 97% Xhosa speaking [38]. Poverty is extremely high, with 38% of individuals unemployed and 89% earning less than R6,400 (approximately 475 USD) per month. More than half of the residents are rural to urban migrants and 64% of adults have not completed high school [38]. There is a high prevalence of overweight and obesity [39] and prevalence of DM among Black Africans is approximately 13%, having increased more than 50% over 20 years [40].

Patient and Public Involvement:

Community Partners

Project implementation is conducted in partnership with two well-established NGOs that use CHWs from the community to support the health of over 9,000 individuals in Khayelitsha and surrounding communities. Our intervention is delivered through adaptation of the NGO's existing programs that use CHWs to provide health-related services to small community groups or "clubs" of approximately 10-50 individuals who meet in homes or community facilities. CHWs provide such services as health monitoring, medication delivery, education, physical activity, meals, wellness programming, and income generating activities. NGOs work collaboratively with local health clinics to both refer patients and receive referrals of patients many of whom have diabetes and cardiovascular disease. CHWs meet regularly (varying by NGO and club from daily to monthly) with their designated groups. Many groups

also function independently providing meals and social activities to members on a regular basis.

Involvement in study design

Our team's preliminary work involved extensive formative research with club members, CHWs and community leaders to better understand cultural norms, barriers and facilitators surrounding physical activity, diet and body image [10]. In partnership with CHWs, a training manual and pilot program was developed, which demonstrated the feasibility of using health clubs to encourage walking [41]. Additional pilot work included development and evaluation of three intervention sessions based on the DPP. Two pairs of CHWs were trained to deliver three DPP pilot sessions to participants, and both CHW and participant feedback were incorporated into the development of the complete program. To develop the complete *Lifestyle Africa* program for the present study, we formed two community advisory boards (CABs) in two Khayelitsha area neighborhoods to guide the development of a culturally appropriate and sustainable program. Members included a number of CHWs, community residents with DM and/or CVD, local experts in DM and CVD, and community leaders capable of guiding and supporting dissemination (e.g., a neighborhood elder and a representative of the provincial Department of Health). The CABs provide input and assistance with all aspects of the project including naming the intervention program, assisting with program development, reviewing intervention content and materials, and providing input on program logistics. Members attend quarterly meetings as well as participate in work groups focused on specific tasks (e.g., adapting the DPP manual, reviewing or trying out suggested adaptations of the DPP, or reviewing text messages).

Trial Design:

This is a 2-arm parallel group cluster RCT with balanced randomization (1:1) and a cross-over of the control arm after the main outcome assessment (Figure 1). CHWs mostly work individually or in pairs with a particular group, but in some cases CHWs work as trios or work with more than one group. For this reason, the unit of randomization is CHW "team" (individual, pair or trio). CHW teams randomized to intervention receive training and provide the intervention to their support groups. CHW teams

randomized to control provide treatment as usual to their support groups. After approximately one year of intervention, control CHW teams are also trained in the intervention and their support groups are crossed over to the intervention arm. Participants in both arms are assessed at the end of the first and second year.

Participants/Recruitment:

To recruit participants, two initial sessions were developed to introduce and explain the purpose and nature of the *Lifestyle Africa* program. CHWs are trained to deliver these sessions which follow a similar format to the main *Lifestyle Africa* sessions. At the introductory sessions, interested club members are invited to return for an eligibility screening and enrollment session. To serve our NGO partners and to be sensitive to community wishes, our goal is to invite all eligible members of 28 clubs (~18 members each) served by our partner NGOs to participate in the intervention and to enroll as many as feasible in the study. The eligibility criteria were therefore designed to be as inclusive of club members as possible. The inclusion criterion for support group members is being overweight or obese (BMI ≥ 25 kg/m2). Exclusion criteria are: (1) having an unsafe level of blood pressure [>160 (systolic) and/or >100 mm (diastolic)] [42], (2) elevated blood sugar [HbA1C > 11] [42] (3) being pregnant, breast-feeding or planning pregnancy within two years; (4) chronic use of oral steroid medication (which may affect weight loss); and (5) not intending to stay in the group over the next two years.

Randomization:

Randomization of support groups was conducted by the project statistician using a numbered list of the CHW teams and their associated groups. CHW teams are stratified within NGO. A computerized random number generator was used to create the allocation scheme. CHW groups have been randomized prior to enrollment of participants and launch of the intervention in order to know which CHWs need to be ready to deliver the intervention. It is therefore not feasible to blind CHWs or participants.

Interventions:

(1) Lifestyle Africa

Adaptation of the DPP: In developing *Lifestyle Africa*, we aimed to retain key elements from the CDC National DPP [22,43] while making necessary cultural, educational, and language adaptations relevant to the community. CDC's National DPP consists of 16 "core" sessions delivered over 6 months and 15 "post-core" sessions focused on maintaining participants' engagement in the program. Participants are encouraged to lose 7% of body weight and exercise 150 mins/ week. Central components of the program include self-monitoring of caloric intake and physical activity along with other social-cognitive and problem-solving theory elements [43].

The primary adaptation was to eliminate the need for a high-level health professional (such a nutritionist or dietitian) to deliver the core sessions of the program by providing session content on video (Katula et al., 2011). With expert content provided via video the role of CHWs is to show the video, serve as group facilitator, and ensure engagement with the video material. Videos were developed in Xhosa and use a presenter/narrator in conjunction with photos and animation. Frequent pauses are built into the video session during which CHWs prompt participants with interactive questions and activities such as completing worksheets that reinforce and personalize video content. Activities are designed to minimize writing and allow for participants to engage orally if needed (e.g., through discussion with a partner.) Participants receive a program book in Xhosa (or English if preferred) with educationally and culturally adapted handouts and forms needed for each session (e.g., physical activity tracking sheets, goal setting forms). The visual elements of the video were designed to be culturally sensitive, for example by depicting the individuals and scenes representative of the target community. To aid CHWs, each video has an accompanying session guide that provides step-by-step guidance on materials, procedures and the verbal prompts and questions needed to facilitate the session. To avoid excessive session length the *Lifestyle Africa* program consists of 17 rather than 16 core sessions.

Other key adaptations included those made because, unlike the original DPP, participants in *Lifestyle Africa* are not actively seeking treatment in the form of lifestyle behavior change. Therefore, in

addition to the 17 core sessions, we created two additional "recruitment sessions" that follow the same format (i.e., video delivered with pauses for discussion) to provide information on the rationale for participating in a diet and exercise program. To account for participants' levels of health literacy and numeracy we expanded educational content (e.g., explained the physiology of diabetes and cardiovascular disease; explained the meaning of a kilojoule), simplified explanations, reduced calculations, and "chunked" information by interspersing it with discussion and related activities. We also bolstered motivational aspects of the DPP through the addition of elements of Motivational Interviewing a method of counseling designed to strengthen motivation by fostering participant's own reasons for change (e.g., exploring personal values, asking participants to express their own reasons for change). According to Motivational Interviewing principles the counselor's style or manner of counseling is also important (e.g., person-centered and autonomy supportive rather than directive or persuasive; use of reflective listening rather and open questions rather than closed questions and confrontation). For this reason a Motivational Interviewing and group facilitation skills training curriculum was also developed for CHWs to provide the skills necessary for delivering the sessions in a Motivational Interviewing consistent manner[44].

A final adaptation capitalizes on the widespread use of cell phones in the developing world and increasing evidence of the potential benefit of text messaging to help promote behavior change [37]. A empirically based text message system was developed in which participants are provided with two messages per day (morning and lunch time) to provide reminders, foster motivation and self-efficacy, affirm ongoing efforts, and help with implementation planning (i.e., behavior change tips). The same messages are delivered to all participants, but weekly message content refers to each of the core sessions and is timed to match the participant's session progress.

