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Complete List of Authors:	Jia, Weiping; Shanghai Jiaotong University Affiliated Sixth People's Hospital; Chinese Diabetes Society Zhang, Puhong ; The George Institute at Peking University Health Science Center, Diabetes Program; The George Institute for Global Health, Faculty of Medicine, University of New South Wales Duolikun, Nadila; The George Institute at Peking University Health Science Center, Diabetes Program Zhu, Dalong; Nanjing Medical University, Department of Endocrinology Li, Hong; Sir Run Run Shaw Hospital Affiliated to School of Medicine, Zhejiang University, Department of Endocrinology Bao, Yuqian; Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Department of Endocrinology and Metabolism Li , Xian; The George Institute for Global Health at Peking University Health Science Center Liu, Yu; Beihang University, School of Computing
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A study protocol for the ROAd to hierarchical Diabetes Management At Primary care (ROADMAP) study in China: a cluster randomised controlled trial

Weiping Jia[1,2]*, Puhong Zhang[3,4]*, Nadila Duolikun[3], Dalong Zhu[5], Hong Li[6], Yuqian Bao[1], Xian Li[3,4], Yu Liu[7], ROADMAP study group

[1] Shanghai Jiaotong University Affiliated Sixth People's Hospital, Shanghai 200233, China.

[2] Chinese Diabetes Society, Beijing 100710, China

[3] The George Institute for Global Health at Peking University Health Science Centre, Beijing 100088, China.

[4] The George Institute for Global Health, Faculty of Medicine, University of New South Wales, NSW 2050. Australia

[5] Department of Endocrinology, Drum Tower hospital affiliated to Nanjing University Medical School, Nanjing 210008, China.

[6] Department of Endocrinology, Sir Run Run Shaw Hospital Affiliated to School of Medicine, Zhejiang University, Hangzhou 310016, China.

[7] School of Computing, Beihang University, Beijing 100191, China

***Joint first author**

Correspondence to:
Professor Weiping Jia
Institution: Shanghai Diabetes Institute, Shanghai Clinical Centre for Diabetes, Shanghai Key Laboratory of Diabetes Mellitus, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China
Address: 600 Yishan Road, Shanghai 200233, P.R.China
E: wpjia@sjtu.edu.cn;
T: 86-21-64369181ext 8922;
F: 86-21-64368031

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ABSTRACT

Introduction: As the management of diabetes mellitus in the community remains suboptimal, we aimed to determine the effectiveness of an integrated, service provider empowering, and hierarchical diabetes management model of care in China.

Methods and analysis: A cluster randomised controlled trial, ROAd to hierarchical Diabetes Management At Primary care (ROADMAP), will involve 19008 patients with type 2 diabetes mellitus recruited from primary care clinics in 864 communities across 144 counties/districts of 24 provinces in China. Communities within each county/district are randomly assigned to intervention arm or usual care. In the intervention arm, a 4-in-1 intervention is provided that includes structured capacity building on the management of diabetes and screening for complications, contracting of standardized services, mobile health information system (*Graded ROADMAP*) support, reimbursement for service delivery, and health education and real-time communication through a smartphone app (*Your Doctor*). The primary outcome is glycated haemoglobin (HbA1c) control at one year. Secondary outcomes include control rate of ABC (HbA1c, blood pressure and LDL-c) targets and fasting blood glucose, hypoglycaemia episodes, and health-related quality of life (EQ-5D).

Ethics and dissemination: The trial has been approved by the Institutional Review Board at Shanghai Sixth People's Hospital. Findings on effectiveness of intervention will be widely disseminated through peer-reviewed journals, conference presentations and other mechanisms.

Trial Registration: The study is registered at Chinese Clinical Trial Registry (ChiCTR-IOC-17011325).

ARTICLE SUMMARY

Strengths and limitations of this study

- This is a large-scale cluster clinical trial being carried out in diverse primary care settings of most provinces in China. The sample size allows a formative evaluation of a complex service intervention overall, and in subgroups of developed and less-developed, urban and rural regions.
- A standardised 4-in-1 comprehensive management package intends to upskill, support and empower doctors in primary care settings to manage patients with type 2 diabetes mellitus that extends beyond the study.
- The intervention delivery is supported by 2 designated mobile health based information system (*Graded ROADMAP, Your Doctor*), recording the condition of participants, receipt of services and health education and communications, to ensure continuity of care with secure access.
- A comprehensive integrated mobile application project and data management system is used to ensure efficiency and quality of the study implementation, and provide transferable experience for the management in future large-scale studies.
- We suggest caution in generalising any intervention benefits to the broader diabetes population, since the recruitment is limited to people with established type 2 diabetes mellitus registered for receiving services under the Essential Public Health Service Package in China.

INTRODUCTION

Type 2 diabetes mellitus (T2D) imposes major morbidity, mortality and financial burden in all health systems.[1-3] Globally, there are an estimated 425 million people are with T2D and one fourth of them reside in China where there are enormous challenges to their management in the very large population across diverse settings.[1, 4-6] Although an Essential Public Health Services (EPHS) package was introduced to provide universal access to services for patients with chronic diseases in primary care in China in 2009,[7] and there have been annual increases in governmental subsides subsequently,[8] there remain considerable gaps in care. Despite being entitled to at least four free blood glucose tests, and consultations for treatment and lifestyle advice, each year, patients registered for EPHS control of T2D, with less than 40% of having adequate blood glucose control (HbA1c <7.0%),[9] and only 5.6% with optimal control of combined ABC (HbA1c, blood pressure [BP] and low density lipoprotein [LDL-C]) targets.[10] Achieving effective T2D management is heavily dependent on having organised and responsive primary care services.[11, 12]

A national guideline for promoting a graded diagnosis and treatment system was launched[13] in China in 2015, in line with the Healthy China 2030 policy[14] to establish a cooperative hierarchical health service system. However, as the readiness for change in primary care varies across regions and economic context,[15, 16] further work is required to operationalize defined action plans. We outline the protocol for a study with the aim of determining the effectiveness of a service-delivery intervention in a cluster clinical trial called ROAd to hierarchical Diabetes Management At Primary care (ROADMAP). The intervention follows Chinese Diabetes Society guidance recommendations[17] to empower primary care providers in a collaborative tiered care system with a mobile-based health information and referral management system to deliver contracted services for T2D in China.

METHODS AND ANALYSIS

Trial design, study settings and electronic supportive system

ROADMAP is a community-based, cluster randomised controlled trial being conducted across hundreds regional medical centres in district/county hospitals of urban and rural regions in China (Figure 1). Primary care centres (i.e. community health services [CHS] centres in cities and towns, of urban and rural areas, respectively) and their subordinate primary care clinics (so called CHS stations in urban areas, and village clinics in rural areas) provide medical services with EPHS to local residents. A detailed structural description of structure of health services in China is available in the supplementary appendix. Throughout the study period, two websites (patient list uploading website, trial management website) and two smartphone apps (*ROADMAP Assistant*, *ROADMAP mEDC*) were designedly developed and applied to support project implementation and data collection. Another 2 apps (*Graded ROADMAP, Your Doctor*) was developed and used as intervention tool in this study. The functions and its target users of these involving electronic system are summarised in Table 1.

Table1 Electronic information systems used in ROADMAP study

Name of the system	Main functions	User
Patient list uploading website	Uploading the basic information of patients with type 2 diabetes who have been registered in the Essential Public Health Service System. The patient list is the pool of participants whom will be selected at random from by ROADMAP Assistant and confirmed later by the community/village doctors	County coordinators [a]
ROADMAP Assistant app	Site selection, qualification check of staff and organization, training and readiness check before undertake major research activates such as baseline and end-of-study assessment, cluster randomization, and others.	County coordinators; CRAs [b]
ROADMAP mEDC app	Patient screening and recruitment, patient data collection (baseline & end-of-study), and registration of loss-to-follow-up and drop-out.	Investigators responsible for data collection; CRAs
Graded ROADMAP app	Create participants' electronic health record, record activities and results of each intervention services, and patient referral	Care teams [c]
Your Doctor app	Health education, real time online communication with contracted care team	Care teams; participants
Trial management website	Trial progress monitoring, performance review, statistics and reporting	Authorised investigators; CRAs

a: A county/district level investigator who acts as a contact person, reports to the principal investigator of the county/district hospital, and coordinates the project implementation.
b: CRA: Clinical Research Associate
c: A care team is composed of three doctors/nurses respectively from primary care clinic and primary care centre and regional medical centre. Each participant in the community/village receives continuous standard patient-centred healthcare services from the care team under a contract in ROADMAP study.

Selection of study sites and participants

Figure 1 shows that 19008 patients with T2D are to be selected from 864 communities/villages of 144 districts/counties in 24 (out of 31) provinces of mainland China. Study sites at all levels are selected with the support of a mobile trial management app, *ROADMAP Assistant.* Table 2 details the inclusion/exclusion criteria for study sites and participants. Study sites have been evenly stratified by developed urban or rural, and less-developed urban or rural area, according to economic development level[18] and geographical location.

In each community/village (cluster), a full list of patients with T2D (usually >50) registered at a primary care clinic, are uploaded to a purpose-built website to allow 30 patients to be selected at random for contacting by clinic doctors to confirm their eligibility and invite them to participate in the study.

Table 2 Eligibility criteria for study sites and participants in ROADMAP study

Screening targets	Eligibility criteria description
Study site at different levels	
Province	• At least one provincial principal investigator with high impact in diabetes research is available and approved by ROADMAP working group. • Provinces which are planning to develop or have had established a primary healthcare service based on electronic referral system will be excluded due to potential technological conflict.
District/County	• County hospital should be the main healthcare providing institution rather than tertiary hospital to avoid affecting the process pf patient referral and future impact evaluation. • There is no generalized m-health-based referral system whereas the provision of an adequate level of community healthcare facilities and service is available. • Local health authorities are aware of and support the trial with the willingness of involvement, anticipating to become an exemplary centre of diabetes management. • There is at least one diabetes specialist able to take the role of county principal investigator/doctor to deliver training, support treatment and receive referral, as well as one county coordinator to facilitate trail implementation and fidelity assurance, also manage local study funds. • There are at least one eligible streets/towns available. • Legitimate healthcare facility that can provide formal invoices for all trial-incurred transactions.
Street/Town	• The methods and instruments are readily available to perform high-quality laboratory tests, includes: plasma glucose test, routine urinalysis, lipid profile, blood creatinine, liver function and ECG, having a non-mydriatic fundus camera is preferred. • Insulin is available in storage of essential medicine. • All participating doctors possess smart phones and are capable of using application. • There are 6 potential eligible communities/villages available. • T2D patients who were registered in the essential public healthcare service system and their general information and contact detail are well-documented.
Community/Village	• More than 35 registered patients with established T2D in village. • The village is not involving in any other clinical trial, neither partial nor the whole. There is no m-health based referral system in use. • All participating doctors possess and are capable of using smart phone (iOS 7 or Android 4.4 and above). No difficulty in installing and using applications. • Community or village doctors are willing to participate the trial.
Participants	
Included patient	• With established type 2 diabetes； • Aged 18-75； • Has been living in the community for more than 6 months and no plan of moving out； • Voluntarily recruited and has provided informed consent.
Excluded patient	• Patients with any situation deemed to be inadequate to continue by any investigators; • Women in the process of, or plan for, pregnancy or breastfeeding； • Has been involved in any other clinical trials within 6 months.

