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# Study protocol for the SMART2D adaptive implementation trial: a cluster randomised trial comparing facility-only care with integrated facility and community care to improve type 2 diabetes outcomes in Uganda, South Africa and Sweden

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## ABSTRACT

**Introduction** Type 2 diabetes (T2D) is increasingly contributing to the global burden of disease. Health systems in most parts of the world are struggling to diagnose and manage T2D, especially in low-income and middle-income countries, and among disadvantaged populations in high-income countries. The aim of this study is to determine the added benefit of community interventions onto health facility interventions, towards glycaemic control among persons with diabetes, and towards reduction in plasma glucose among persons with prediabetes.

**Methods and analysis** An adaptive implementation cluster randomised trial is being implemented in two rural districts in Uganda with three clusters per study arm, in an urban township in South Africa with one cluster per study arm, and in socially disadvantaged suburbs in Stockholm, Sweden with one cluster per study arm. Clusters are communities within the catchment areas of participating primary healthcare facilities. There are two study arms comprising a facility plus community interventions arm and a facility-only interventions arm. Uganda has a third arm comprising usual care. Intervention strategies focus on organisation of care, linkage between health facility and the community, and strengthening patient role in self-management, community mobilisation and a supportive environment. Among T2D participants, the primary outcome is controlled plasma glucose; whereas among prediabetes participants the primary outcome is reduction in plasma glucose.

**Ethics and dissemination** The study has received approval in Uganda from the Higher Degrees, Research and Ethics Committee of Makerere University School of Public Health and from the Uganda National Council for Science and Technology; in South Africa from the Biomedical Science Research Ethics Committee of the University of the Western Cape; and in Sweden from the Regional Ethical Board in Stockholm. Findings will be disseminated through peer-reviewed publications and scientific meetings.

**Trial registration number** ISRCTN11913581; Pre-results.

## Strengths and limitations of this study

- The Self-Management and Reciprocal learning for the prevention and management of Type 2 Diabetes adaptive implementation trial will evaluate the added benefit of community intervention strategies on type 2 diabetes outcomes, beyond optimised health facility strategies in Uganda, South Africa and Sweden, exemplifying a low-income, middle-income and high-income setting (disadvantaged population), respectively, all facing challenges in tackling the type 2 diabetes burden.
- The intervention we are implementing and evaluating is built on evidence-based strategies that have been contextualised based on formative research and collaboration with local and subnational stakeholders, to ensure acceptability and feasibility for scale up.
- The study design will allow comparison and reciprocal learning on what works and what does not across settings.
- The adaptive trial design and the monitoring of the implementation process allow for the intervention to be adapted to the contextual needs and to draw lessons for the scale-up implementation in other contexts.
- As the intervention will be implemented as a package of intervention elements, we will be unable to evaluate the effectiveness of specific intervention elements.

## INTRODUCTION

Type 2 diabetes (T2D) and prediabetes are increasingly contributing to the global burden of disease.[1] The global burden of diabetes in adults >18 years old is projected to increase from an estimated 415 million (prevalence of 8.8%) in 2015 to 642 million (prevalence of 10.4%) by 2040. The most dramatic change is expected to come from the projected increase in the number individuals with T2D in Sub-Saharan Africa (SSA) from 14.2 million in 2015 to 34.2 million, an increase of more than 100%.[2] Of all individuals with T2D worldwide, 80% live in low-income and middle-income countries (LMICs). There are also major differences in the prevalence and access to care between immigrants and the general population, especially in high-income countries (HICs), due to difficulties in integrating migrant population into the receiving healthcare system.[3] For example, in Canada, immigrants from South Asia, Latin America, the Caribbean and SSA have a 2–3 times greater risk of developing diabetes than their counterparts in the general population.[4]

Further, globally the proportion of undiagnosed diabetes is high, standing at 46.5%. In high-income regions like Europe, of all persons with T2D, 39.3% are undiagnosed.[2] Low-income countries in Africa have the highest prevalence of undiagnosed diabetes, estimated at 66.7%.[2] Health systems in most parts of the world are struggling to diagnose and manage T2D effectively, especially in LMIC, and among disadvantaged populations in high-income countries (d-HIC).

The economic burden of diabetes is very high too. Health spending due to diabetes in 2015 was estimated at US$5374 per person with diabetes in HICs, compared with US$ 401 in LMIC. Compared with HICs, people living in LMIC pay a larger out-of-pocket share of health expenditure because they have limited access to health insurance and publicly available medical services.[2]

It is clear that T2D is a global burden affecting HICs and LMICs in different ways. Whereas evidence for prevention and management is solid from efficacy and implementation trials,[5 6] efforts to contextualise such evidence to LMIC or d-HIC are limited. There is a need to identify context relevant interventions that can potentially work across different income settings, aimed at improving the prevention and management of T2D. Further, effective management of T2D and similar chronic conditions require a multidisciplinary approach beyond the biomedical. A multidisciplinary approach focusing on the individual, his or her family, community and environment and their interlinkages and interdependencies is more relevant,[7] with added emphasis on self-management support.[8] The content of biomedical care and self-management support for people with diabetes has been well-elaborated, including guidelines for health systems operating in resource limited settings.[9] Yet, the implementation of contextualised strategies taking into account this multidisciplinary approach has been limited.