In addition to the video-based core sessions 12 post-core sessions were developed. These are reduced in length but follow the same format (weigh-in, review and discussion of progress toward goal(s) from the prior session, delivery and discussion of new content, goal setting for the next session). New content is brief and delivered by the CHW using scripted language and straightforward handouts.

CHW training: CHWs working for our partner NGOs are not required to have any specific educational background but must have basic reading, writing, and arithmetic skills sufficient to maintain attendance registers, medication logs, and assess and record weight, height etc. CHWs also have received basic training as part of their employment as CHWs (e.g., in home-based care, chronic disease management, and wellness). Training for *Lifestyle Africa* facilitators consists of 3 days of didactic training and 8 weekly half day sessions of experiential training as mock *Lifestyle Africa* participants conducted in Xhosa by local research team members. Didactic training includes basic training in diabetes and diabetes management, behavior change principles, Motivational Interviewing, and group facilitation. CHWs are also trained in use of the video projectors, and logistical and study-related safety procedures. Content of Motivational Interview training was also adapted to limit jargon, and to adapt concepts and experiential learning activities to CHW cultural values, language and educational level. For example, "MI Spirit" was distilled as "What is effective counseling?" and focused on the need to listen and reflect before giving advice. Experiential training involved CHWs discussing their own experiences with making behavior change. "Evocation and eliciting change talk" was described in terms of "building motivation or 'a strong why'". Experiential training involved exploring goals and values related to behavior change. Content was adapted to be culturally relevant (e.g., use of culturally relevant values such as "at peace with ancestors"). With regard to MI core skills, training and practice emphasized the use of open-ended questions and reflections.

CHW's reviewed and practiced key activities after each session (e.g., conduct weigh in, conduct opening facilitation, provide feedback on food logs) during their training as mock *Lifestyle Africa* participants. In subsequent mock sessions (where these activities were repeated) they were asked on a rotational basis to act as facilitators (e.g., lead the opening facilitation, facilitate goal-setting and action planning). A checklist was used to confirm all CHW's had satisfactorily conducted all key elements of the program.

Delivery: To avoid disruption of the study during the year-end holiday season that is widely observed in the community, enrollment takes place in February and March following the break and

intervention begins immediately after each club is enrolled. Control group clubs begin the intervention one year after the intervention arm begins. CHWs are asked to deliver the program weekly (or biweekly if needed to fit the schedule of the group) but adjustments are made to allow for days when club members do not meet (e.g., on days when many members collect pension payments or days of neighborhood disruptions due to protests etc.). Session attendance, weight, and activity minutes are tracked by CHWs using standardized forms. After clubs complete the 17 core sessions they continue with monthly sessions until the final assessment.

Fidelity Monitoring: Research staff will observe at least the first ten sessions for each CHW team and taper observations over time to at least one session every 5-8 weeks. Checklists are used to verify adherence to key session protocol elements (e.g., completed weigh in, followed verbal prompts, used projector correctly etc.). Adherence to MI principles and group facilitation behaviors are evaluated using rating scales (poor/never to excellent/always) adapted from the OnePass measure for MI competence [45].

(2) Usual care (wait list)

For clubs randomized to usual care, CHWs continue to lead clubs in their usual activities (e.g., approximately monthly monitoring of weight, blood pressure and blood glucose, delivery of medication). Although usual care may include education and health monitoring, there is no systematic, structured means by which lifestyle change is facilitated on an ongoing basis.

Data Collection:

Clubs are enrolled in two waves separated by 12 months. Each wave follows the same procedure for enrollment and assessment (see Figure 1). Recruitment and enrollment of each wave takes approximately two months over February and March of the calendar year. The baseline assessment is conducted at enrollment. Follow-up assessments occur at the end of the enrollment year (approximately 8 months after enrollment) and the end of the second year (approximately 20 months after enrollment). These follow-up assessments are timed to occur before most participants leave for their December-

January holiday season break. The follow-up assessment at the end of Year 1 is the main outcome time point. The follow-up assessment at the end of Year 2 is used to evaluate long term outcomes for the intervention arm as well as the effects of the control arm receiving the intervention. Consistent with local norms participants receive a R150 (approximately $12USD) gift voucher for completing each assessment.

Assessments are conducted by study staff who travel to club sites or nearby suitable locations. At enrollment, club members complete informed consent, eligibility screening, and baseline assessment. All participants are assessed on demographics, eligibility criteria, and key outcome measures (i.e., Body Mass Index [BMI], blood pressure, and HbA1c). At the end of assessments, study staff give each participant a feedback form with their biometric data and explain their results. Due to resource limitations and logistics, only a randomly selected sub-sample of 12 participants per club complete the lipids and self-report survey assessments described below. All survey measures were translated to Xhosa and back-translated to English. During this process, we applied some minor cultural adaptations to increase relevance and comprehensibility of certain items and also harmonized some response scales across instruments to reduce complexity for respondents. All data are collected by trained Xhosa speaking interviewers using tablets and the REDCap data management system [46].

Measures:

The primary outcome will be percentage of weight lost between baseline and the first follow-up assessment. Weight is measured to the half kilogram with a standard electronic scale. Participants are asked to wear light clothing and to fast the morning of enrollment. They are asked to remove footwear, heavy clothing/accessories prior before being weighed. Height is measured in order to calculate Body Mass Index (BMI) to determine eligibility. Height is measured to the nearest millimeter with the participant standing straight against a standard stadiometer. BMI is calculated as weight in kilograms divided by the square of height in meters.

Blood pressure is assessed by staff with calibrated portable automated instruments (Omrons HBP1300), averaging two or three independent measurements according to American Heart Association

Council on High Blood Pressure Research Methods [49]. Non-fasting HbA1c, triglycerides, and LDL cholesterol are measured via automated assay from a capillary sample using an Afinion AS100 analyzer [47]. Medication use is assessed by asking participants to bring all their medications to the enrollment session. Interviewers recorded the medication name and dose including use of HIV antiretroviral medications.

Demographic measures are assessed via participant survey and include age, gender, education level, income level, and housing type. Dietary intake focuses on intake of whole grains, fruits and vegetables, fiber, and sugar, measured with an adaptation of the NHANES Dietary Screener Questionnaire [51,52]. Physical activity is measured using the International Physical Activity Questionnaire-Short Form [53], and health-related quality of life is measured with the Veterans RAND 12-item Health Survey [54,55].

Data Analysis:

Power analysis

Power analyses were conducted using the Optimal Design software for cluster-randomized trials with person-level outcomes. Prior studies of lifestyle interventions have indicated that the intra-class correlation coefficient (ICC) of the main outcome (percent weight loss) will likely be small (e.g., .01). Therefore, values of .01 and .05 were considered in the power analysis for conservative estimation. Because of the community-based nature of the trial, the study committed to enroll as many eligible and interested club members as possible. The power analysis was therefore used to determine the adequacy of the anticipated sample size. At the time of conducting our power analysis, we had one NGO partner and anticipated a sample of 54 clusters averaging approximately 10 participants each for a total N of 540. However, government changes in NGO designated areas of responsibility and withdrawal from participation in the trial of one branch of our NGO partner changed our plans. After recruiting a second NGO partner we anticipate 28 total clusters averaging 18-19 participants for a total N of 518. In order to allow for up to 25% attrition, cluster sizes of 19 and 15 were included in the power analysis. Assuming an

ICC of .01, we projected that we would have 0.80 power to detect even small effect sizes of 0.28 and 0.31 with cluster sample sizes of 19 and 15 respectively. If we conservatively assume an ICC of 0.05, we projected we would still have 0.80 power to detect effect sizes of 0.35 and 0.37 with sample sizes of 19 and 15 per cluster. Using the pooled standard deviation from Look AHEAD (5.8), the largest trial of overweight/obese type-2 diabetic patients [24] and a conservative estimate of a 3.15% weight loss for the treatment group and a 1% loss for the control group, a conservative estimated effect size for weight-loss in the current study would be 0.37. This estimate is larger than the effect we will be able to detect with .80 power as we will be able to detect a percent weight loss difference of 1.6-1.7% between groups.