Randomisation

Randomisation is performed centrally through an application built-in module in the *ROADMAP Assistant*. The randomization module could only be activated when the baseline assessments of all 6 clusters (communities/villages) within each same district/county is completed. The module automatically assigns these clusters either to intervention or control in a 2:1 ratio (i.e. 4 clusters to intervention, 2 to control).

Interventions

The basic intervention consists of four elements: (i) capacity building for service providers at primary care institutions (PHIs); (ii) team-based contracted standardised services; (iii) mobile-health-based information support, and; (iv) reimbursement for service delivery. An additional *electronic supportive system* intensive component is available to participants with a smartphone who are willing to download an App (*Your Doctor*) to receive messages for health education and allow them to perform real-time communication with their service providers.

Capacity building: A minimum of 2 compulsory structured training sessions aim to better prepare service providers with transferable knowledge and skills to enhance the quality of care. An initial provincial group session, trainers using local dialect introduce concepts, strategies, targets and measurements. This is followed by meetings at district/county levels that provide training to address theoretical and operational barriers to T2D management and screening. County/district investigators receive a package of training materials and a tutorial for periodic review. Investigators in the control group only attend trainings for baseline and final assessment data collection procedures.

The study also addresses problems of facility infrastructure incapacity by providing equipment for blood glucose monitoring toolkits with testing consumables. The toolkit provides a portable electronic glucose meter and smartphone bundle to enable blood glucose readings to be synchronised in real-time to an intervention app, *Graded ROADMAP*, via Bluetooth. Also,

128Hz tuning forks and 10g nylon monofilaments are provided to allow screening for peripheral neuropathy.

Contracted standardised services: A signed service contract between three-tiered care team and community participants aims to inform and engage stakeholders. The care team comprises three doctors/nurses in each primary care clinic and primary care centre and regional medical centre. As frontline healthcare providers, the doctors/nurses at primary care clinics deliver the majority of planned services that include: blood glucose monitoring (at least twice monthly; one fasting blood glucose and one postprandial blood glucose); BP measurement (at least once monthly); body weight measurement (at least twice monthly), diabetic peripheral neuropathy screen (at least once annually); lifestyle and medication counselling; and timely specialist referral as necessary to upstream care centres via the smartphone app, *Graded ROADMAP*. Doctors at medical centres are available to provide advice on management and recommendations regarding admission to hospital.

M-health based information support: All healthcare services, referral requests and responses, and performance reviews in the intervention arm are supported by the *Graded ROADMAP* app, with different levels of access according to levels of service providers. Electronic health information is created for each patient to allow tracking of laboratory results, monitoring of medication changes, and to provide reminders, risk warnings, and notification of referrals. All these data are only accessible within the contracted care team. Those participants who are familiar with smartphone applications are invited to install an app (Your Doctor) that supports health education through the postings of self-management messages, and allows interactive real-time communication. Active users are defined as those with a login to the program at least once monthly.

Reimbursement for service delivery: Modest payments (RMB 55 per participants averagely) are made every 3 months to compensate providers according to the amount of extra work hours of

service delivery and as an incentive for adherence to the program. The performance of a service is appraised by the aggregated data from an algorithm incorporating blood glucose/BP measurements and control, the number of screens for any complication of T2D and necessary referrals.

Usual care

Participants in the control arm will continue receiving usual care throughout the study period. Provision of usual diabetes management at primary care facilities follows current practice under EPHS package.

Outcomes

The primary outcome is the change of HbA1c control rate (at target <7%) from baseline to one year. Secondary outcomes include levels and control rates of ABC (HbA1c <7.0 %, BP <140/80 mmHg and LDL-C <100 mg/dL or 2.6 mmol/L) targets, and fasting blood glucose, episodes of hypoglycaemia (blood glucose <3.9 mmol/L), and mean changes in health-related quality of life on the EQ-5D.

Data collection and management

Table 3 outlines the procedures for collecting baseline and end-of-study data through a secure password protected mobile electronic data capture (mEDC) app, *ROADMAP mEDC*, and by trained investigators who are blinded to allocation and not involved in implementing the intervention. The primary outcome will be obtained from a centrally-distributed point-of-care analysis of HbA1c (A1C EZ 2.0).[19] Anthropometric measurements are taken with the patient barefoot in light clothing. Standard laboratory tests of blood and urine samples, including fasting glucose, lipid profile, creatinine, and kidney function, will be performed by qualified laboratories at regional medical centres. Two extra blood samples (blood biochemistry analysis and HbA1c) and one urine sample from each village will be audited for accuracy. The mEDC

has embedded features to allow logic checks and photography of source documents to support real-time data collection process overseen.

Table 3 Data collection outline of ROADMAP study

Assessment Description	Patient screening	Baseline assessment	End-of-study assessment
Informed consent	X		
Eligibility	X	X	
Reasons for non-participation	X	X	
Demographics, socio-economic status		X	
Medical history, diabetes-related complications screenings		X	X
Anthropometric measurements, physical examination, vital signs		X	X
Diabetes self-management		X	X
Costs of healthcare use		X	X
Medications and treatment adherence		X	X
Laboratory results		X	X
Quality of life questionnaire		X	X
Loss-to-follow-up/drop-out questionnaire			X

All data collection, storage and reporting conforms to China privacy laws, and individual participant identifiers are encrypted and masked. The study will be monitored regularly by an independent data management team at The George Institute for Global Health. All the data collected and reported is compliant with China privacy laws and without individual participant identification. Feedback and queries raised on data integrity, authenticity and accuracy, as well as schedule management, are achieved using unique identifier reporting. Only aggregated/de-identified data will appear on reports or publications generated from the study. Any participant-level dataset sharing with other parties will be recorded and formulated in written contractual agreements.

Sample size estimation

This study aims to recruit 19,008 patients with T2D from 864 communities in 24 provinces in China, which equate to 22 patients from each community. Accounting for potential loss to follow-up of 14%, a sample size of 16416 participants (10944 in intervention and 5472 in control groups, with 2:1 ratio) at one year will provide a power of 89% (2-sided α 0.05) to detect a ≥5% absolute increase in the primary outcome in the intervention group. The sample size calculation assumes that 40% of participants will have well controlled HbA1c (< 7%) at the end of the study in the control group,[6] with an intra-class correlation coefficient of 0.15 based on our previous ORBIT study.[20] Furthermore, we expect that 50% (5472) of participants in the intervention group will possess smartphones and be active users of the Your Doctor app, thus forming an intensive intervention subpopulation (i.e. a smaller cluster size of 9 participants), which will provide 86% and 99% power to detect absolute increases of 5% and 10% of HbA1c control, respectively, compared to the control group.

Project management

A trial monitoring website presents aggregated regional routinely collected data on community/township/county/provincial levels of intervention clusters to allow researchers, investigators and doctors in the intervention group to monitor the fidelity of intervention and study progress. Central and on-site monitoring of the accumulating data is undertaken by the project management team. All required qualification assessments for institutions/personnel involved in the study, including their training and investigative procedures, are recorded and photographed for reference. During each site visit, local investigators and trial staff assist research monitoring in verifying patient eligibility, data authenticity and implementation consistency, schedule compliance, and in providing all relevant source documents.

Outcome analysis

All analyses will be undertaken at the participant level and based on the intention-to-treatment principle. The primary analysis will be unadjusted, but adjusted analyses can also be undertaken on the primary and secondary outcomes. The primary endpoint, adequate control of HbA1c at 12 months, will be analysed using log-binomial regression with generalized estimation equation (GEE) to account for clustering within communities. Pre-specified subgroup analyses will be conducted according to economic development level of province, urban/rural areas, and basic/intensive intervention. A similar method will be applied for the secondary binary outcomes. Linear regression with GEE will be used for all continuous variables. No adjustment will be made for multiplicity, as will only a small number of efficacy outcomes and most of them are correlated.

Process evaluation

Given the widespread geographical coverage of participating sites, there are likely to be differences in the update of the ROADMAP intervention across different regions. A process evaluation is therefore incorporated to identify implementation barriers and its acceptability to improve the quality of implementation and intervention fidelity. A mixed method approach will be adopted to assess routinely collected data analysed to assess the amount of delivered services against the protocol (e.g. blood glucose/pressure monitoring data) and qualitative data through stakeholder interviews.

Economic evaluation

This will assess cost-effectiveness/utility from a health sector perspective, with a trial-based component and beyond-trial modelled evaluation of long-term costs and benefits, assessed an incremental cost effectiveness ratio. The within-trial cost includes direct input of intervention costs on trainings, blood glucose testing device and consumables, information system development and maintenance, and service reimbursement, as well as health care use during

intervention period. The effectiveness/utility will be according to the change on HbA1c within one year, and modelled on health-related quality of life based on the literature for the relationship of HbA1c reduction and prevention of T2D complications and improved health-related quality of life. Sensitivity analyses will be carried out to examine different scale-up scenarios in different strata.

Governance

Execution of the study is managed by a working group under the supervision of a Steering Committee, chaired by the lead principal investigators (PI) and representatives of the Chinese Diabetes Society (CDS) and central government. The working group comprises delegates of China representative office of The George Institute for Global Health, CDS, Bethune Charity Foundation and provincial investigators.