The project titled 'A people-centred approach through Self-Management and Reciprocal learning for the prevention and management of Type-2-Diabetes (SMART2D)' aims at contributing to the implementation gap highlighted above. Given the global nature of the diabetes problem, the project is being implemented in three settings comprising three population groups namely, a rural population in a LIC (Uganda); an urban population in a MIC (South Africa); and an urban, socially disadvantaged and mainly immigrant population in a HIC (Sweden). The aim of the SMART2D trial is to contextualise integrated care comprising health facility plus community intervention strategies for prevention and management of T2D, informed by an adapted theory of change (ToC) and formative research; and to evaluate the feasibility and the incremental cost of implementing the interventions in an adaptive implementation trial. This paper describes the protocol of the implementation trial.

## METHODS AND ANALYSIS

### Study design

The study was designed as an adaptive implementation trial using cluster sampling, with two study arms; an integrated care arm comprising optimal health facility plus community intervention strategies versus facility only intervention strategies. A cluster is the community within the catchment area of the participating health facility. Prior to initiation of the trial, the clusters at each of the country sites were assigned to the study arms of the trial. In Sweden and South Africa, where primary care processes are already adequately established based on the respective national guidelines for diabetes management, we are testing the added benefit of integrated care, against facility only care. In Uganda where primary care processes for T2D are not yet part of standard of care, the trial has three arms: integrated care and facility only care as two intervention arms, and usual care (with no intervention) as the control arm.

### Context, targeted sites and populations

The trial is being conducted in three settings, reflecting three contexts in which health systems are still struggling to diagnose and manage T2D effectively. In Uganda, a low-income country, the trial is being conducted at nine primary healthcare facilities (health centre level III and level IV), located in the two rural districts of Iganga and Mayuge in the eastern part of the country. These are the primary healthcare facilities at which persons with diabetes first interface with the healthcare system for diabetes care. Health centre level III serves approximately 20 000 people at subcounty level, with health services including outpatient services, normal deliveries, limited in-patient care and tuberculosis (TB) treatment. It is headed by a clinical officer and has a laboratory that conducts basic tests (malaria, urine, blood sugar and TB). Health centre level IV is a mini-hospital serving approximately 100 000 people at county level. It is headed by a medical doctor and has nursing officers with diverse skills.

In South Africa, the trial is being conducted at two community health centres (CHCs) in the Khayelitsha township in Cape Town in the Western Cape. Both CHCs provide primary healthcare, including chronic care services, and fall under the provincial authority. The two facilities were purposively selected based on their demographic similarity, catchment areas and exclusion from other trials.

In Sweden, the trial is being conducted in two urban districts within Stockholm municipality representing d-HIC. These are socially disadvantaged suburbs and comprise predominantly immigrant communities (approximately 56%) and together have a total population of about 55 000. Each of the districts is catered to by a state-run primary healthcare centre, participating in the study. Since the suburbs chosen varied in terms of the composition of immigrant groups and the overall socioeconomic status; and the participating health centres varied in terms of staff capacity and services; the catchment area of each of the participating health centres was divided into zones using postal codes. These zones were randomly allocated to primary versus integrated care, while being careful to prevent contamination and spillover.

## Intervention

We developed a ToC to guide phased development of the interventions. To optimise contextualisation and cross-context lessons, intervention development included four phases: (1) literature review on diabetes and self-management to inform the development of a generic ToC, (2) situation analysis/needs assessment with a generic and contextualised topic guide for data collection, (3) synthesis of situation analysis in each country to identify both local contextualised and common needs across contexts and (4) finalisation and agreement on a common intervention framework with generic strategies and key elements, with contextualised health facility and community intervention strategies as the output. Online supplementary file s1 summarises the ToC process used.

The primary care intervention comprise two key health facility strategies: (1) organisation of care and (2) strengthening of the patient role in self-management, each with a number of intervention elements. Intervention elements are only implemented if they are currently lacking or in need of strengthening. For example, Uganda lacks most of the elements for both strategies, while Sweden and South Africa mainly need strengthening of the patient role. Key facility intervention elements under each strategy were developed and contextualised for implementation across the settings, as described in table 1.

The integrated care interventions include the above described health facility strategies and three key community strategies, that is: (1) community mobilisation, (2) strengthen the supportive environment and (3) involving a community extension (ie, linkage between facility and community). Similarly, community intervention elements were developed and contextualised for implementation across the settings, as described in table 2.

Taken together, the integrated care strategies address the six pillars of the chronic care edifice as specified by the chronic care model,[10] that is, (1) community resources and policies, (2) healthcare organisation, (3) self-management support, (4) delivery system design, (5) decision support and (6) clinical information system. Figure 1 illustrates the implementation strategy and timing of community interventions, as well as the health facility interventions.

## Participants

Participants are residents within the designated clusters at each country site. Individuals are eligible for enrolment if they are: currently residing in, and have resided in their respective communities for at least 6 months prior to enrolment; aged between 30 and 75 years; have no plans of migrating out of the study area over the next 12 months from the date of enrolment; able to provide written informed consent; agree to home visits and follow-up contacts as part of study participation; have not been previously diagnosed with diabetes for longer than 12 months; and have a positive confirmatory test of prediabetes or diabetes. Pregnancy and serious mental disability are exclusion criteria.

## Recruitment

A generic recruitment algorithm was developed and modified by each site to fit the local context by focusing on locally relevant methods and tests. Each site uses different strategies to mobilise communities; screen potential participants; and recruit those who fulfil the criteria as described below.