Planned analytic strategy

To accommodate the cluster randomized design, all analyses will be conducted with a multilevel modeling framework using SAS PROC MIXED. In this design, participants (Level-1 units) will be nested within CHW pairs (Level-2 units). Primary analyses will use an intention-to-treat strategy. Exploratory analyses will also examine low vs. high dose (i.e., sessions attended) effects. Unconditional models will be examined with each dependent variable to determine the amount of between and within cluster variance. Some questions involve comparison of effects between conditions and some involve change within a condition.

Preliminary analyses will examine baseline equivalence across the two treatment conditions on variables that may impact outcome (e.g., medication use) to identify covariates for the main analyses. To address the primary research question regarding differences in % weight loss at the end of Year 1, % weight loss from baseline to the end of Year 1 will be the dependent variable in the multi-level model described above. The significance of the fixed effect for treatment group will indicate if there are differences in overall outcomes across groups. Anticipated effects are directional in that *Lifestyle Africa* participants should respond better than control participants. Similar models will be evaluated for each of the secondary outcomes. Relevant covariates will be added to the models as appropriate (e.g., use of diabetic medications for weight loss).

To determine if the *Lifestyle Africa* intervention group maintains its response to the intervention over the second year, scores at the Year 1 assessment will be compared to those at the Year 2 assessment. Random intercepts for health club and participant nested within health club will be included in the model. The significance of the fixed effect for time will indicate whether or not participants were able to maintain their response. This type of maintenance model will be evaluated for each of the outcomes of interest individually. Similar models will be used to examine intervention response within each of the study arms to determine if intervention effectiveness is replicated in the control group. If there are no differences between groups in the assessments taken just prior to participating in the *Lifestyle Africa* intervention, we will combine the groups and examine potential predictors of treatment effectiveness such as fidelity at level two and attendance at level one.

Monitoring:

A Data Safety Monitoring Board (DSMB) oversees the study and approved the stopping rules. The DSMB operates independently from the study investigators and the funder and comprises members based in the United States and South Africa and includes a psychologist, a physician, a doctor of public health, and a statistician with expertise relevant to the trial. Details of the DSMB operating procedures are described in the DSMB charter. The DSMB may require termination (stopping rules) or modification of the study for: (1) any perceived safety concern including concerns related to adverse events or (2) because of severe failure to recruit or retain participants. There is no interim analysis or stopping rule related to an interim analysis because the intervention involves minimal risk to participants and even in the absence of indications of weight loss, the intervention may yield other educational or psychological benefits. In addition, stopping for reasons other than safety could be negatively perceived by community partners, CHWs, and club members. As part of usual care, CHWs and supervising nurses monitor the health of participants and refer patients to their physician, or local health clinic, or emergency service as needed. Study staff continuously monitor unanticipated problems or serious adverse events which can be identified by CHWs, NGO staff, participants, participants' families, participants' physicians or other

health professionals. Events are investigated, documented, and reported to the principal investigators who report to the DSMB in accord with their regulations and to the Institutional Review Board (IRB) and the funder if appropriate.

Ethics and Dissemination

Our study protocol has been approved by the Institutional Review Boards (IRBs) at the University of Cape Town (the primary IRB) and Children's Mercy Kansas City and the University of the Western Cape. Any amendments are approved by the IRB. Protocol modifications are communicated to study staff during regular meetings and when relevant, to CHWs and participants through personal outreach and through regular meetings with NGO partners. Written informed consent is collected from all participants prior to eligibility screening and enrollment. Multiple protections for participant confidentiality are in place. Participant identifiers (name and contact information) are marked as an identifier in REDCap and are then censored when the database is downloaded for analysis. Only trained study staff have access to REDCap databases during data collection. All identifying information will be removed with the deletion of the REDCap project at the end of the study. Consent forms and signature logs for reimbursements will be secured in a locked file cabinet within a locked office on a secured floor.

A full data package will be maintained by the investigators for at least seven years after data collection is complete. Third-party access to the full data package will be addressed by the investigators on a case-by-case basis. Results will be disseminated through publication in peer-reviewed journals and conference presentations. *Lifestyle Africa* curricula will be made available to local stakeholders such as Universities and the Department of Health. Study progress and findings will also be updated on clinicaltrails.gov (#NCT03342274).

Discussion

The growing burden of NCDs in low and middle-income countries presents a critical need for evidence-based interventions that address behavioral contributors to the prevention and management of

CVD and DM. Our study aims to adapt one of the strongest existing evidence-based lifestyle behavior change interventions to the context of low-income, under-resourced urban areas of sub-Saharan Africa and rigorously assess its impact in a cluster RCT. Results will inform both the feasibility and effectiveness of an intervention delivery model that uses CHWs as facilitators, video as the primary medium for delivering content, and enhancement of the DPP with Motivational Interviewing principles and a text message system. This will be an important addition to similar efforts that have targeted more educated and resourced populations in India [48].

Successful outcomes will hinge on both successful program delivery as well as participant engagement and retention. The main outcomes will therefore need to be interpreted in the context of key aspects of study implementation including the success of training CHWs, the reliability and fidelity with which sessions are delivered, and the engagement of participants. Upon completion of the study, a process evaluation is planned to enhance understanding of the outcomes by assessing CHW and participant perspectives on the strengths and weaknesses of the program. Through training and technical support the project also aims to build capacity in partner NGOs to continue the program after the study has been completed.

Strengths of the study include its community engaged development process which has led to an intervention design that fits with the existing models of care of our partner NGOs and may be transferable to programs aimed at other NCDs. The study's pragmatic design, including broad inclusion criteria, should also lead to findings that are relevant and generalizable to many communities in low and middle-income countries. Although the study is pragmatic and the result of a community-engaged process, it uses a rigorous cluster randomized design with objective measurements of key biometric and biologic outcomes related to diabetes and cardiovascular disease. Chief among the challenges of the trial will be to achieve adequate reliability and fidelity in the delivery of the intervention in the context of an impoverished environment where resources are limited, residents are taxed trying to meet their basic needs, and social disruptions (e.g., strikes, protests, crime) are frequent. Limitations include low precision

of measures like dietary and physical activity recalls as well as limitations of measure breadth due to low literacy.

Regardless of the efficacy findings of the study, results should provide an important first step in understanding how lifestyle interventions such as the DPP might be disseminated in similar communities with few resources and low levels of education and literacy. Studies evaluating lifestyle behavior change interventions in low and middle-income countries are vital for addressing the epidemic of diabetes and cardiovascular disease.

Figure legend: Figure 1: Flow of study procedures (repeated for each of two waves of participants)

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Competing Interests

The authors declare no competing interests.

Author Contributions

All authors made substantial contributions to the design of the study. DC and EAH drafted the manuscript and all others contributed to revising it critically for important intellectual content. All authors reviewed and approved of the final version submitted for publication and agree to be accountable for all aspects of the work in ensuing that questions related to accuracy and integrity are appropriately investigated and resolved.