Trial status

After the launch of pilot phase in March 2017, the first provincial site for the main study was initiated on 2 June, 2017. Up to December 2018, 19,149 participants had been validly recruited from 864 communities in 144 districts/counties in 25 participating provinces (one more province than the scheduled 24 due to difficulty in finding a sufficient eligible district/ county hospital). Baseline assessments are complete and the intervention has commenced in 576 communities from 25 provinces. The final end-of-study assessment is due in August 2019 and database lock is anticipated for September 2019.

Involvement of doctors and patients

Regional PIs and doctors from PHIs have had input into the study design, pilot testing phase and implementation of the intervention through roundtable and periodical national/regional review meetings. Participating doctors are informed of study progress through monthly newsletters and progress reports. Patients with T2D in different areas have been interviewed for needs analysis at the preparatory and pilot phases, and will be interviewed again about

implementation barriers and facilitators as part of a process evaluation at the end of the study. To encourage active engagement, participants receive their results from baseline and end-of-study assessments. The main results of the study will be disseminated to doctors and participants to boost community involvement in T2D management beyond the study.

ETHICS AND DISSEMINATION

Ethics committee approval was obtained from the Institutional Review Board at Shanghai Sixth People's Hospital, where the lead PI is affiliated with, before the study commenced. Written approval from each participating site was granted by the local hospital research ethics committee, and other relevant regional regulatory bodies. Signed informed consent is obtained from all trial participating doctors and patients prior to participant recruitment. Findings from this study will be widely disseminated through peer-reviewed journals, conference presentations, social media, and other mechanisms.

DISCUSSION

We outline the design for a large cluster clinical trial which is evaluating the effectiveness of an innovative 4-in-1 T2D management model of care in China that is expected to generate evidence for future scale up. Given the disparities in care according to different contexts, the study areas are randomised according to stratification of developed urban or rural, or less-developed urban or rural. The large sample size will enable us to test the effectiveness of the intervention overall and across each strata, and will intend to collect information on the barriers and facilitators of the intervention to better for an understanding of its implementation and future scale up.

As all participants have been randomly recruited from lists of those T2D in the community, they are likely to be broadly representative of those with the condition in the real-world and thus enhance the generalisability of the results. The study is provides a unique opportunity to assess the epidemiology of established T2D and its management and complications in China. We recognise, however, that our findings may not be extrapolated to those with undiagnosed or unregistered T2D.

Intervention fidelity is a major challenge, especially considering the complexity of ROADMAP, the number of study sites, and the shortage in qualified PHI workforce. M-health technology-mediated strategies have therefore been developed and applied to prevent and address inconsistencies which may occur throughout the implementation. Research quality is further challenged because the research is mainly carried out at the grassroots level where most researchers have limited experience in research. The use of mEDC system facilitated the conduct of the study with standard procedures and quality control checks. For pragmatic reasons, study sites were initiated in stages, which allowed lessons learnt to be transferred sequentially.

Taking account of the diversity of the population under investigation, ROADMAP offers a unified, portable, centrally assessed, instrument for managing HbA1c, thus avoiding measurement error arising from the use of multiple devices/systems. However, caution is warranted in comparisons of routinely collected blood and urine testing through difference methods and laboratory skills across laboratories at county hospitals.

We chose one year as the duration of the intervention but there is the risk of that unexpected temporal changes in regional policy adjustments around the services and financing of primary healthcare services could influence the interpretation of the outcomes. We anticipate that our findings and implementation processes from this real world trial will help improve our primary health care system, and result in improvements of the management of T2D in China.

Abbreviations: ROADMAP: Road to Hierarchical Diabetes Management at Primary Care Settings in China; HbA1c: glycated haemoglobin; EQ-5D: European Quality of Life 5-Item questionnaire; T2D: type 2 diabetes mellitus; BP: blood pressure; LDL-C: low-density lipoprotein cholesterol; EPHS: essential public health services; CHS: community healthcare service; mEDC: mobile electronic data capture; PHI: primary care institution; GEE: generalized estimation equation; PI: principle investigator.

Authors' contributions: WJ and PZ conceived the project, designed the study, equally. All authors contributed to the development of the intervention and evaluation. ND and PZ wrote the first draft of the manuscript. YL led the development of the electronic systems involved in ROADMAP intervention and trial management. XL was the statistician of the study. All authors contributed to the refinement of the study protocol and approved the final manuscript.

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Competing interests: None declared.

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Figure Legend

Figure 1 Flowchart of the ROADMAP study

Supplementary

Appendix: Structure of primary care system in China

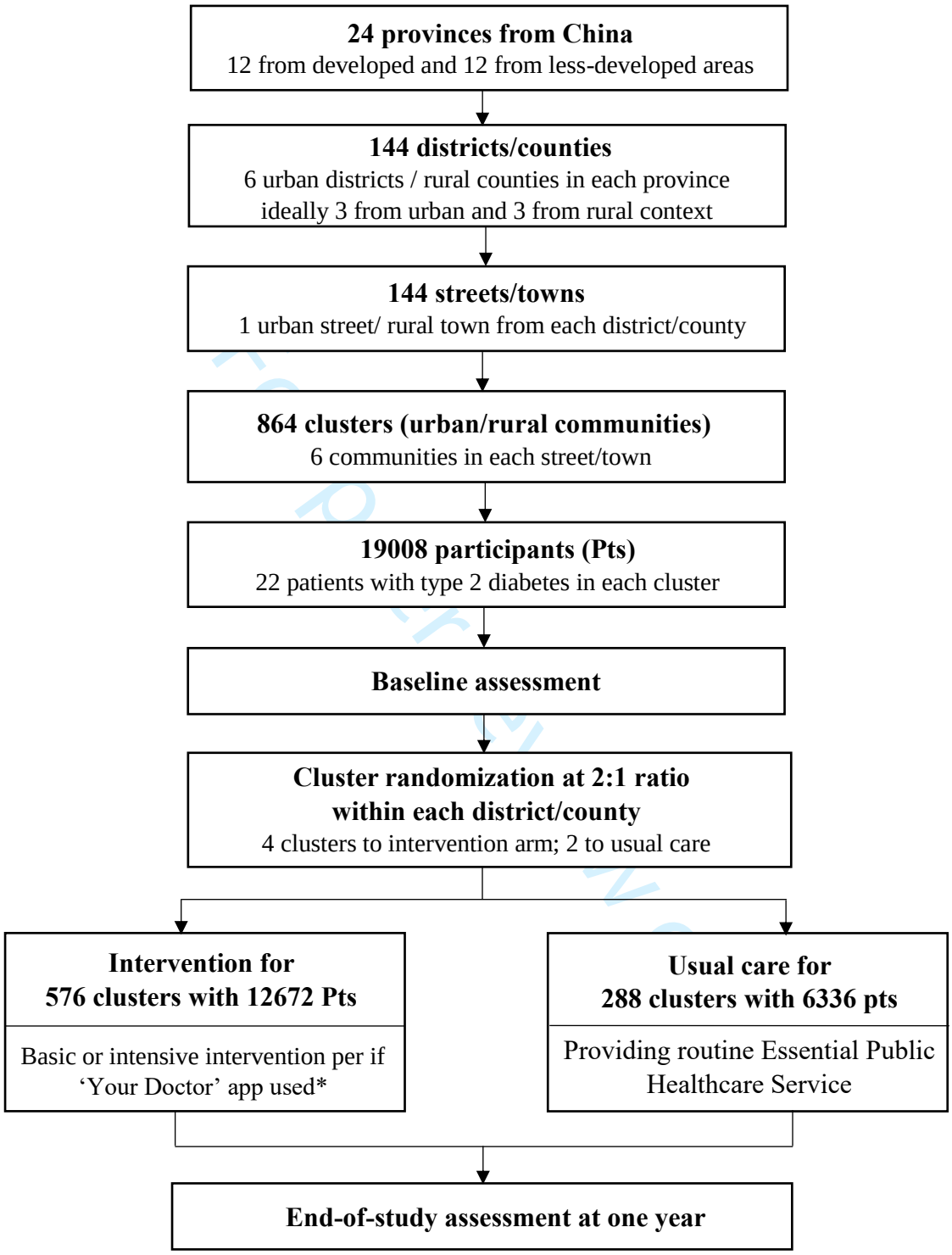

Figure 1 Flowchart of ROADMAP study

*Your Doctor app is available for those participants who possess a smart phone and capable of using applications, enabling health education and real-time communication with doctors. Patients who have used 'Your Doctor' app will be treated as receiving intensive intervention.

Supplementary appendix: Structure of primary care system in China

As shown in the figure below, the primary healthcare system in China is designed to provide the EPHS and generalist clinical care through differently organized urban and rural components. Supervised by the county/district government, mostly through a division of the Health Commission, the primary healthcare system mainly consists of a township hospital and its satellite village clinics in a rural town, or a community healthcare service (CHS) centre and its subordinated CHS stations in an urban street. Nearly one thirds of CHS stations and village clinics are privately (or jointly) owned while majority of PHIs are government-funded. The EPHS are provided either through publicly-owned PHIs by direct governmental subsidises or private PHIs consuming government purchased services. The county/district health commission, or delegated CDC, supervises and evaluates the performance of EPHS of entire county/district. The involvement of county/district hospitals in EPHS is increasing but still remain incompact. One township in rural area or a street in urban area is commonly composed of 5-30 communities, each community usually consists a population of more than 1000 dwellers. (Ref: People's Republic of China health system review. Manila: WHO Regional Office for the Western Pacific; 2015)

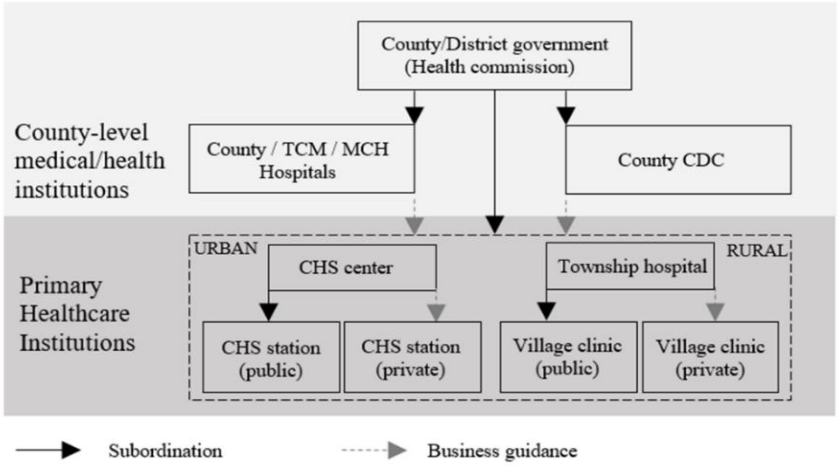

Figure Structure of primary care system in China

* TCM: Traditional Chinese Medicine; MCHI: Maternal and Children Health Institution; CDC: Centre of Disease Control and prevention; CHS: Community Healthcare Service.