### Uganda

Within each cluster, trained Field Research Assistants (FRA) approach households explaining the study to household members, and seeking consent for screening for possible participation in the study. FRAs seek a written pre-eligibility screening informed consent from adult members of the household and administer a short screening form based on the inclusion criteria listed above to consenting adults. An appointment is then made with potentially eligible household members to return early morning on an agreed date, for a fasting plasma glucose (FPG) test. If the first FPG test is at least 6.1 mmol/L, a second appointment is made for a repeat FPG test. If the second FPG is also at least 6.1 mmol/L, the household member is referred to the respective cluster health facility for further screening to confirm eligibility. The household member is advised to report to the health facility within 7 days after an overnight fast without exercise or smoking. On presentation to the health facility, a third FPG test is conducted to confirm eligibility. Eligible subjects are classified as having prediabetes if at least two of their FPG test results are between 6.1 and 6.9 mmol/L, or as having

**Table 1** Facility strategies and elements, and their contextualisation across settings

| Facility strategies | Key elements | South Africa | Sweden | Uganda |
|---|---|---|---|---|
| 1. Organisation of care process | a. Available and functioning minimal infrastructure adequate | Pre-existing but standardised for trial:<br>▶ Glucometers and strips<br>▶ Automatic BP machines<br>▶ Weighing scales<br>▶ Stadiometers<br>▶ Measuring tapes | Pre-existing but standardised for trial:<br>▶ Glucometers and strips<br>▶ Automatic BP machines<br>▶ Weighing scales<br>▶ Stadiometers<br>▶ Measuring tapes | By SMART2D:<br>▶ Glucometers and strips<br>▶ HbA1c analyser and test kits<br>▶ Automatic BP machines<br>▶ Weighing scales<br>▶ Stadiometers<br>▶ Measuring tapes<br>▶ Medicines to cover stockout |
| | b. Guidelines and task identification | Pre-existing:<br>▶ PACK guidelines for health workers at primary care level<br>By SMART2D:<br>▶ Patient flow chart | Pre-existing:<br>▶ Clinical guidelines for T2DM, overweight and obesity and healthy lifestyle<br>By SMART2D:<br>▶ Screening algorithm<br>▶ Patient flow chart | By SMART2D:<br>▶ Clinical guideline including a task shifting guideline<br>▶ Clinical algorithm posters with patient flow chart |
| | d. Information system to follow-up patients | Pre-existing:<br>▶ System for patient register with patient appointment cards | Pre-existing:<br>▶ Digital registration<br>▶ System to trace/follow-up defaulters via mail and telephone (max three calls after one visit missed) | By SMART2D:<br>▶ Manual patient register filled in daily by HCW, with appointment diary, appointment cards and contact information forms<br>▶ Patient tracking in two steps: (1) by phone and (2) via care companion (after each missed visit) |
| 2. Strengthen patient role in self-management | a. Brief motivational, behavioural coaching for behaviour change | Pre-existing:<br>▶ Individual lifestyle counselling by HCW and health education delivered in groups by health promoters<br>By SMART2D:<br>▶ Skill-enhancement/standardisation of delivery of motivational, behavioural coaching | Pre-existing:<br>▶ Individual lifestyle counselling by HCW<br>By SMART2D:<br>▶ Skill-enhancement/standardisation of delivery of motivational, behavioural coaching | By SMART2D:<br>▶ Health education and motivational, behavioural coaching in groups by HCW |
| | b. Overview of care process and patient role | By SMART2D:<br>▶ Patient flowchart<br>▶ Brief patient info/health education material | By SMART2D:<br>▶ Patient flow chart<br>▶ Patient brochure and care companion role at visit 2 (or enrolment) by SMART2d | By SMART2D:<br>▶ Brief patient info/health education material at enrolment |
| | c. Access to measuring devices | No self-monitoring devices at facility<br>By SMART2D:<br>▶ Self-monitoring instructions in health education material | By SMART2D:<br>▶ Pedometers at visit 2<br>▶ Self-monitoring instructions in health education material | No self-monitoring, devices provided at facility<br>By SMART2D:<br>▶ Self-monitoring instructions in health education material |

BP, blood pressure; HbA1c, haemoglobin A1c; HCW, healthcare worker; PACK, practical approach to care kit; SMART2D, self-management and reciprocal learning for the prevention and management of type 2 diabetes; T2DM, type 2 diabetes mellitus.