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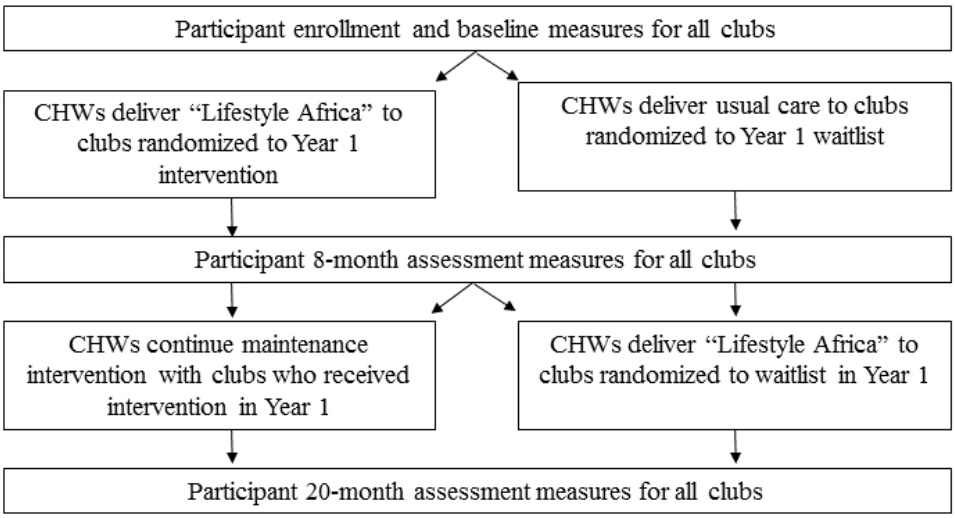

Flow of study procedures (repeated for each of two waves of participants)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	___1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	___2_____
	2b	All items from the World Health Organization Trial Registration Data Set	throughout document and NCT trial registry
Protocol version	3	Date and version identifier	__1_____
Funding	4	Sources and types of financial, material, and other support	__19_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	__1_____
	5b	Name and contact information for the trial sponsor	__19_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	None (see p. 21)

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	__N/A_____
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	__3-5_____
	6b	Explanation for choice of comparators	__6_____
Objectives	7	Specific objectives or hypotheses	___5-6_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	___7-8_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	__6_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	__8_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	__9-12_____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	__16_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	_12 (fidelity monitoring)_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_12 (usual care)_

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	__6____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	_Figure 1; p. 7
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	__14-15__
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	___8___
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	___8____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	__N/A (8)_
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	__8_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	___N/A (8)_
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	___N/A___

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_12-14 _____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_12, 15__
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	__13____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	_15-16__
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_15-16__
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	__15___

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	__16___
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	___16___
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	__16-17__

Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	____N/A__
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	___17___
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	____17____
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	___17_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	___N/A_____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	___17_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	___19_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	__17_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	__N/A_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	___17_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	19___
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_N/A_____

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary File
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	__N/A_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

BMJ Open

Adapting the Diabetes Prevention Program for low and middle-income countries: Protocol for a cluster randomized trial to evaluate "Lifestyle Africa"

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Adapting the Diabetes Prevention Program for low and middle-income countries: Protocol for a cluster randomized trial to evaluate "Lifestyle Africa"

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Abstract

Introduction: Low and middle-income countries like South Africa are experiencing major increases in burden of non-communicable diseases such as diabetes and cardiovascular conditions. However, evidence-based interventions to address behavioral factors related to these diseases are lacking. Our study aims to adapt the CDC's National Diabetes Prevention Program (DPP) within the context of an under-resourced urban community in Cape Town, South Africa.

Methods/analysis: The new intervention (*Lifestyle Africa*) consists of 17 weekly sessions delivered by trained community health workers (CHW). In additional to educational and cultural adaptations of DPP content, the program adds novel components of text messaging and CHW training in motivational interviewing. We will recruit overweight and obese participants (BMI $\geq$ 25 kg/m^2) who are members of 28 existing community health clubs served by CHWs. In a two-year cluster randomized control trial, clubs will be randomly allocated to receive the intervention or usual care. After Year 1, usual care participants will also receive the intervention and both groups will be followed for another year. The primary outcome analysis will compare percentage of baseline weight loss at Year 1. Secondary outcomes will include diabetes and cardiovascular risk indicators (blood pressure, hemoglobin A1C, lipids), changes in self-reported medication use, diet (fat and fruit and vegetable intake), physical activity, and health-related quality of life. We will also assess potential psychosocial mediators/moderators as well as cost-effectiveness of the program.

Ethics/dissemination: Ethical approval was obtained from the University of Cape Town and Children's Mercy. Results will be submitted for publication in peer-reviewed journals and training curricula will be disseminated to local stakeholders.

Trial registration: NCT03342274; Pre-results

Strengths and Limitations

- Community-engaged development ensures the intervention fits the cultural context and existing models of care.
- Broad participant inclusion criteria will help produce relevant, more generalizable findings.
- Cluster-randomized design will lead to a rigorous evaluation of the intervention.
- Biometric and biologic measures are rigorous outcome indicators.
- Low resource environment will make delivering the intervention reliably and with fidelity challenging.

Introduction

The World Health Organization estimates that of the 56.4 million global deaths in 2015, almost 40 million (70%) were due to non-communicable diseases (NCDs)[1]. The leading causes were cardiovascular diseases (CVD) with a substantial number also coming from diabetes mellitus (DM). Over three-quarters of deaths attributed to NCDs in 2015 occurred in low and middle-income countries, where the disproportionate burden of NCDs is expected to continue to increase [1,2].

As a result of globalization and economic advancement, countries like South Africa are experiencing an "epidemiological transition" in which disease prevalence is shifting from primarily infectious disease and under-nutrition to primarily non-communicable diseases and over-nutrition [2]. These trends have been attributed to rising incomes and urbanization in low and middle-income countries which leads to a shift from eating unrefined carbohydrates to a greater intake of fats, sweeteners and animal source foods, as well as highly-processed foods, sometimes referred to as a "nutrition transition"[3,4]. The negative effects of this dietary change are compounded by reductions in physical activity, which are associated with urban lifestyles [5]. Contributing factors include the limited availability of affordable, healthy food in poorer areas, combined with the increased availability of fast foods and cheap snacks that are high in fats and sugar [6], sedentary employment [4,5], limited outdoor space and high rates of street violence [7–9]. Cultural beliefs and practices may also contribute. For example, obesity is less stigmatized, and even valued, in many African cultures because it is associated with dignity, wealth, and being treated well by one's husband; whereas weight loss is regarded as a source of stigma and a sign of disease, in particular of HIV/AIDS [10].

Although signs of epidemiological transition have been observed in many low and middle income countries, studies suggest that the speed at which this transition appears to be occurring in South Africa is particularly striking [8,11–16]. Fifty-four percent of South African adults are overweight and 28.3% are obese—a statistic that has risen from 17.6% in 1996 and 22.9% in 2006 [17]. South African women have the highest prevalence of obesity in sub-Saharan Africa at 40% [18]. Furthermore, hypertension affects

46% of women and 44% of men nationally [19].