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	Yes, ChiCTR
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1&18
	5b	Name and contact information for the trial sponsor	18
	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	15&18
	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)	13&14&15

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	1
	6b	Explanation for choice of comparators	1
Objectives	7	Specific objectives or hypotheses	1
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)	2
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	2
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)	7&8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-11
	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)	8
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	13&14
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
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	11
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)	10&15

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	13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7&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	9
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	9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7&9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	16
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	11&12, further details are available on request
	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	Available on request

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	11-14
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	14&15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
	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)	14
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	13&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	N/A
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	12
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13&14
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	16
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)	16

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8&16
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
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	11&12
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
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	12&16
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	Not applicable
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	12&15&16
	31b	Authorship eligibility guidelines and any intended use of professional writers	16
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	12
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Available on request
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	11&12

*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.

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A study protocol for the ROAd to hierarchical Diabetes Management At Primary care (ROADMAP) study in China: a cluster randomised controlled trial

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Keywords:	DIABETES & ENDOCRINOLOGY, PRIMARY CARE, PUBLIC HEALTH

A study protocol for the ROAd to hierarchical Diabetes Management At Primary care (ROADMAP) study in China: a cluster randomised controlled trial

Weiping Jia[1,2]*, Puhong Zhang[3,4]*, Nadila Duolikun[3], Dalong Zhu[5], Hong Li[6], Yuqian Bao[1], Xian Li[3,4], Yu Liu[7], ROADMAP study group

[1] Shanghai Jiaotong University Affiliated Sixth People's Hospital, Shanghai 200233, China.

[2] Chinese Diabetes Society, Beijing 100710, China

[3] The George Institute for Global Health at Peking University Health Science Centre, Beijing 100088, China.

[4] The George Institute for Global Health, Faculty of Medicine, University of New South Wales, NSW 2050. Australia

[5] Department of Endocrinology, Drum Tower hospital affiliated to Nanjing University Medical School, Nanjing 210008, China.

[6] Department of Endocrinology, Sir Run Run Shaw Hospital Affiliated to School of Medicine, Zhejiang University, Hangzhou 310016, China.

[7] School of Computing, Beihang University, Beijing 100191, China

***Joint first author**

Correspondence to:
Professor Weiping Jia
Institution: Shanghai Diabetes Institute, Shanghai Clinical Centre for Diabetes, Shanghai Key Laboratory of Diabetes Mellitus, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China
Address: 600 Yishan Road, Shanghai 200233, P.R.China
E: wpjia@sjtu.edu.cn;
T: 86-21-64369181ext 8922;
F: 86-21-64368031

Keywords: Type 2 diabetes, management, primary care, cluster trial, mobile health.

Word count: 3734

ABSTRACT

Introduction: Diabetes management in primary care remains suboptimal in China, despite its inclusion in the Essential Public Health Service (EPHS). We aimed to evaluate the effectiveness of a mobile health (mHealth) based and three-tiered diabetes management system in diverse Chinese contexts.

Methods and analysis: This is a cluster randomised controlled trial, named ROAd to hierarchical Diabetes Management At Primary care (ROADMAP). 19008 patients with type 2 diabetes (T2D) were recruited from primary care clinics in 864 communities across 144 counties/districts of 24 provinces. Eligible participants were adult patients diagnosed with T2D and registered for diabetes management in communities. Patients within the same communities (clusters), were randomly allocated into the intervention or control arm for one-year in a 2:1 ratio. The control arm patients received usual care as EPHS packaged: at least four blood glucose (BG) and blood pressure (BP) tests, and lifestyle and medication instruction, yearly, from primary care providers. The intervention arm patients received at least two BG and one BP tests, monthly, and lifestyle and treatment instruction from a three-tiered contracted team. A mHealth platform, *Graded ROADMAP,* enabled test results uploading and sharing, and patient referral within the team. The intervention participants will be further divided into basic or intensive intervention group according to whether they were actively using the *Your Doctor* App. The primary outcome is the BG control rate with glycated haemoglobin (HbA1c) <7.0%. Secondary outcomes include control rates and changes of ABC (HbA1c, BP and LDL-c) and fasting BG, hypoglycaemia episodes, and health-related quality of life (EQ-5D).

Ethics and dissemination: The trial has been approved by the Institutional Review Board at the Shanghai Sixth People's Hospital. Findings on the intervention effectiveness will be disseminated through peer-reviewed journals, conference presentations and other relevant mechanisms.

Trial Registration: The study is registered at Chinese Clinical Trial Registry (ChiCTR-IOC-17011325).

ARTICLE SUMMARY

Strengths and limitations of this study

- This is a large-scale cluster clinical trial being implemented in diverse primary care settings of most provinces in China. The sample size allows for a formative evaluation of a complex service intervention overall, and in subgroups of developed and less-developed, urban and rural regions.
- A standardised 4-in-1 comprehensive management package is designed to empower the capabilities of primary care to improve the overall diabetes management in real-world settings beyond this study.
- The intervention delivery is supported by 2 designated mobile based information system (*Graded ROADMAP, Your Doctor*), recording the condition of participants, receipt of services and health education and communications, to ensure the continuum of care with secure access.
- A centrally-distributed, portable instrument was applied for measuring the primary outcome, HbA1c, playing a role as a centralized laboratory, thus ensuring the comparability of HbA1c level.
- We suggest caution in generalising any intervention benefits to the broader diabetes population, since the recruitment is limited to people with diagnosed type 2 diabetes registered for receiving services under the Essential Public Health Service Package in China.

INTRODUCTION

Type 2 diabetes (T2D) imposes major morbidity, mortality and financial burden across all health systems.[1-3] Globally, there are an estimated 425 million people with T2D and one fourth of them reside in China where enormous challenges of diabetes management exist given the large population across diverse settings.[1, 4-6] Although an Essential Public Health Services (EPHS) package, with annual increases in governmental subsides[7] was introduced to provide universal access to services for patients with chronic diseases in primary care in China in 2009,[8] considerable gaps in care remain. The EPHS packaged services are delivered by primary care providers through community healthcare service (CHS) centres (sub-district level) and stations (community level) in urban areas, and township hospitals and village clinics in rural areas. Management of those with T2D is an explicit focus of the EPHS package.[4, 9] By 2017, there were over 9100 CHS centres, 25500 CHS stations, 36 500 township hospitals and 632 000 village clinics in operation nationwide.[10] (Further structural details of the primary care service delivery in China is available in supplementary appendix 1). Patients registered for T2D management of EPHS are entitled to at least four free blood glucose (BG) tests, and consultations for treatment and lifestyle advice each year.[7] Despite an increasing number of patients receiving T2D management services, from 18.5 million in 2011 to 31.2 million in 2017,[11] fewer than 40% of had adequate BG control (HbA1c <7.0%),[12] with only 6% achieving optimal control of combined ABC (HbA1c, blood pressure [BP] and low density lipoprotein [LDL-C]) targets.[13]

Achieving effective T2D management is heavily dependent on an organised and responsive primary care system.[14, 15] Inadequate capacity of primary healthcare providers, inefficient resource utilization, and most importantly, fragmented delivery of care, have been identified as major challenges in primary care that have potentially impeded the improvement in diabetes control.[4, 16-21] It is reported, over 25% of doctors at CHS centres and 45% at township hospitals have not reached the educational requirement for a licensed assistant doctor. Twelve percent of village clinic doctors were below the

required education level for their position and one-third of primary healthcare providers do not receive annual training, a requirement of the authorities.[4] A skills shortage as a result of inadequate education and training contributes to poorer quality care, partially explaining why patients tend to bypass primary care facilities and present to hospitals.[22] Also, the fragmentation of the service delivery system and a lack of interoperable information systems, have hindered the integration of the primary care and specialty care in secondary and tertiary hospitals, obstructing the coordination and continuum in care.[4]

In 2015, national guidelines promoting a graded diagnosis and treatment system was introduced[23] in China, in line with the Healthy China 2030 policy[24] to establish a cooperative, hierarchical health service system. Whilst evidence on the effectiveness of mHealth-based strategies which involve service delivery design to improve diabetes management are demonstrated,[25-31] its adaptability in primary care facilities varies across different economic contexts and regions.[32, 33] We therefore outline the protocol for a study with the aim of evaluating the effectiveness of a mHealth-based, service-delivery intervention in a cluster randomised controlled trial called ROAd to hierarchical Diabetes Management At Primary care (ROADMAP). The intervention follows the recommendations from the Chinese Diabetes Society guideline [34] to empower primary care providers in a collaborative tiered care system with a mobile-based health information and referral management system to deliver standardized services for patients with T2D in China.

METHODS AND ANALYSIS

Trial design and study contexts

ROADMAP is a community-based, cluster randomised controlled trial, comparing the effectiveness between the proposed intervention and the usual care on diabetes management in diverse primary care settings (Figure 1). Within the intervention arm, participants will be further divided into basic

and intensive intervention subgroups, based on whether an optional health education smartphone application is used. The trial will be conducted in over 800 communities in more than 20 provinces of China. To better integrate clinical services and primary care, the implementation of the trial involves three tiers of healthcare institutions: regional medical centres (tier Ⅲ: hospitals at urban district/rural county level), primary care centres (tier Ⅱ: [CHS] centres at urban sub-district/ township hospitals at rural town level) and their subordinate primary care clinics (tier Ⅰ: urban CHS stations and rural village clinics at level of community [also refer to village in rural area hereinafter]).

Study sites selection and participants

Table 1 details the inclusion/exclusion criteria for study sites selection at multiple levels, including provincial, district and county level, sub-district and town level, and community level. 24 provinces will be selected nationally. In general, 6 counties, and 6 of its subordinate communities from each county will be selected in each province. In each community (cluster), an average of 22 participants will be selected at random via a purpose-built website from a full list of T2D patients, normally with over 50 registrants, from local EPHS recipient registry in each community.