**Table 2** Community strategies and elements, and their contextualisation across settings

| Community strategies | Key elements | South Africa | Sweden | Uganda |
|---|---|---|---|---|
| 1. Community mobilisation | a. Messages on lifestyle and diabetes for community members/key stakeholders | Pre-existing:<br>► Diabetes SA leaflets distributed by SMART2D at community awareness raising event(s) | By SMART2D:<br>► Brochures on timely care seeking; risk monitoring and screening; healthy lifestyle distributed at different places and events in community | By SMART2D:<br>► Oral information at household visits for screening purpose |
| 2. Strengthen support from the environment | a. Peer group programme | By SMART2D:<br>► Peer group facilitator topic guide and manual for nine sessions of mixed groups with people with prediabetes and diabetes | By SMART2D:<br>► Peer group facilitator topic guide and manual for nine sessions of mixed groups with people with prediabetes and diabetes | By SMART2D:<br>► Peer group facilitator topic guide and manual for nine sessions of mixed groups with people with prediabetes and diabetes |
| | b. CC/HLB involvement | CHWs will take on the role of CC/HLB<br>Pre-existing:<br>► PACK CHW guidelines<br>By SMART2D:<br>► Skill enhancement of motivational, behavioural coaching to | CC is a family member, relative, friend and neighbour<br>By SMART2D:<br>► Brochure describing CC role and tasks<br>► Identification of CC at facility visit 2<br>► Invitation to peer groups and activities | CC is a family member, relative, friend and neighbour<br>By SMART2D:<br>► CC guideline for HCW to instruct patient on CC selection and tasks<br>► Identification at month 1(CC)/3 (HLB)<br>► Invitation to health facility visits and peer group meetings |
| | c. Promoting supportive physical environment | By SMART2D:<br>► Community walks±PhotoVoice as part of peer group programme | By SMART2D:<br>► Physical activity and healthy food-related activities as part of peer group activities linking with community resources through municipalities/NGOs<br>► Community walks as part of peer-group activities | By SMART2D:<br>► Community walks as an optional activity for peer group |
| 3. Community extension | a. Community link team | By SMART2D:<br>► Support to CHWs to act as liaison between facility and community | Pre-existing:<br>► Citizen offices with prevention coordinators and citizen hosts helping citizens and linking them with different public, private and non-governmental organisations and services<br>By SMART2D:<br>► Utilisation of the existing networks of citizens offices and bringing T2DM on their agenda<br>► Mobilisation for recruitment through the network<br>► Linkage of the network with peer groups | By SMART2D:<br>► Formal introduction meeting between peer leader and facility nurses<br>► Peer leaders to remind peer group participants to go to visits, contact with health facility if loss to follow-up/problems<br>► HCW delivering health education remind participants to attend peer group meetings |

CC, care companion; CHW, community health worker; HbA1c, haemoglobin A1c; HCW, healthcare worker; HLB, healthy lifestyle buddy; NGOs, non-government organisations; PACK, practical approach to care kit; SMART2D, self-management and reciprocal learning for the prevention and management of type 2 diabetes; T2DM, type 2 diabetes mellitus.