Considering the public health and economic impacts of NCDs, national and provincial health departments in South Africa have declared promotion of healthy lifestyles a public health priority [20]. Despite the need for effective and affordable interventions for combating DM and CVD, there is a dearth of research devoted to developing and evaluating NCD interventions in low and middle income settings, particularly in Africa. Globally, one of the most notable examples of effective interventions based on lifestyle change is the Diabetes Prevention Program (DPP) which the Centers for Disease Control has adopted and disseminated in the United States as the National DPP [21]. Through 16 core sessions delivered by "lifestyle coaches", the original DPP aimed for its participants to engage in at least 150 minutes of moderate physical activity per week and to reduce initial body weight by 7% over 6 months. Its original randomized control trial (RCT) among individuals with impaired glucose tolerance reported a 58% reduction in DM incidence [22]. A more recent RCT examining long-term effects of a group-based version of the DPP among 5,000 overweight and obese individuals with Type-2 DM (the Look AHEAD trial) showed an average loss of 8.6% of initial body weight in the lifestyle intervention group (compared to 0.7% for controls) and 4.7% at the 4-year follow-up [23–25]. In addition, there were significant improvements in glucose control as well as reductions in blood pressure, triglycerides, HDL cholesterol and medication use.

With evidence of its effectiveness among adults with pre-diabetes as well as adults with diabetes, the DPP has also been adapted for several real-world settings within the U.S. including YMCAs [26,27], African American Churches [28], community hospitals [29], community health-care facilities [30], as well as through online social networks and mobile phone platforms [31]. Adaptions of the DPP designed to be delivered by lay community health workers (CHWs) have also been successful [32,33]—some achieving weight loss in the range of 6-7% [27,33], comparable to the 8.6% observed in the original trial [23] and consistent with recommended weight loss goals for diabetes risk reduction [34].

Although the DPP has been shown to have strong outcomes when adapted for community settings in the U.S., this adaptation has not yet been extended to low and middle-income settings. For example,

the mode of delivery in the United States has been through trained health or allied health professionals with post-graduate training and backgrounds in nutrition or behavior change [22]. This is not feasible in most low-resource environments due to costs and/or the lack of trained public-health professionals. Delivering services at medical facilities may also hinder attendance because of the time loss and cost of local travel. Furthermore, the content of sessions also needs to be adapted to be suitable for the prevailing literacy and numeracy levels of both providers and recipients of the program, and to take into account the unique food preferences, cooking and shopping patterns of the region. Cultural norms that affect food preferences or attitudes about body weight or weight loss, as well as environmental barriers that affect access to food or ability to exercise, need to be addressed. For example, many individuals in South Africa live in crowded informal (shack) settlements that may lack reliable electricity, space, access to affordable produce, cold storage of fresh food, and places that are safe to exercise. In addition to barriers, there may be unique facilitators that can support intervention delivery in low and middle-income countries. For example, many countries provide community-based care using CHWs offering opportunities to tap existing social support networks and a community-based health infrastructure [35]. Also, cell phone use is high offering the opportunity to deliver supportive text messages which have been shown to enhance the effectiveness of behavior change interventions [36,37].

The purpose of our study is to use a community-engaged adaption process to develop and test a new version of the DPP ("*Lifestyle Africa*") tailored to overweight and obese adults in low-income, urban areas of sub-Saharan Africa. The key adaption is to design the program so that it can be delivered by CHWs. In South Africa CHWs are typically drawn from the local community and have similar levels of education as the target population. Evaluation of Lifestyle Africa is based on a community-based cluster randomized controlled trial (RCT) conducted in partnership with two NGOs that provide chronic disease care to individuals with DM and/or CVD using CHWs. CHWs are used to provide medication delivery and health monitoring to individuals who are members of "support groups" or "health clubs". Care is provided from approximately February through November each calendar year due to the year-end holiday season during which most community members travel to their rural homes for an extended period. CHWs

and their associated support groups are randomized to receive *Lifestyle Africa* or to serve as a treatment-as-usual control. The primary outcome analysis will compare percentage weight loss from baseline to follow-up at the end of the year between *Lifestyle Africa* and usual care participants. Secondary outcomes are DM and cardiovascular risk indicators (blood pressure, hemoglobin A1C, lipids), changes in medication use, diet (fat, fruit and vegetable intake), physical activity, and health related quality of life (HRQOL).

Methods and Analysis

Setting:

This study is being conducted in the area of Khayelitsha, a fast-growing urban township of Cape Town, South Africa. Khayelitsha residents are 99% Black African and 97% Xhosa speaking [38]. Poverty is extremely high, with 38% of individuals unemployed and 89% earning less than R6,400 (approximately 475 USD) per month. More than half of the residents are rural to urban migrants and 64% of adults have not completed high school [38]. There is a high prevalence of overweight and obesity [39] and prevalence of DM among Black Africans is approximately 13%, having increased more than 50% over 20 years [40].

Patient and Public Involvement:

Community Partners

Project implementation is conducted in partnership with two well-established NGOs that use CHWs from the community to support the health of over 9,000 individuals in Khayelitsha and surrounding communities. Our intervention is delivered through adaptation of the NGO's existing programs that use CHWs to provide health-related services to small community groups or "clubs" of approximately 10-50 individuals who meet in homes or community facilities. CHWs provide such services as health monitoring, medication delivery, education, physical activity, meals, wellness programming, and income generating activities. NGOs work collaboratively with local health clinics to both refer patients and receive referrals of patients many of whom have diabetes and cardiovascular disease. CHWs meet

regularly (varying by NGO and club from daily to monthly) with their designated groups. Many groups also function independently providing meals and social activities to members on a regular basis.

Involvement in study design

Our team's preliminary work involved extensive formative research with club members, CHWs and community leaders to better understand cultural norms, barriers and facilitators surrounding physical activity, diet and body image [10]. In partnership with CHWs, a training manual and pilot program was developed, which demonstrated the feasibility of using health clubs to encourage walking [41]. Additional pilot work included development and evaluation of three intervention sessions based on the DPP. Two pairs of CHWs were trained to deliver three DPP pilot sessions to participants, and both CHW and participant feedback were incorporated into the development of the complete program. To develop the complete *Lifestyle Africa* program for the present study, we formed two community advisory boards (CABs) in two Khayelitsha area neighborhoods to guide the development of a culturally appropriate and sustainable program. Members included a number of CHWs, community residents with DM and/or CVD, local experts in DM and CVD, and community leaders capable of guiding and supporting dissemination (e.g., a neighborhood elder and a representative of the provincial Department of Health). The CABs provide input and assistance with all aspects of the project including naming the intervention program, assisting with program development, reviewing intervention content and materials, and providing input on program logistics. Members attend quarterly meetings as well as participate in work groups focused on specific tasks (e.g., adapting the DPP manual, reviewing or trying out suggested adaptations of the DPP, or reviewing text messages).

Trial Design:

This is a 2-arm parallel group cluster RCT with balanced randomization (1:1) and a cross-over of the control arm after the main outcome assessment (Figure 1). CHWs mostly work individually or in pairs with a particular group, but in some cases CHWs work as trios or work with more than one group. For this reason, the unit of randomization is CHW "team" (individual, pair or trio). CHW teams randomized

to intervention receive training and provide the intervention to their support groups. CHW teams randomized to control provide treatment as usual to their support groups. After approximately one year of intervention, control CHW teams are also trained in the intervention and their support groups are crossed over to the intervention arm. Participants in both arms are assessed at the end of the first and second year.

Participants/Recruitment:

To recruit participants, two initial sessions were developed to introduce and explain the purpose and nature of the *Lifestyle Africa* program. CHWs are trained to deliver these sessions which follow a similar format to the main *Lifestyle Africa* sessions. At the introductory sessions, interested club members are invited to return for an eligibility screening and enrollment session. To serve our NGO partners and to be sensitive to community wishes, our goal is to invite all eligible members of 28 clubs (~18 members each) served by our partner NGOs to participate in the intervention and to enroll as many as feasible in the study. The eligibility criteria were therefore designed to be as inclusive of club members as possible. The inclusion criterion for support group members is being overweight or obese (BMI ≥ 25 kg/m2). Exclusion criteria are: (1) having an unsafe level of blood pressure [>160 (systolic) and/or >100 mm (diastolic)] [42], (2) elevated blood sugar [HbA1C > 11] [42] (3) being pregnant, breast-feeding or planning pregnancy within two years; (4) chronic use of oral steroid medication (which may affect weight loss); and (5) not intending to stay in the group over the next two years.