Participants will be patients with diagnosed T2D and registered for receiving EPHS in the participating communities. Individuals are eligible for enrolment if they meet following inclusion criteria: aged 18-75 years; residing in the community for the last 6 months with no plan of relocating; voluntary participation with informed consent. Patients will be excluded if: they had severe physical or psychological problems; were unable to attend the site visit; unable to consciously answer questions; were women in the process of, or planning for, pregnancy or breastfeeding; and those who have participated in any other clinical trials within the last 6 months.

Table 1 Eligibility criteria for study sites in ROADMAP study

Study site at different levels	Eligibility criteria description
Province	• At least one provincial principal investigator with high impact in diabetes research is available and approved by ROADMAP working group. • Provinces planning to develop or have had established a primary healthcare service based on electronic referral system will be excluded due to a potential technological conflict.
District/County	• County hospitals should be the main healthcare providing institution rather than tertiary hospitals to avoid affecting the process of patient referral and future impact evaluation. • There is no generalized m-health-based referral system in place, and an adequate level of community healthcare facilities and service is available. • Local health authorities are aware of, support and are willing to be involved with the trial, anticipating to become an exemplary centre of diabetes management. • There is at least one diabetes specialist able to take the role of county principal investigator/doctor to deliver training, support treatment and receive referral, as well as one county coordinator to facilitate trail implementation and fidelity assurance, also manage local study funds. • There are at least one eligible sub-districts/towns available within each district/county. • Legitimate healthcare facility that can provide formal invoices for all trial-incurred transactions.
Sub-district/Town	• The methods and instruments are readily available to perform high-quality laboratory tests, including: plasma glucose test, routine urinalysis, lipid profile, blood creatinine, liver function and ECG, having a non-mydriatic fundus camera is preferred. • Insulin is available in storage of essential medicines. • All participating doctors possess smart phones and are capable of using applications. • There are 6 potential eligible communities available within each sub-district/town. • T2D patients registered in the essential public healthcare service system have documented general information and contact details.
Community	• More than 35 registered patients with diagnosed T2D in community. • The community is not involved in any other clinical trial. There is no m-health based referral system in use. • All participating doctors possess and are capable of using smart phone (iOS 7 or Android 4.4 and above). No difficulty in installing and using applications. • Community doctors are willing to participate the trial.

Randomisation

Randomisation will be performed centrally via a password-protected, encrypted smartphone application interface, stratified by provincial ranking of GDP per capita in fiscal year of 2017 [35], with upper and lower half categorized as developed and less-developed, respectively, and locality including urban and rural areas as per national administrative area category in 2017. Following baseline data collection, these 6 communities (i.e. clusters) will be randomized to either receive the intervention or continue with usual care in a 2:1 ratio (i.e. 4 clusters to intervention, 2 to control).

Interventions

The basic intervention consists of four elements: 1) capacity building for service providers at primary care facilities; 2) team-based contracted standardised services; 3) mobile-health-based information support, and; 4) reimbursement for service delivery. The basic intervention elements are elaborated in the next paragraph. There is an additional intensive component available to participants with smartphones willing to use *Your Doctor*. *Your Doctor* is a smartphone application supporting health education (examples are available in the supplementary appendix 2) and treatment instruction through real-time within-app interaction between the patients and their contacted doctors. Active users are defined as those with a login to *Your Doctor* at least 6 times throughout the one-year study period. At the end of study, participants in the intervention arm will be divided into two groups (basic or intensive), based on their level of activity on *Your Doctor.*

Capacity building: Two compulsory structured training sessions will be held at the provincial and county level. The initial provincial level training session is for doctors from participating county hospitals. This will be followed by training at the district/county level, where the qualified trainers provide training for the sub-district/township and community doctors. The training materials were developed by the working group based on current

diabetes guidelines, with the purpose of upskilling service providers by addressing theoretical and operational barriers to T2D management and treatment in primary care settings. The contents include: 1) diabetes epidemiology and economic burden; 2) classification and diagnosis of diabetes; 3) hierarchical diagnosis and treatment of diabetes; 4) diabetes lifestyle intervention; 5) diabetes medication; 6) BG monitoring; 7) diabetic retinopathy; 8) diabetic nephropathy; 9) diabetic peripheral neuropathy; and 10) diabetic lower limb vascular diseases. The trainings are standardized to ensure the service would be delivered in the same manner. A package of training materials, including a set of PPT slides and videos, will be sent to all doctors in the intervention arm for periodic review. Investigators in the control arm will only attend trainings for subject recruitment and data collection procedures for baseline and end-of-study assessments.

Team-based contracted services: A three-tiered care team will be assembled for each participating community. The team members comprise of three doctors respectively from the primary care clinic, primary care centre, and regional medical centre. The primary care doctors will play a key role in routine contacting, monitoring and evaluation, service delivery and lifestyle instructions to the patients. Doctors in the regional medical centres will provide further consultation or treatment if referred to. A service contract will be signed between the care team doctors and participants to acknowledge the engagement and inform stakeholders' responsibilities. (A full list of contracted services are available in the supplementary appendix 3.) The planned services are listed in Table 2 with comparison to those in EPHS as usual care.

Table 2. Diabetes management related training, technical support and health services provided for intervention and control arms

Items	Control arm (usual care per EPHS)	Intervention arm (Strengthened care in addition to EPHS)
Capacity building for primary care providers	Provided by local health bureau, aims to implement EPHS, no national standard training material.	Trained by qualified trainers using national standard training materials, addressing major gaps in knowledge and skills in diabetes management, including diabetic peripheral neuropathy screening.
Technical support	Equipped with BG meter, BP monitor, and body weight/height scale. Mostly equipped with electronic medical record system but unable to communicate with local medical centres.	Equipped with (1) a portable electronic BG meter which enables the test result uploaded to an electronic information platform in real-time; (2) *Graded ROADMAP*, the platform, developed by the working group, acts as an electronic medical record system with features of communication with electronic BG monitors and patient referral among doctors in the same care team; and (3) a set of 128Hz tuning forks and 10g nylon monofilaments used to screen peripheral neuropathy.
Basic BG monitoring	At least four times of fasting BG test per year	Monthly or more frequently, ideally one fasting and one postprandial BG each time, emphasized as compulsory, with the hypothesis that the increased BG monitoring can improve behaviour change and medication activities.
Basic BP monitoring	At least four times per year	Monthly or more frequently, emphasized as compulsory.
Diabetic peripheral neuropathy screening	Not required	At least once per year with the hypotheses that (early) knowledge of diabetes complications can improve the adherence to diabetes control. This was suggested to start at the beginning of intervention.
Diet, physical exercise and medication instruction	Each time during face to face visit	Face to face, together with remote(online) communication through "Your Doctor", an App supporting health education and treatment instruction through interactive real-time communication between the contacted doctors and patients (intensive intervention sub-group).
Patient referral	Major indications: 1) BG remains uncontrolled for two consecutive visits; 2) adverse drug reactions does not improve after two consecutive visits; or 3) new or aggravated complications. Pathway: no designated pathway, patients can seek service from any doctor in any hospital according to their wishes.	Indications: similar to those in control arm. Pathway: through the App of "*Graded ROADMAP*" with the hypotheses that the referral with contracted team through the mHealth platform and largely improve the referral and diabetes control. This App has different end-users. A primary care doctor can make the appointment for the patient by selecting a referral doctor (usually the doctor in the same team) and date based on the availability of upstream doctors and wishes of patients. The medical record, including the trend of BG and medications could be accessed by all the authorized doctors.

EPHS: Essential Public Health Service; BG: blood glucose; BP: blood pressure.

M-health based information support: Most intervention activities will be carried out by or through *Graded ROADMAP* App (some user interfaces are displayed in the supplementary appendix 4), including medical information recording, BG/BP monitoring, processing of referral requests and responses (referral indications are available in the supplementary appendix 5), and performance reviews. The user ends vary with the services provided by different users. Patient data are only accessible within the contracted care team to ensure the continuum in care. For intensive group patients, *Your Doctor* App will be used to share their BG/BP results and interact with their doctors for better diabetes control.

Reimbursement for service delivery: Non-mandatory seasonal payments, RMB 55 per participant averagely, are suggested every 3 months to compensate care providers' extra work hours for additional service delivery and also serve as a "fee for performance" incentive for protocol compliance. The performance of the service is appraised by the aggregated data from an algorithm incorporating BG/BP measurements and control, the number of screening for any complication of T2D and necessary referrals. The amount of the reimbursement is capped at RMB 220 Yuan for each patient per year. It is estimated to be equivalent to one-tenth of per capita public input for EPHS, which is acceptable by the government if the intervention is effective.

To sum up, with support of *Graded ROADMAP*, the key and fundamental intervention in our study is to offer the patients with access to more frequent BG and BP monitoring services, and followed by corresponding instructions on lifestyle modification and medication treatment.

Usual care

Participants in the control arm will continue receiving usual care provided by primary care facilities, as per EPHS regulations. For community patients with T2D, the key services provided by primary care facilities were presented in Table 2. Several other related services in EPHS include developing personal health records, updating health records after follow-ups,

population based health education, health management for the elderly with annual services including lifestyle and health assessment, physical examination, and health guidance for the elderly over 65 years of age, and hypertension management also included in Table 2.[7] Theoretically, all services provided to usual care were also delivered to the intervention arm.

Outcomes

The primary outcome is the change of BG control rate with glycated haemoglobin (HbA1c) <7.0% between baseline and one year follow-up. Secondary outcomes include levels and control rates of ABC (HbA1c <7.0 %, BP <140/80 mmHg and LDL-C <2.6 mmol/L) targets, and fasting BG (FBG <7.0 mmol/L), episodes of hypoglycaemia (BG <3.9 mmol/L), and mean changes in health-related quality of life on the EQ-5D.

Data collection and management

Table 3 outlines the procedures for collecting baseline and end-of-study data through a secure password protected mobile electronic data capture (mEDC) App. The data collecting investigators who are unware of the allocation are trained and not involved in intervention implementation. The primary outcome will be obtained from a centrally-distributed HbA1c analyser (A1c EZ 2.0) for point-of-care testing.[36] Anthropometric measurements are taken with the patient barefoot in light clothing. Standard laboratory tests of blood and urine samples, including fasting glucose, lipid profile, creatinine, and kidney function, will be performed by qualified laboratories at regional medical centres. Two extra blood samples (blood biochemistry analysis and HbA1c) and one urine sample from each village will be audited for accuracy. The mEDC has embedded features to allow logic checks and photography of source documents to support real-time data collection process overseen.