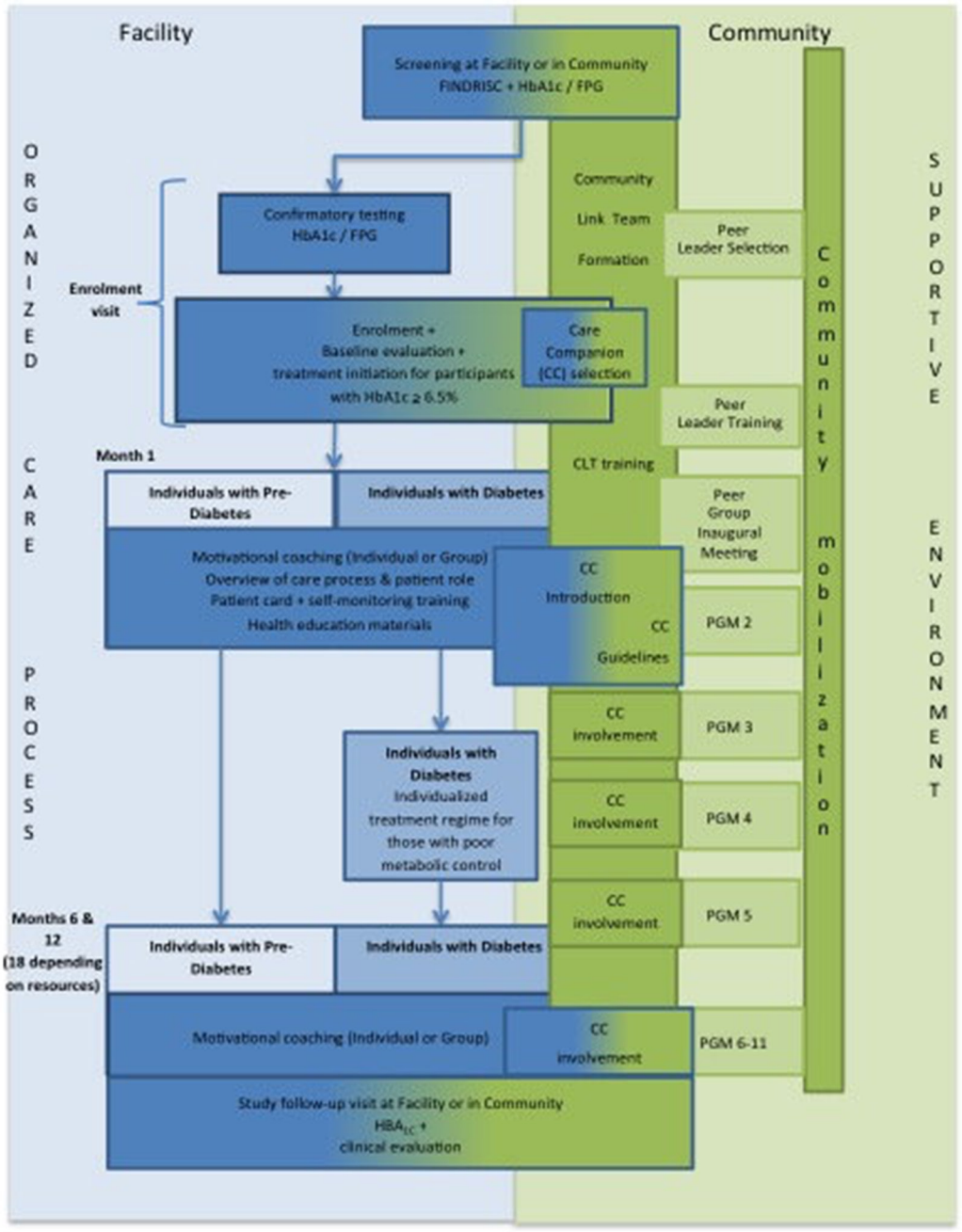


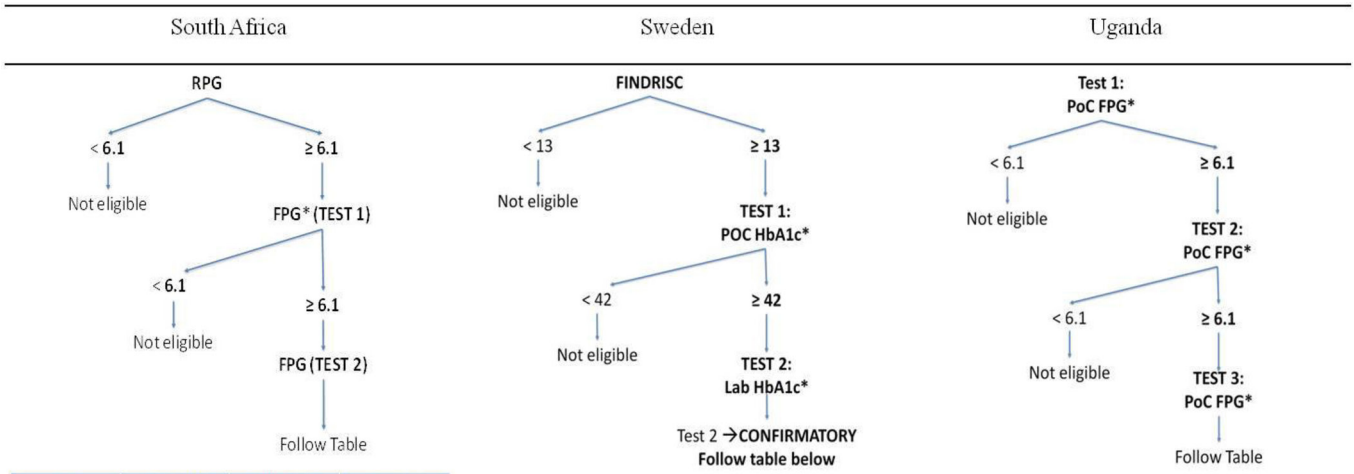

**Figure 1** Flow chart for the SMART2D facility (blue) and community (green) interventions. CC, care companion or healthy lifestyle buddy; CLT, community link team; FINDRISC, Finland Diabetes Risk; FPG, fasting plasma glucose; PGM, peer group meeting; SMART2D, Self-Management and Reciprocal learning for the prevention and management of Type 2 Diabetes.

diabetes if at least two FPG test results are >6.9 mmol/L, as illustrated in figure 2 for Uganda.

### South Africa

Study investigators conduct a community awareness raising campaign in partnership with the local branch of a national non-government organisation (NGO) to drive participant recruitment. The venue is a central location, which draws large numbers of visitors, such as a shopping mall located in close proximity to the study facilities. Awareness campaigners screen consenting adults to identify potential trial participants and conduct a random plasma glucose (RPG) test. This is followed by referral of eligible subjects to the health facility for an FPG, in line with the diagnostic criteria of the practical approach to care kit (PACK) guidelines for primary care. Subjects with a RPG ≥6.1 mmol/L are given a referral note and advised to visit their health facility within a week, after an overnight fast and they are advised to report with no exercise or smoking.

Recruitment takes place at the two selected study facilities, when visiting the facility for routine clinical care or




| RPG (mmol/L) | (FPG Test 1) (mmol/L)* | (FPG Test 2) (mmol/L)* | Outcome |
|---|---|---|---|
| FPG > 6.1 | FPG ≥ 7.0 | FPG < 6.1 | NOT ELIGIBLE |
| | | FPG= 6.1-6.9 | Pre-D: RECRUIT |
| | | FPG ≥ 7.0 | T2D: RECRUIT |
| | FPG= 6.1-6.9 | FPG < 6.1 | NOT ELIGIBLE |
| | | FPG= 6.1-6.9 | Pre-D: RECRUIT |
| | | FPG ≥ 7.0 | T2D: RECRUIT |

| Test 1 (POC HbA1c)* | Test 2 (Lab HbA1c)* | Outcome |
|---|---|---|
| HbA1c = 42-47 | HbA1c = 42-47 | Pre-D: RECRUIT |
| | HbA1c ≥ 48 | T2D: RECRUIT |
| | HbA1c < 42 | NOT ELIGIBLE |
| HbA1c ≥ 48 | HbA1c ≥ 48 | T2D: RECRUIT |
| | HbA1c = 42-47 | Pre-D: RECRUIT |

| Test 1 (PoC FPG)* | Test 2 (PoC FPG)* | Test 3 (PoC FPG)* | Outcome |
|---|---|---|---|
| FPG = 6.1-6.9 | FPG ≥ 7.0 | FPG= 6.1-6.9 | Pre-D: RECRUIT |
| | | FPG ≥ 7.0 | T2D: RECRUIT |
| | FPG= 6.1-6.9 | FPG < 6.1 | Pre-D: RECRUIT |
| | | FPG= 6.1-6.9 | Pre-D: RECRUIT |
| FPG ≥ 7.0 | FPG= 6.1-6.9 | FPG= 6.1-6.9 | Pre-D: RECRUIT |
| | | FPG ≥ 7.0 | T2D: RECRUIT |