Randomization:

Randomization of support groups was conducted by the project statistician using a numbered list of the CHW teams and their associated groups. CHW teams are stratified within NGO. A computerized random number generator was used to create the allocation scheme. CHW groups have been randomized prior to enrollment of participants and launch of the intervention in order to know which CHWs need to be ready to deliver the intervention. It is therefore not feasible to blind CHWs or participants.

Interventions:

(1) Lifestyle Africa

Adaptation of the DPP: In developing *Lifestyle Africa*, we aimed to retain key elements from the CDC National DPP [22,43] while making necessary cultural, educational, and language adaptations relevant to the community. CDC's National DPP consists of 16 "core" sessions delivered over 6 months and 15 "post-core" sessions focused on maintaining participants' engagement in the program. Participants are encouraged to lose 7% of body weight and exercise 150 mins/ week. Central components of the program include self-monitoring of caloric intake and physical activity along with other social-cognitive and problem-solving theory elements [43].

The primary adaptation was to eliminate the need for a high-level health professional (such a nutritionist or dietitian) to deliver the core sessions of the program by providing session content on video (Katula et al., 2011). With expert content provided via video the role of CHWs is to show the video, serve as group facilitator, and ensure engagement with the video material. Videos were developed in Xhosa and use a presenter/narrator in conjunction with photos and animation. Frequent pauses are built into the video session during which CHWs prompt participants with interactive questions and activities such as completing worksheets that reinforce and personalize video content. Activities are designed to minimize writing and allow for participants to engage orally if needed (e.g., through discussion with a partner.) Participants receive a program book in Xhosa (or English if preferred) with educationally and culturally adapted handouts and forms needed for each session (e.g., physical activity tracking sheets, goal setting forms). The visual elements of the video were designed to be culturally sensitive, for example by depicting the individuals and scenes representative of the target community. To aid CHWs, each video has an accompanying session guide that provides step-by-step guidance on materials, procedures and the verbal prompts and questions needed to facilitate the session. To avoid excessive session length the *Lifestyle Africa* program consists of 17 rather than 16 core sessions.

Other key adaptations included those made because, unlike the original DPP, participants in *Lifestyle Africa* are not actively seeking treatment in the form of lifestyle behavior change. Therefore, in addition to the 17 core sessions, we created two additional "recruitment sessions" that follow the same format (i.e., video delivered with pauses for discussion) to provide information on the rationale for participating in a diet and exercise program. To account for participants' levels of health literacy and numeracy we expanded educational content (e.g., explained the physiology of diabetes and cardiovascular disease; explained the meaning of a kilojoule), simplified explanations, reduced calculations, and "chunked" information by interspersing it with discussion and related activities. We also bolstered motivational aspects of the DPP through the addition of elements of Motivational Interviewing a method of counseling designed to strengthen motivation by fostering participant's own reasons for change (e.g., exploring personal values, asking participants to express their own reasons for change). According to Motivational Interviewing principles the counselor's style or manner of counseling is also important (e.g., person-centered and autonomy supportive rather than directive or persuasive; use of reflective listening rather and open questions rather than closed questions and confrontation). For this reason a Motivational Interviewing and group facilitation skills training curriculum was also developed for CHWs to provide the skills necessary for delivering the sessions in a Motivational Interviewing consistent manner[44].

A final adaptation capitalizes on the widespread use of cell phones in the developing world and increasing evidence of the potential benefit of text messaging to help promote behavior change [37]. A empirically based text message system was developed in which participants are provided with two messages per day (morning and lunch time) to provide reminders, foster motivation and self-efficacy, affirm ongoing efforts, and help with implementation planning (i.e., behavior change tips). The same messages are delivered to all participants, but weekly message content refers to each of the core sessions and is timed to match the participant's session progress.

In addition to the video-based core sessions 12 post-core sessions were developed. These are reduced in length but follow the same format (weigh-in, review and discussion of progress toward goal(s)

from the prior session, delivery and discussion of new content, goal setting for the next session). New content is brief and delivered by the CHW using scripted language and straightforward handouts.

CHW training: CHWs working for our partner NGOs are not required to have any specific educational background but must have basic reading, writing, and arithmetic skills sufficient to maintain attendance registers, medication logs, and assess and record weight, height etc. CHWs also have received basic training as part of their employment as CHWs (e.g., in home-based care, chronic disease management, and wellness). Training for *Lifestyle Africa* facilitators consists of 3 days of didactic training and 8 weekly half day sessions of experiential training as mock *Lifestyle Africa* participants conducted in Xhosa by local research team members. Didactic training includes basic training in diabetes and diabetes management, behavior change principles, Motivational Interviewing, and group facilitation. CHWs are also trained in use of the video projectors, and logistical and study-related safety procedures. Content of Motivational Interview training was also adapted to limit jargon, and to adapt concepts and experiential learning activities to CHW cultural values, language and educational level. For example, "MI Spirit" was distilled as "What is effective counseling?" and focused on the need to listen and reflect before giving advice. Experiential training involved CHWs discussing their own experiences with making behavior change. "Evocation and eliciting change talk" was described in terms of "building motivation or 'a strong why'". Experiential training involved exploring goals and values related to behavior change. Content was adapted to be culturally relevant (e.g., use of culturally relevant values such as "at peace with ancestors"). With regard to MI core skills, training and practice emphasized the use of open-ended questions and reflections.

CHW's reviewed and practiced key activities after each session (e.g., conduct weigh in, conduct opening facilitation, provide feedback on food logs) during their training as mock *Lifestyle Africa* participants. In subsequent mock sessions (where these activities were repeated) they were asked on a rotational basis to act as facilitators (e.g., lead the opening facilitation, facilitate goal-setting and action planning). A checklist was used to confirm all CHW's had satisfactorily conducted all key elements of the program.

Delivery: To avoid disruption of the study during the year-end holiday season that is widely observed in the community, enrollment takes place in February and March following the break and intervention begins immediately after each club is enrolled. Control group clubs begin the intervention one year after the intervention arm begins. CHWs are asked to deliver the program weekly (or biweekly if needed to fit the schedule of the group) but adjustments are made to allow for days when club members do not meet (e.g., on days when many members collect pension payments or days of neighborhood disruptions due to protests etc.). Session attendance, weight, and activity minutes are tracked by CHWs using standardized forms. After clubs complete the 17 core sessions they continue with monthly sessions until the final assessment.

Fidelity Monitoring: Research staff will observe at least the first ten sessions for each CHW team and taper observations over time to at least one session every 5-8 weeks. Checklists are used to verify adherence to key session protocol elements (e.g., completed weigh in, followed verbal prompts, used projector correctly etc.). Adherence to MI principles and group facilitation behaviors are evaluated using rating scales (poor/never to excellent/always) adapted from the OnePass measure for MI competence [45].

(2) Usual care (wait list)

For clubs randomized to usual care, CHWs continue to lead clubs in their usual activities (e.g., approximately monthly monitoring of weight, blood pressure and blood glucose, delivery of medication). Although usual care may include education and health monitoring, there is no systematic, structured means by which lifestyle change is facilitated on an ongoing basis.