Table 3 Data collection outline of ROADMAP study

Informed consent	X		
Eligibility	X	X	
Reasons for non-participation	X	X	
Demographics, socio-economic status		X	
Medical history, diabetes-related complications screenings		X	X
Anthropometric measurements, physical examination, vital signs		X	X
Diabetes self-management		X	X
Costs of healthcare use		X	X
Medications and treatment adherence		X	X
Laboratory results		X	X
Quality of life questionnaire		X	X
Loss-to-follow-up/drop-out questionnaire			X

Data collection, storage and reporting conforms to China's privacy laws. Individual participants are encrypted and de-identified. Feedback and queries raised on data integrity, authenticity and accuracy, as well as schedule management, are achieved using unique identifier reporting. Findings raised from this study will be reported without individual participant identification.

Project management

A trial monitoring website presents aggregated regional routinely collected data on community/township/county/provincial levels of intervention clusters to allow researchers, investigators and doctors in the intervention group to monitor the intervention fidelity and study progress. Central and on-site monitoring of routinely collected data is undertaken by a project management team. All required qualification assessments for institutions/personnel involved in the study, including their training and investigative procedures, are recorded and photographed for reference. During each site visit, local investigators and trial staff assist research monitoring in verifying patient eligibility, data authenticity and implementation consistency, schedule compliance, and in providing all relevant source documents.

Sample size estimation

This study aims to recruit 19,008 patients with T2D from 864 communities in 24 provinces in mainland China, which equates to 22 patients from each community. Accounting for potential loss to follow-up of 14% in patients, a sample size of 16416 participants (10944 in intervention and 5472 in control groups, with 2:1 ratio) at one year will provide a power of 89% (2-sided α 0.05) to detect a ≥5% absolute increase in the primary outcome in the intervention group. The sample size calculation assumes that 40% of participants will have well controlled HbA1c (< 7%) at the end of the study in the control group,[13] with an intra-class correlation coefficient of 0.15 based on our previous ORBIT study.[37] Furthermore, assuming that 50% (5472) of participants in the intervention group will possess smartphones and become active users of the *Your Doctor* App at their discretion, thus forming an intensive intervention subpopulation (i.e. a smaller cluster size of 9 participants), which will provide 86% and 99% power to detect absolute increases of 5% and 10% of HbA1c control, respectively, compared to the control group.

Outcome analysis

All analyses will be conducted at the participant level following the intention-to-treat principle. The primary endpoint, adequate control of HbA1c at one year, will be compared between all intervention groups and all control groups. The primary analysis of the intervention effect will be conducted by using a log-binomial regression with generalized estimating equations (GEE) to account for clustering within communities with adjustment of baseline HbA1c as a continuous covariate. Secondary analyses will include 1) covariate-adjusted analyses, on the primary outcome, 2) comparison of the intensive vs. basic intervention groups by exploring if there is an additional effect from intensive intervention, and 3) subgroup analyses. A detailed statistical analysis plan is anticipated to be published prior to database lock or attached to the main paper.

Process evaluation

Given the widespread geographical coverage of participating sites, the staffing model and implementation of the ROADMAP intervention may differ across different regions. A process evaluation will be conducted during implementation to assess the compliance of each intervention component and identify the implementation barriers and facilitators, also the acceptability to improve the implementation quality and intervention fidelity. A mixed-methods approach will be adopted using routinely collected data (e.g. BG/BP monitoring data) and stakeholder interviews. The lessons from different regions with different staffing models will be helpful to guide the future intervention diffusion to different primary care settings.

Economic evaluation

The economic evaluation will assess cost-effectiveness/utility from a health sector perspective, with a trial-based component and beyond-trial modelled evaluation of long-term costs and benefits, assessed using an incremental cost effectiveness ratio. The within-trial cost will include intervention costs on trainings of staff, BG testing device and consumables, information

system development and maintenance, and service reimbursement, as well as healthcare use during the trial period. The effectiveness/utility will be according to the change on HbA1c within one year, and modelled on health-related quality of life based on the literature for the relationship of HbA1c reduction and prevention of T2D complications and improved health-related quality of life. Sensitivity analyses will be carried out to examine different scale-up scenarios in different strata.

Governance

Execution of the study is managed by a working group under the supervision of a Steering Committee, chaired by the leading principal investigators (PI) and representatives of the Chinese Diabetes Society (CDS) and central government. The working group comprises delegates of China representative office of The George Institute for Global Health, CDS, Bethune Charity Foundation and provincial investigators.

Trial status

After the launch of the pilot phase in March 2017, the first provincial site for the main study was initiated on 2 June, 2017. Up to December 2018, 19,149 participants had been validly recruited from 864 communities in 144 districts/counties in 25 participating provinces. One more province was recruited due to the difficulty in finding sufficient eligible district/ county hospitals as planned in 24 provinces. Baseline assessments are complete and the intervention has commenced in 576 communities from 25 provinces. The final end-of-study assessment is due in October 2019 and database lock is anticipated for December 2019.

Patient and public involvement

Regional investigators and doctors from primary care facilities have had input into the study design, the development of the intervention tools, pilot testing phase and implementation of the intervention through roundtable and periodical national/regional review meetings. Participating doctors will be informed of study progress through monthly newsletters and progress reports.

Patients with T2D in different areas have been interviewed for needs analysis at the preparatory and pilot phases, and will be interviewed again about implementation barriers and facilitators and the burden of their participation as part of a process evaluation at the end of the study. To encourage active engagement, participants receive their results from baseline and end-of-study assessments. The main results of the study will be disseminated to doctors and participants to boost community involvement in T2D management beyond the study.

ETHICS AND DISSEMINATION

Ethics committee approval was obtained from the Institutional Review Board at Shanghai Sixth People's Hospital, where the leading PI is affiliated with, before the study commenced. Written approval from each participating site was granted by the local hospital research ethics committee, and other relevant regional regulatory bodies. Signed informed consent is obtained from all trial participating doctors and patients prior to participant recruitment. Findings from this study will be widely disseminated through peer-reviewed journals, conference presentations, social media, and other mechanisms.

DISCUSSION

We outline the design for a large cluster clinical trial to evaluate the effectiveness of an innovative 4-in-1 T2D management model of care in China, to generate evidence for future scale up. Given the disparities in care under different contexts, the study areas are randomised according to stratification of developed or less-developed, urban or rural areas. The large sample size will enable us to appraise the effectiveness of the intervention overall and across each strata. Meanwhile, information collected on the barriers and facilitators of the intervention will better inform post-evaluation implementation and future scale up.

ROADMAP is complex in the intervention design per se, and its implementation. We prepared for almost two years to develop and pilot the intervention as well as the project management and data collection system with the involvement of local doctors, patients and project manager. To make the one year intervention implemented successfully, we did not launch the project in 25 provinces (the plan was 24 provinces) in parallel, but launched one by one within a whole year, allowing lessons learnt to be transferred sequentially. Due to the limited research implementation experiences of most primary care investigators, it causes great challenges to ensure the quality of research implementation at the grassroots level. The use of two mobile phone based project management and data collection systems (mEDC) helped to facilitate the implementatoin of the study with standard procedures and quality.

Intervention fidelity is another major challenge, especially considering the complexity of the ROADMAP, such as the number of study sites, and the shortage in qualified primary care workforce. M-health technology-mediated strategies have therefore been developed and applied to prevent and address inconsistencies occuring throughout the implementation. Besides, a governance system has been built up which includes provincial primary investigators and endorsed by the Chinese Diabetes Society.

Reimbursement, or pay for performance, may affect the service providers' motivation and quality of care. It might be argued that if the reimbursement is only given to the intervention group, the effectiveness between the two arms would be incomparable. The study working group set a cap to the payment amount. On one hand, the reimbursement intends to serve as an additional workload compensation for the staff in the intervention groups. On the other hand, since it would be included as intervention-based cost, its cost-effectiveness may inform further policy adoption. During project implementation, local medical centres will determine the provision of reimbursements. The actual amount of this payment will be recorded in the project management system for health economics analysis.

To address the inconvenience and huge cost of centralized laboratory tests, we adopted a unified, portable, proven accurate instrument for measuring HbA1c, thus avoiding measurement error arising from the use of discrepant devices/systems. However, all other laboratory tests were performed by local county hospitals. The machines, methods and laboratory skills are different amongst hospitals although all of the routine sample (blood and urine) tests are under supervision and authorized by the government. We also collected the information of machines and methods for biochemical testing from all the participating hospitals.

China's health reform is still ongoing. Policy around the services delivery and financing of primary healthcare may encounter regional adjustment during the intervention period. We will record relevant policy changes but it still could potentially influence implementation and outcomes.

As all participants have been randomly recruited from the lists of those registered T2D in the communities, they are likely to be broadly representative of those with the condition in the real-world and thus enhance the generalisability of the results. We recognise, however, that our findings may not be extrapolated to those with undiagnosed or unregistered T2D.

We anticipate that ROADMAP would be implemented successfully, and the evaluation processes conducted with high quality. Most importantly, we hope this real-world trial could successfully contribute to the improvement of the management of T2D in China.

Abbreviations: ROADMAP: Road to Hierarchical Diabetes Management at Primary Care Settings in China; HbA1c: glycated haemoglobin; EQ-5D: European Quality of Life 5-Item questionnaire; T2D: type 2 diabetes mellitus; BG: blood glucose; BP: blood pressure; FBG: fasting blood glucose; LDL-C: low-density lipoprotein cholesterol; EPHS: essential public health services; CHS: community healthcare service; mEDC: mobile electronic data capture; GEE: generalized estimation equation; PI: principle investigator.

Authors' contributions: WJ and PZ conceived the project, designed the study, equally. WJ, PZ, ND, DZ, HL, YB and XL contributed to the design of the intervention and the evaluation. ND and PZ wrote the first draft of the manuscript. YL led the development of the electronic systems involved in ROADMAP intervention and trial management. XL was the statistician

of the study. All authors contributed to the refinement of the study protocol and approved the final manuscript.