**Figure 2** Recruitment algorithm. *FPG and HbA1c values based on WHO recommendation. FINDRISC, Finland Diabetes Risk; FPG, fasting plasma glucose; HbA1c, haemoglobin A1c; PoC, point-of-care; T2D, type 2 diabetes.

on referral from the community as per the above outlined protocol. Subjects are classified as having diabetes if two consecutive FPG tests >6.9 mmol/L, or as having prediabetes if two consecutive FPG tests are between 6.1 mmol/L and 6.9 mmol/L. A third FPG test (tiebreaker) is conducted if the first two test results are not consistent to classify a subject as either having diabetes or prediabetes as illustrated in figure 2 for South Africa. Persons meeting the above criteria are invited to participate in the trial.

### Sweden

Participants are recruited into the trial through community screening and from the participating health centres. The research team together with health centres and municipalities have identified opportunities and spaces in the community to carry out screening activities. Both research staff and outreach workers from the municipalities are involved in mobilising community members and inviting them to participate in the screening, by: (1) facilitating access to the target population through local NGOs, immigrant associations, religious bodies, such as churches and mosques and cafes or other ventures owned by immigrant groups and (2) identifying and facilitating access to spaces to set up the screening activities such as shopping malls, local library, municipality hall or other public spaces such as swimming halls.

Community screening activities are carried out by the research team on weekdays and weekends using a combination of Finland Diabetes Risk (FINDRISC),[11] and haemoglobin A1c (HbA1c) test (both point-of-care and laboratory based) using a recruitment algorithm summarised in figure 2 for Sweden. All individuals with HbA1c values in the diabetes or prediabetes range are referred to the health centres to be recruited and enrolled into the primary care only arm, or the integrated care arm based on the postal code of their area of residence. In addition, patients with T2D registered at the participating health centres who fulfil the inclusion criteria are invited by the diabetes nurse (and the implementation manager of the research team) through a phone call to participate in the study.

## Enrolment and baseline measurements

Once eligibility is confirmed, written informed consent is obtained, and subjects are enrolled. Trained study staff administer a standardised baseline questionnaire to obtain basic participant data comprising demographic and socioeconomic measures; medical and medication history; behavioural measures (diet, tobacco use, alcohol use, physical activity and foot care); and physical measures (weight, height, waist circumference and blood pressure).

As the intervention strategies use the principles of self-determination theory (SDT),[12] the questionnaire also collects data on components of the SDT including; level of social support the participant is receiving, sources of such social support, self-efficacy, autonomy support, self-regulation, psychological adjustment, quality of life, stress and diabetes knowledge. Further, HbA1c test, FPG (Uganda and South Africa only) and clinical examination are performed. For participants with diabetes, baseline data are collected on out-of-pocket expenditure, including outpatient costs, hospitalisation costs over the past 12 months, and household expenditure. At the end of these procedures, participants are given a pedometer, which they are instructed

to wear for the next 7 days to record a 7 day number of footsteps. Participants return the pedometer after the 7 days to record the number of steps made. Data are collected in a staggered manner to minimise respondent burden. Details of the data collection tools used in the study are provided in online supplementary file s2. In addition, a process evaluation guide checklist has been developed to measure the delivery of the intervention. It is inspired by the Reach, Effectiveness, Adoption, Implementation and Maintenance (RE-AIM) framework[13] and implementation fidelity framework[14] and has a number of common elements for all sites, that are linked to the most important intervention strategies in the facility and the community: a facility care checklist; a monitoring tool for motivational coaching sessions and for peer support sessions. In addition to this minimum set, sites will develop additional monitoring and process evaluation tools based on their needs and resources. Each country team does regular research site visits and intercountry site conference calls are held with the implementation teams. The information from these calls and from the site visits are recorded, to keep track of the challenges in implementation and adaptation to the intervention. The first participant was enrolled in February, April and August 2017 in Uganda, Sweden and South Africa, respectively.

## Follow-up

Participants with T2D report back monthly (or on an ad hoc basis in South Africa and Sweden), for clinical re-evaluations and management, and medication refill. In cases where participants miss their study visit appointment, each country site uses the participant defaulter tracing approach as outlined in table 1. Participants report back to the health facility for follow-up evaluations at month 12, at which time corresponding end-line measures to those described above are collected.

## Study outcomes

### Primary outcomes

Among participants with prediabetes, the primary outcome of interest is overall reduction in plasma glucose between baseline and month 12. We hypothesise that participants with prediabetes at facilities in the integrated care arm will on average have a higher reduction in their HbA1c reading by the end of follow-up compared with participants with prediabetes at facilities in the primary care arm (or usual care arm in Uganda).

Among participants with T2D, the primary outcome of interest is controlled plasma glucose levels. A participant will be classified as having had their plasma glucose controlled if their HbA1c reading at month 12 is <7.0%, or at least 2.6% below baseline reading. We hypothesise that among participants with T2D, the proportion with controlled plasma glucose in the facility plus community arm will be higher by the end of follow-up, compared with participants with controlled plasma glucose in the facility only arm (or usual care arm in Uganda).