Data Collection:

Clubs are enrolled in two waves separated by 12 months. Each wave follows the same procedure for enrollment and assessment (see Figure 1). Recruitment and enrollment of each wave takes approximately two months over February and March of the calendar year. Enrollment for wave 1 began in February of 2018. The baseline assessment is conducted at enrollment. Follow-up assessments occur at

the end of the enrollment year (approximately 8 months after enrollment) and the end of the second year (approximately 20 months after enrollment). Although the goal was to conduct assessments 12 and 24 months after enrollment, the timing of the enrollment and follow-up assessments had to be adjusted to avoid the December-January holiday season break when the most participants leave their neighborhoods to return to their rural homes. To minimize attrition and interference in program participation due to holiday travel, we therefore enroll participants and begin the program as early as possible in the calendar year (immediately after participants return from their holiday break) and conduct our year 1 follow-up assessment as late as possible in the calendar year (just before participants leave for their holiday break). For similar reasons the year 2 assessment is conducted 12 months after the year 1 assessment, just before participants leave for their holiday break.

The follow-up assessment at the end of Year 1 is the main outcome time point. The follow-up assessment at the end of Year 2 is used to evaluate long term outcomes for the intervention arm as well as the effects of the control arm receiving the intervention. Consistent with local norms participants receive a R150 (approximately $12USD) gift voucher for completing each assessment.

Assessments are conducted by study staff who travel to club sites or nearby suitable locations. At enrollment, club members complete informed consent, eligibility screening, and baseline assessment. All participants are assessed on demographics, eligibility criteria, and key outcome measures (i.e., Body Mass Index [BMI], blood pressure, and HbA1c). At the end of assessments, study staff give each participant a feedback form with their biometric data and explain their results. Due to resource limitations and logistics, only a randomly selected sub-sample of 12 participants per club complete the lipids and self-report survey assessments described below. All survey measures were translated to Xhosa and back-translated to English. During this process, we applied some minor cultural adaptations to increase relevance and comprehensibility of certain items and also harmonized some response scales across instruments to reduce complexity for respondents. All data are collected by trained Xhosa speaking interviewers using tablets and the REDCap data management system [46].

Measures:

The primary outcome will be percentage of weight lost between baseline and the first follow-up assessment. Weight is measured to the half kilogram with a standard electronic scale. Participants are asked to wear light clothing and to fast the morning of enrollment. They are asked to remove footwear, heavy clothing/accessories prior before being weighed. Height is measured in order to calculate Body Mass Index (BMI) to determine eligibility. Height is measured to the nearest millimeter with the participant standing straight against a standard stadiometer. BMI is calculated as weight in kilograms divided by the square of height in meters.

Blood pressure is assessed by staff with calibrated portable automated instruments (Omrons HBP1300), averaging two or three independent measurements according to American Heart Association Council on High Blood Pressure Research Methods [47]. Non-fasting HbA1c, triglycerides, and LDL cholesterol are measured via automated assay from a capillary sample using an Afinion AS100 analyzer [48]. Medication use is assessed by asking participants to bring all their medications to the enrollment session. Interviewers recorded the medication name and dose including use of HIV antiretroviral medications.

Demographic measures are assessed via participant survey and include age, gender, education level, income level, and housing type. Dietary intake focuses on intake of whole grains, fruits and vegetables, fiber, and sugar, measured with an adaptation of the NHANES Dietary Screener Questionnaire [49]. Physical activity is measured using the International Physical Activity Questionnaire-Short Form [50], and health-related quality of life is measured with the Veterans RAND 12-item Health Survey [51,52].

Data Analysis:

Power analysis

Power analyses were conducted using the Optimal Design software for cluster-randomized trials with person-level outcomes. Prior studies of lifestyle interventions have indicated that the intra-class

correlation coefficient (ICC) of the main outcome (percent weight loss) will likely be small (e.g., .01). Therefore, values of .01 and .05 were considered in the power analysis for conservative estimation. Because of the community-based nature of the trial, the study committed to enroll as many eligible and interested club members as possible. The power analysis was therefore used to determine the adequacy of the anticipated sample size. At the time of conducting our power analysis, we had one NGO partner and anticipated a sample of 54 clusters averaging approximately 10 participants each for a total N of 540. However, government changes in NGO designated areas of responsibility and withdrawal from participation in the trial of one branch of our NGO partner changed our plans. After recruiting a second NGO partner we anticipate 28 total clusters averaging 18-19 participants for a total N of 518. In order to allow for up to 25% attrition, cluster sizes of 19 and 15 were included in the power analysis. Assuming an ICC of .01, we projected that we would have 0.80 power to detect even small effect sizes of 0.28 and 0.31 with cluster sample sizes of 19 and 15 respectively. If we conservatively assume an ICC of 0.05, we projected we would still have 0.80 power to detect effect sizes of 0.35 and 0.37 with sample sizes of 19 and 15 per cluster. Using the pooled standard deviation from Look AHEAD (5.8), the largest trial of overweight/obese type-2 diabetic patients [24] and a conservative estimate of a 3.15% weight loss for the treatment group and a 1% loss for the control group, a conservative estimated effect size for weight-loss in the current study would be 0.37. This estimate is larger than the effect we will be able to detect with .80 power as we will be able to detect a percent weight loss difference of 1.6-1.7% between groups.

Planned analytic strategy

To accommodate the cluster randomized design, all analyses will be conducted with a multilevel modeling framework using SAS PROC MIXED. In this design, participants (Level-1 units) will be nested within CHW pairs (Level-2 units). Primary analyses will use an intention-to-treat strategy. Exploratory analyses will also examine low vs. high dose (i.e., sessions attended) effects. Unconditional models will be examined with each dependent variable to determine the amount of between and within cluster

variance. Some questions involve comparison of effects between conditions and some involve change within a condition.

Preliminary analyses will examine baseline equivalence across the two treatment conditions on variables that may impact outcome (e.g., medication use) to identify covariates for the main analyses. If groups differ at baseline, baseline values will be added to the models as covariates. To address the primary research question regarding differences in % weight loss at the end of Year 1, % weight loss from baseline to the end of Year 1 will be the dependent variable in the multi-level model described above. The significance of the fixed effect for treatment group will indicate if there are differences in overall outcomes across groups. Anticipated effects are directional in that *Lifestyle Africa* participants should respond better than control participants. Similar models will be evaluated for each of the secondary outcomes. Relevant covariates will be added to the models as appropriate (e.g., use of diabetic medications for weight loss).

To determine if the *Lifestyle Africa* intervention group maintains its response to the intervention over the second year, scores at the Year 1 assessment will be compared to those at the Year 2 assessment. Random intercepts for health club and participant nested within health club will be included in the model. The significance of the fixed effect for time will indicate whether or not participants were able to maintain their response. This type of maintenance model will be evaluated for each of the outcomes of interest individually. Similar models will be used to examine intervention response within each of the study arms to determine if intervention effectiveness is replicated in the control group. If there are no differences between groups in the assessments taken just prior to participating in the *Lifestyle Africa* intervention, we will combine the groups and examine potential predictors of treatment effectiveness such as fidelity at level two and attendance at level one.

Monitoring:

A Data Safety Monitoring Board (DSMB) oversees the study and approved the stopping rules. The DSMB operates independently from the study investigators and the funder and comprises members

based in the United States and South Africa and includes a psychologist, a physician, a doctor of public health, and a statistician with expertise relevant to the trial. Details of the DSMB operating procedures are described in the DSMB charter. The DSMB may require termination (stopping rules) or modification of the study for: (1) any perceived safety concern including concerns related to adverse events or (2) because of severe failure to recruit or retain participants. There is no interim analysis or stopping rule related to an interim analysis because the intervention involves minimal risk to participants and even in the absence of indications of weight loss, the intervention may yield other educational or psychological benefits. In addition, stopping for reasons other than safety could be negatively perceived by community partners, CHWs, and club members. As part of usual care, CHWs and supervising nurses monitor the health of participants and refer patients to their physician, or local health clinic, or emergency service as needed. Study staff continuously monitor unanticipated problems or serious adverse events which can be identified by CHWs, NGO staff, participants, participants' families, participants' physicians or other health professionals. Events are investigated, documented, and reported to the principal investigators who report to the DSMB in accord with their regulations and to the Institutional Review Board (IRB) and the funder if appropriate.