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Data sharing statement: The de-identified participant-level data, clinical research forms and statistical code generated and/or analysed during the ROADMAP study are not publicly available due to confidentiality requirements but are available from the corresponding author on reasonable request after January 1st , 2021. Also, any data cross-border transfer must obtain official approval for relevant governmental authorities. Any data/dataset sharing with other parties will be recorded and formulated in written contractual agreements.

Funding statement: This study receives its principle funding from following organizations: 1. Bethune Charity Foundation provides BG monitoring and supporting decision-making system, BG monitoring equipment (smart BG meters) and consumables and project implementation fund required in the study (path-through cost for county hospitals to support the intervention, data collection and performance incentives, etc.) as scheduled in accordance with the provisions of this agreement.; 2. George Institute for Global Health provides financial and personnel support for, including but not limited to, training, IRB, project and data management, qualitative analysis, statistics and result publication.

Competing interests: None declared.

Word count: 3734

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Figure Legend

Figure 1 Flowchart of the ROADMAP study

Supplementary

Appendix 1: Structure of primary care system in China

Appendix 2: Examplars of messages for health education in Your Doctor

Appendix 3: List of contracted services

Appendix 4: User interface of *Graded ROADMAP* App

Appendix 5: Referral indications for diabetes patients

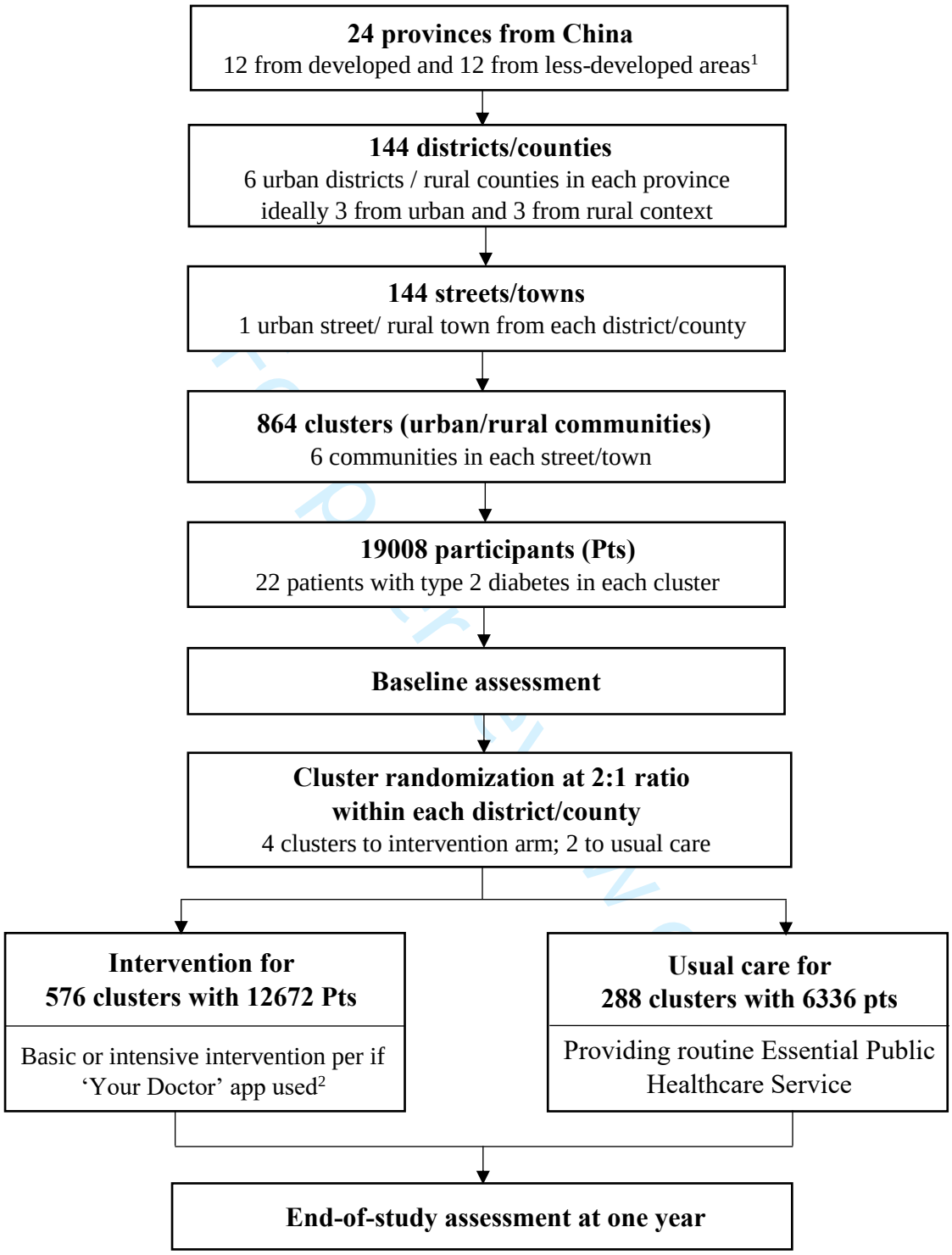

Figure 1 Flowchart of ROADMAP study

[1.] Provinces sit in the upper half of provincial GDP per capita in fiscal year of 2017 are classified into developed areas, and those at lower half are less-developed areas, urban or rural are classified per national administrative area category in 2017.

[2.] Your Doctor app is available for those participants who possess a smart phone and capable of using applications, enabling health education and real-time communication with doctors. Patients who have used 'Your Doctor' app will be regarded as receiving intensive intervention.

Structure of primary care system in China

As shown in the figure below, the primary healthcare system in China is designed to provide the essential public healthcare service (EPHS) and generalist clinical care through differently organized urban and rural components. Supervised by the county/district government, mostly through a division of the Health Commission, the primary healthcare system mainly consists of a township hospital and its satellite village clinics in a rural town, or a community healthcare service (CHS) centre and its subordinated CHS stations in an urban sub-district. Nearly one thirds of CHS stations and village clinics are privately (or jointly) owned while majority of primary healthcare institutions (PHIs) are government-funded. The EPHS are provided either through publicly-owned PHIs by direct governmental subsidises or private PHIs consuming government purchased services. The county/district health commission, or delegated CDC, supervises and evaluates the performance of EPHS of entire county/district. The involvement of county/district hospitals in EPHS is increasing but remain incompact. One township in rural area or a sub-district in urban area is commonly composed of 5-30 communities, each community usually consists a population of more than 1000 dwellers. (Ref: People's Republic of China health system review. Manila: WHO Regional Office for the Western Pacific; 2015)

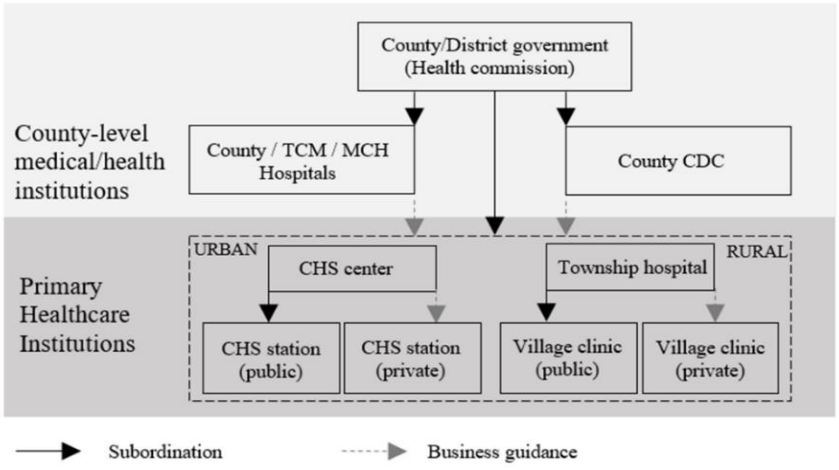

Figure Structure of primary care system in China

* TCM: Traditional Chinese Medicine; MCHI: Maternal and Children Health Institution; CDC: Centre of Disease Control and prevention; CHS: Community Healthcare Service.

By 2017, there were 9147 community health centres, 25505 community health stations, 36551 township health centres and 632057 village clinics in China. The total technical staff of community health centres and township health centres numbered 554694 and 1360272, respectively. Village clinic staff numbered 1243 000. 1.3 % of the staff in community health service centres had a master's degree or above, 29.5 % had a bachelor's degree, 41.4 % had a junior college degree, 25.3 % had a technical secondary school degree, and 2.5 % had a high school degree or below. The educational background of workforce at township hospital was 0.1% for postgraduates or above, 12.3% for undergraduates, 41.5% for junior colleges, 42.3% for technical secondary schools, and 3.8% for senior high schools or below.

(Ref: National Health and Family Planning Commission of the People's Republic of China. China health and family planning statistical yearbook 2017. Beijing: Peking Union Medical College Publishing House, 2018 [in Chinese]).

Examples of messages for health education in Your Doctor app

1. Ideal weight for diabetics.
2. Ideal blood pressure for diabetics.
3. Ideal blood lipid of diabetics.
4. Early warning signals of diabetic ketoacidosis.
5. How to prevent exercise-related hypoglycaemia? Here are three tips you need to know！
6. Focus on the changeable risk factors for diabetes!
7. Arrange your diet with plate method!
8. Measure your meal with your hand!
9. Spices have secrets, too!
10. How should insulin-treated diabetics exercise properly?
11. "Four steps" to develop your own exercise program!
12. How to protect your feet?
13. Early warning signs of "heart" problems!
14. How should diabetics protect kidneys?
15. What should I do if I have diabetic nephropathy?
16. How can urine tests be used to assess kidney health?
17. How can blood and other tests be used to assess kidney health?
18. What aspects should diabetic nephropathy patients adjust their diet?
19. How to detect diabetic retinopathy?
20. How to treat diabetic retinopathy?
21. How to prevent diabetic retinopathy?
22. How do diabetics protect their eyes correctly?
23. Beware of diabetic neuropathy-----a diabetes complication that is easily overlooked!
24. Do you understand the classification of nerves and the effect of diabetes on nerves?
25. What are the symptoms that suggest a diabetic peripheral neuropathy?
26. These symptoms need to see a doctor as soon as possible!
27. What symptoms indicate problems with the autonomic nervous system?
28. What are the complications of diabetic neuropathy?
29. How to prevent diabetic neuropathy?