### Secondary outcomes

Secondary outcomes in this study include:

- incidence of diabetes among participants with pre-diabetes;
- incidence of adverse events, including hospitalisations due to hypoglycaemia- or hyperglycaemia, or complications of diabetes;
- behavioural outcomes, including diet, physical activity, foot care, tobacco and alcohol consumption;
- difference in out-of-pocket expenditure between baseline and end line and incremental (system level) cost of implementing the intervention;
- among participants with diabetes, participant satisfaction with the diabetes treatment provided at the health facilities.

### Sample size

Although the overall aim of the trial is to combine participants across the three country sites, it is recognised that: (a) there will most likely be baseline differences across the country sites reflecting the different population characteristics between country sites and (b) site-specific analysis would be very relevant from a policy and potential scaleup perspective. Thus, the sample size was calculated such that differences between the trial arms can be detected with combined data across all the three sites in regard to the primary outcomes, as well as be detected at each study site separately. Sample size calculations were determined based on the primary outcome measures only, and on the hypothesis that by the end of follow-up, the integrated care arm will be superior to the primary care arm, and to the usual care arm in Uganda, with respect to the primary outcomes.

### Sample size for participants with prediabetes

With the aim of being able to detect a mean difference of at least 3 mmol/mol HbA1c by month 12 between any two study arms, with a SD of 2.5 mmol/mol; the required sample size before adjusting for clustering at an 80% power and 5% level of significance is 34 participants per arm. For this first stage calculations, we used the formula as described in Hayes and Bennett[15] for a continuous outcome.

Given the fixed number of health facilities (clusters), to adjust for clustering we used a formula for a fixed number of clusters and fixed number of participants within clusters as described in Hemming *et al*.[16] Because each country site is using different numbers of clusters; different intercluster correlation coefficient (ICC) values are expected. We were unable to find published literature providing estimates for ICC for HbA1c among persons with prediabetes. We therefore explored various values of ICC for each site, and used values that provided the highest sample sizes to detect the desired effect size. For Uganda, we used an ICC value of 0.200 to obtain a sample size of 112 participants, for South Africa we used an ICC value of 0.044 to obtain a sample size of 129 and for Sweden an ICC value of 0.040 to obtain a sample size

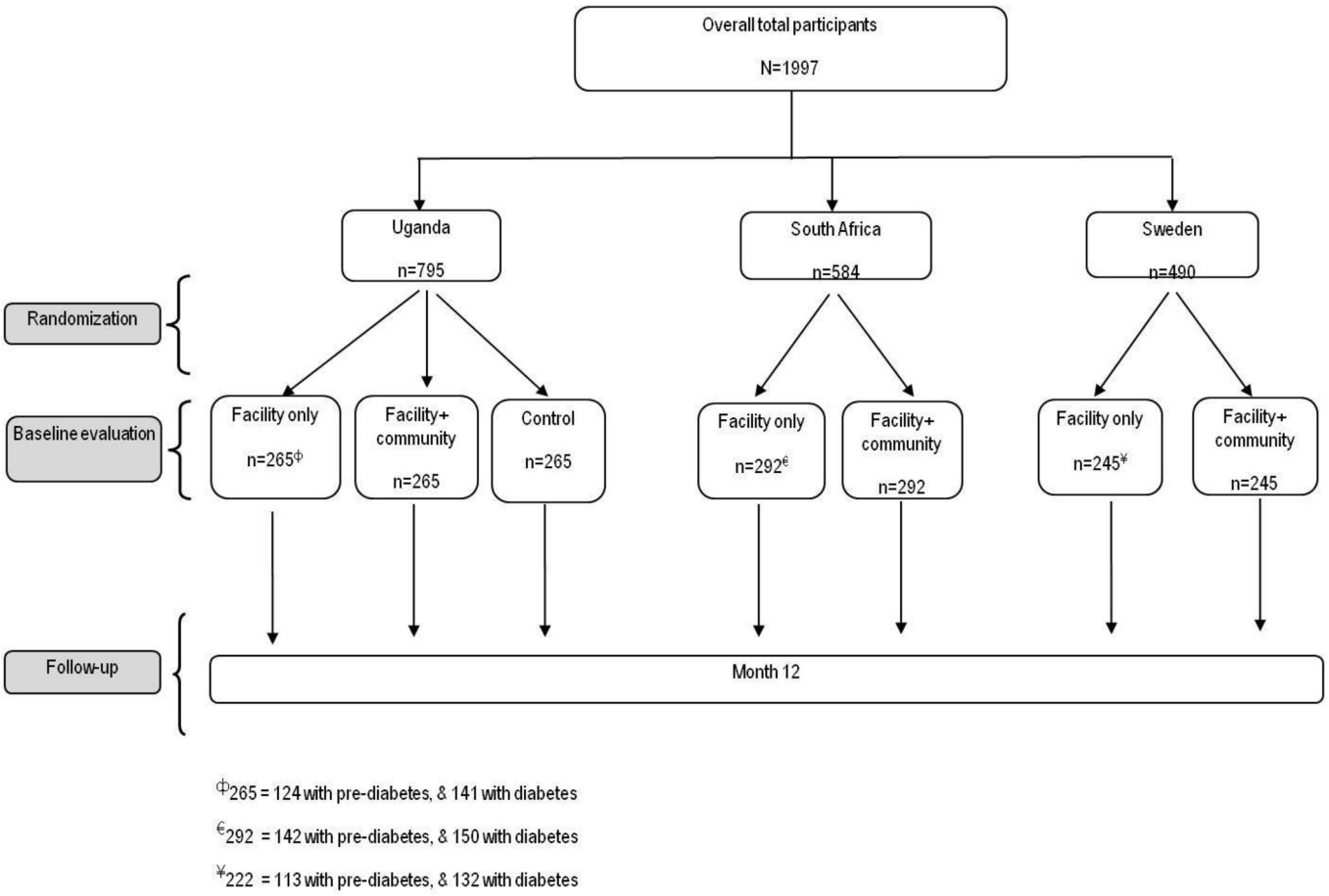



**Figure 3** SMART2D trial profile. SMART2D, Self-Management and Reciprocal learning for the prevention and management of Type-2-Diabetes.

of 102; all per study arm. Allowing for a projected 10% loss to follow-up over the 12 months, the final sample size of participants with prediabetes per study arm is 124 for Uganda, 142 for South Africa and 113 for Sweden.