Ethics and Dissemination

Our study protocol has been approved by the Institutional Review Boards (IRBs) at the University of Cape Town (the primary IRB) and Children's Mercy Kansas City and the University of the Western Cape. Any amendments are approved by the IRB. Protocol modifications are communicated to study staff during regular meetings and when relevant, to CHWs and participants through personal outreach and through regular meetings with NGO partners. Written informed consent is collected from all participants prior to eligibility screening and enrollment. Multiple protections for participant confidentiality are in place. Participant identifiers (name and contact information) are marked as an identifier in REDCap and are then censored when the database is downloaded for analysis. Only trained study staff have access to REDCap databases during data collection. All identifying information will be

removed with the deletion of the REDCap project at the end of the study. Consent forms and signature logs for reimbursements will be secured in a locked file cabinet within a locked office on a secured floor.

A full data package will be maintained by the investigators for at least seven years after data collection is complete. Third-party access to the full data package will be addressed by the investigators on a case-by-case basis. Results will be disseminated through publication in peer-reviewed journals and conference presentations. *Lifestyle Africa* curricula will be made available to local stakeholders such as Universities and the Department of Health. Study progress and findings will also be updated on clinicaltrails.gov (#NCT03342274).

Discussion

The growing burden of NCDs in low and middle-income countries presents a critical need for evidence-based interventions that address behavioral contributors to the prevention and management of CVD and DM. Our study aims to adapt one of the strongest existing evidence-based lifestyle behavior change interventions to the context of low-income, under-resourced urban areas of sub-Saharan Africa and rigorously assess its impact in a cluster RCT. Results will inform both the feasibility and effectiveness of an intervention delivery model that uses CHWs as facilitators, video as the primary medium for delivering content, and enhancement of the DPP with Motivational Interviewing principles and a text message system. This will be an important addition to similar efforts that have targeted more educated and resourced populations in India [53].

Successful outcomes will hinge on both successful program delivery as well as participant engagement and retention. The main outcomes will therefore need to be interpreted in the context of key aspects of study implementation including the success of training CHWs, the reliability and fidelity with which sessions are delivered, and the engagement of participants. Upon completion of the study, a process evaluation is planned to enhance understanding of the outcomes by assessing CHW and participant perspectives on the strengths and weaknesses of the program. Through training and technical support the

project also aims to build capacity in partner NGOs to continue the program after the study has been completed.

Strengths of the study include its community engaged development process which has led to an intervention design that fits with the existing models of care of our partner NGOs and may be transferable to programs aimed at other NCDs. The study's pragmatic design, including broad inclusion criteria, should also lead to findings that are relevant and generalizable to many communities in low and middle-income countries. Although the study is pragmatic and the result of a community-engaged process, it uses a rigorous cluster randomized design with objective measurements of key biometric and biologic outcomes related to diabetes and cardiovascular disease. Chief among the challenges of the trial will be to achieve adequate reliability and fidelity in the delivery of the intervention in the context of an impoverished environment where resources are limited, residents are taxed trying to meet their basic needs, and social disruptions (e.g., strikes, protests, crime) are frequent. Limitations include low precision of measures like dietary and physical activity recalls as well as limitations of measure breadth due to low literacy.

Regardless of the efficacy findings of the study, results should provide an important first step in understanding how lifestyle interventions such as the DPP might be disseminated in similar communities with few resources and low levels of education and literacy. Studies evaluating lifestyle behavior change interventions in low and middle-income countries are vital for addressing the epidemic of diabetes and cardiovascular disease.

Figure legend: Figure 1: Flow of study procedures (repeated for each of two waves of participants)

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study.

Competing Interests

The authors declare no competing interests.

Author Contributions

All authors made substantial contributions to the design of the study. DC led the study design, with other authors collaborating on the design of specific aspects (TP/LT/KR/MZV/EVL/NSL- DPP intervention content; EAH/KR/KG/TP/LT- measures and outcomes; JMS- text message component; KR/KG- motivational interviewing content). KF contributed to the research design and led the development of the statistical analysis plan. DC and EAH drafted the manuscript and all others contributed to revising it critically for important intellectual content. All authors reviewed and approved of the final version submitted for publication and agree to be accountable for all aspects of the work in ensuing that questions related to accuracy and integrity are appropriately investigated and resolved.

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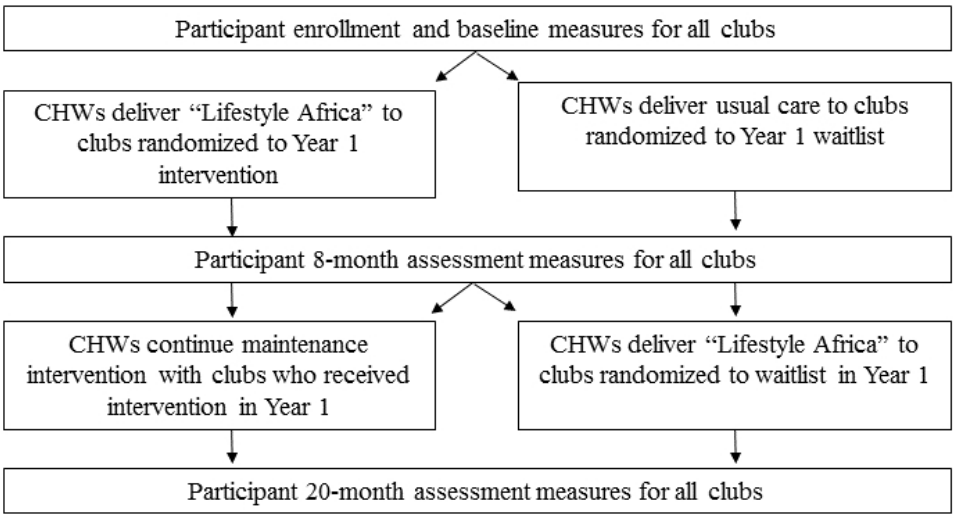

Flow of study procedures (repeated for each of two waves of participants)

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	___1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	___2_____
	2b	All items from the World Health Organization Trial Registration Data Set	throughout document and NCT trial registry
Protocol version	3	Date and version identifier	__1_____
Funding	4	Sources and types of financial, material, and other support	__19_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	__1_____
	5b	Name and contact information for the trial sponsor	__19_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	None (see p. 21)

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	__N/A_____
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	__3-5_____
	6b	Explanation for choice of comparators	__6_____
Objectives	7	Specific objectives or hypotheses	___5-6_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	___7-8_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	__6_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	__8_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	__9-12_____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	__16_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	_12 (fidelity monitoring)_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_12 (usual care)_

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	__6____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	_Figure 1; p. 7
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	__14-15__
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	___8___
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	___8____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	__N/A (8)_
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	__8_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	___N/A (8)_
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	___N/A___

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_12-14 _____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_12, 15__
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	__13____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	_15-16__
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_15-16__
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	__15___

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	__16___
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	___16___
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	__16-17__

Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	____N/A__
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	___17___
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	____17____
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	___17_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	___N/A_____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	___17_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	___19_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	__17_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	__N/A_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	___17_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	19___
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_N/A_____

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary File
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	__N/A_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.