Team-based Contract Service List (ROADMAP)

1. Basic public health services

This includes routine management of patients with chronic diseases (hypertension, type 2 diabetes)

2. Personally tailored diabetes management services (as follow):

2.1 Graded diabetes management according to different health need

Intensive management services for contracted patients with suspected early complications, unstable complications or poorly controlled blood glucose. Routine management services will be provided to contracted patients present well-controlled blood glucose, without complications or stable complications. The management level shall be adjusted once every six months, according to the disease progression.

2.2 Information management via Graded ROADMAP APP

The three-tiered doctor teams are required to upload each follow-up records and out-patient medical records of the contracted patients to the management via the Graded ROADMAP APP. The APP will alarms doctor with abnormal health record automatically, and allows the record sharing within the corresponding team members to provide refined and continuous diabetes management for contracted patients.

2.3 Referral Green Channel

Members of the contracted doctor team will initial referral applications for the contracted patients with referral indications through the APP, and the superior doctors will decide whether accept or decline the referral based on the previous records.

2.4 Monthly planned blood glucose monitoring

Blood glucose monitoring services will be provided monthly according to patients' conditions. The blood glucose reading will be immediately synchronized to the APP, which can be used for treatment reference.

2.5 Patient education platform service

Patients could join the patient education platform by installing a mobile APP, *Your doctor*. Within this APP, patients can interact with the contracted team doctors as online consultation and receive health educational messages.

User interface display of the Graded ROADMAP App

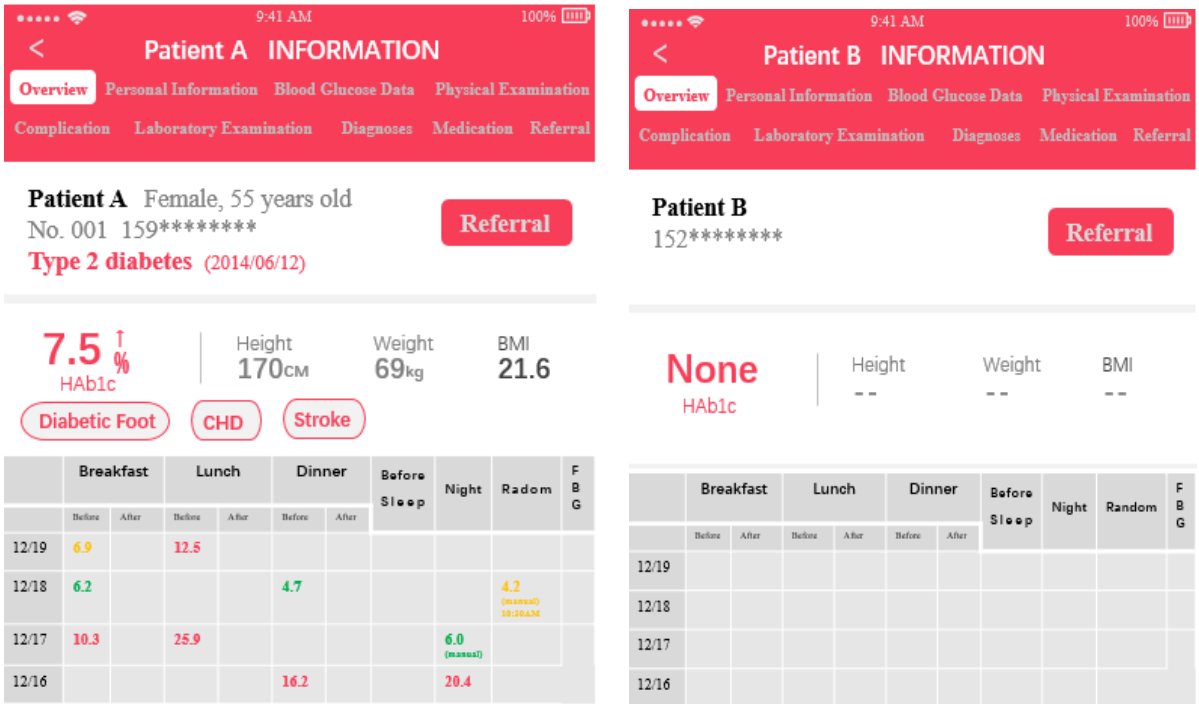

Figure a. User interface of patient's health record at each planned follow-up (community doctor's end)

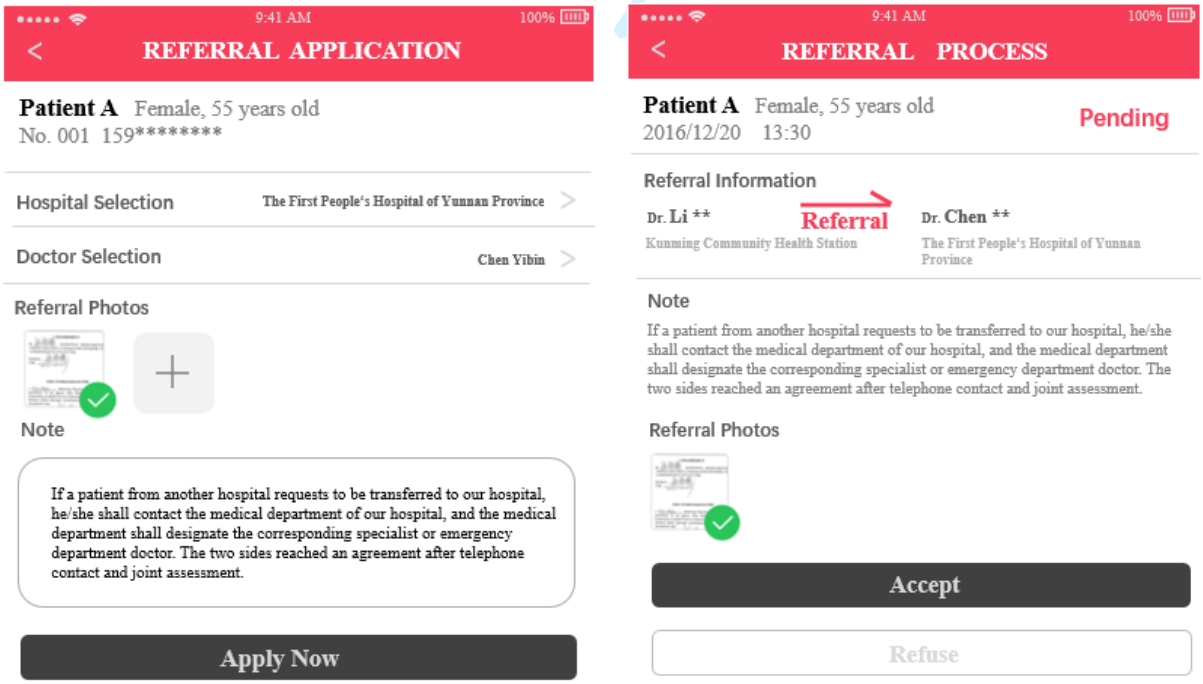

Figure b. User interface of referral request and response

(Left: Referral applied from the tier I community doctor's end; Right: Referral accepted or refused from the tier III hospital doctor's end)

Referral Indications for Primary Health Care Institutions

(Recommended by Chinese Diabetes Society)

The referral priority will be determined by the health record within the Graded ROADMAP App, based on the results of blood glucose monitoring or complication screening. The priority of the referral will affect the suggestive timeframe to seek treatment at higher level healthcare facilities (community health service center/township hospital/hospital).

1. Urgent referral

Patients with type 2 diabetes who present following indications will be suggested immediate refer to emergency or to higher level healthcare facilities within 7 days:

1.1 Diabetic ketosis or ketoacidosis

Blood glucose: 16.7-22.2mmol /L (300-400mg /dl); U-Ket: positive

1.2 Diabetic Nonketotic Hyperosmolar Syndrome

Blood glucose ≥33.3 mmol/L; U-Ket: negative or weak positive

1.3 Hypoglycemia

Hunger, palpitation, clammy limbs, whether or not accompanied by conscious disturbance: blood glucose ≤3.9mmol/L (≤70mg/dl)

2. Routine referral

Patients with type 2 diabetes presenting following indications will be suggested a referral to higher level healthcare facilities within 30 days:

2.1 New patient (patient at her/his first visit)

2.1.1 Serious or deterioration metabolic derangement symptoms, such as thirst, excessive drinking,

polyuria, polyphagia, wasting, fatigue, etc.;

2.1.2 First occurrence of target organ damage, such as coronary heart disease (myocardial infarction) caused by heart, vascular lesions, ischemic or hemorrhagic cerebrovascular disease, intermittent claudication, lower limb pain, and limb damage, ulcer, gangrene;

2.1.3 Foam urine, urine protein appears;

2.1.4 Blurred vision;

2.1.5 Painful neuropathy or abnormal feelings in the lower limbs or the upper and lower extremities, such as hosiery, glove, and numbness, acupuncture, burning, or dull pain, tingling or burning pain;

2.1.6 Multiple infection;

2.1.7 Pregnant and breastfeeding women;

2.1.8 Diabetes perioperative period;

2.1.9 Comorbidity such as liver and kidney dysfunction;

2.1.10 Other severe situations which require hospitalization or intense medication from higher level healthcare facilities.

2.2 Follow-up patient

2.2.1 Consistent poorly controlled blood glucose at 2 follow-ups, with regular treatment;

2.2.2 Well-controlled blood glucose with recurrent elevated blood glucose and not responding to current treatment;

2.2.3 Patient with fluctuant blood glucose and difficult to manage at current healthcare facility;

2.2.5 Newly detected target organ damage during the follow-ups;

2.2.6 Newly occurred unexplainable adverse reactions during anti-diabetic drug treatment.

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	Yes, ChiCTR
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1&20-21
	5b	Name and contact information for the trial sponsor	21
	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	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)	15&17&18

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	2&5
	6b	Explanation for choice of comparators	5&6
Objectives	7	Specific objectives or hypotheses	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)	6&7&9
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&7
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)	7&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)	7
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12&16
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	12&13
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	2&13
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)	17

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	15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7&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	9
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	9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Not applicable
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	13-15, further details are available on request
	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	Available on request

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&14
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	16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	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&16
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	13-15
	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	N/A
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	N/A
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14&15
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	3&18
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)	N/A

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	18
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
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	13&14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	21
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	21
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	12
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	3&17&18
	31b	Authorship eligibility guidelines and any intended use of professional writers	20&21
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	21
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Available on request
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	13&14

*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.