### Sample size for participants with diabetes

Among participants with T2D, we aim at being able to detect a difference of at least 2% in the proportion of participants with diabetes with controlled plasma glucose by month 12 between the trial arms. The required sample size before adjusting for clustering at 80% power and 5% level of significance is 58 participants per arm. Assuming that in the intervention arm we shall attain reduction in plasma glucose per the criteria given above, in 30% of participants with diabetes ($P_1$=0.3). For this first stage calculations, we used the formula as described in Hayes and Bennett[15] for proportions. We found two publications of cluster randomised trials reporting ICC estimates among patient with diabetes one by Littenberg and MacLean in which they report an ICC for HbA1c among patients with diabetes of 0.055[17]; and another by Singh *et al* in which they report an ICC of 0.091.[18] We used these estimates as starting values to explore various values of ICC for each country site, and used values that provided the highest sample sizes to detect the desired effect size. For Uganda, we used an ICC value of 0.0.091 to obtain a sample size of 128 participants, for South Africa we used an ICC value of 0.020 to obtain a sample size of 136 and for Sweden an ICC value of 0.018 to obtain a sample size of 120; all per study arm. Allowing for a projected 10%; the final sample size of participants with diabetes per study arm is 141 for Uganda, 150 for South Africa and 132 for Sweden.

Figure 3 describes the trial profile, which also depicts the distribution of the sample size by country site, study arm and diagnostic category of the participants (diabetes and prediabetes).

## Data management

At each country site, research data is managed by trained data managers, with regular data cleaning, and data is uploaded quarterly into a RedCap software onto a server at the Sweden site via secure links. The database is password protected at all levels, with access only to authorised study staff.

## Planned statistical analysis

### Analyses for primary objectives

Since the unit of analysis for the primary outcome of interest is the individual participants, to minimise the effect of within cluster correlations we will employ generalised estimating equations,[19] to evaluate changes over time in HbA1c values as a continuous variable

among participants with prediabetes; and the proportion of participants with controlled plasma glucose among participants with diabetes, in relation to assigned trial arm. Thus, we will use multivariable linear regression mixed effects modelling with a random intercept, unstructured correlation matrix and robust standard errors, to evaluate changes over time in HbA1c, and logistic regression analysis to compare the proportion of participants with stabilised plasma glucose among participants with diabetes.

### Analyses of secondary objectives

Appropriate statistical analysis techniques will be used to conduct analyses to compare secondary outcomes listed earlier, between the study arms. We recognise that since sample size calculations for this trial were not based on the secondary outcomes, lack of significant differences in analysis of secondary outcomes might either be true lack of differences in these outcomes, or due to the fact that the trial was not sufficiently powered to detect differences in the secondary outcomes. Thus interpretation of findings on secondary outcomes will be done with caution.

## DISCUSSION

The rising burden of T2D and associated cost call for a multidisciplinary approach to address prevention and management. The SMART2D trial we are implementing provides an opportunity to evaluate the effectiveness of a set of context relevant interventions across both community and health facility setting in three different income settings. We believe that findings from this trial will contribute to the evidence currently needed and being generated,[20] regarding the effectiveness of multifaceted approaches to the prevention and management of chronic illnesses like T2D. The findings may also clarify as to how specific components of a multifaceted intervention can be implemented in different contexts, the normalisation process for these interventions, and the cross-lessons from their implementation in low-income, middle-income and high-income settings.

## ETHICS AND DISSEMINATION

Findings from this trial will be disseminated through peer-reviewed publications and through local and international scientific meetings.

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**Contributors** DG, PA, C-GO, JOV, CJS, DS, GT, TP, SP and MD conceptualised the trial. DG, PA, PD, C-GO, JOV, HMA, RWM, EEK, JK, DS, TP, MD and the SMART2D Group are implementing the trial. DG had primary responsibility for final content. All authors participated in writing, read and approved the final manuscript.

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**Competing interests** None declared.

**Patient consent** Not required.

**Ethics approval** Approval for conduct of this trial was obtained from the institutional review boards (IRB) at the respective trial country sites. In Uganda from the Higher Degrees, Research and Ethics Committee of Makerere University School of Public Health (reference number 426), in South Africa from the Biomedical Science Research Ethics Committee of the University of the Western Cape (BM/17/1/36), and in Sweden from the Regional Ethical Board in Stockholm (2016/2521-31/1). In Uganda, further approval was obtained from the Uganda National Council for Science and Technology (reference number HS 2118).

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# Study protocol for the SMART2D adaptive implementation trial: a cluster randomised trial comparing facility-only care with integrated facility and community care to improve type 2 diabetes outcomes in Uganda, South Africa and Sweden

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