

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	A study protocol for the ROAd to hierarchical Diabetes Management At Primary care (ROADMAP) study in China: a cluster randomised controlled trial
AUTHORS	Jia, Weiping; Zhang, Puhong; Duolikun, Nadila; Zhu, Dalong; Li, Hong; Bao, Yuqian; Li, Xian; Liu, Yu

VERSION 1 - REVIEW

REVIEWER	Esther Yee Tak YU the University of Hong Kong, Hong Kong SAR
REVIEW RETURNED	14-Aug-2019

GENERAL COMMENTS	<p>In this protocol paper, the authors described the design of an ongoing (almost completed by now – August 2019) large-scale cluster randomized controlled trial that evaluates the short-term effect of a complex intervention involving 4 different components and different stakeholders in improving glycaemic control of patients with type 2 diabetes mellitus in the current Chinese primary care system. It was impressive that this RCT study could involve 24 provinces and over 18,000 patients, and new electronic platforms had been established to facilitate study operation. However, the paper at present has not allowed readers to clearly understand the actual design of the intervention, and how this intervention work to promote glycaemic control. Also, the comparability of usual care to the intervention was not stated. Further elaboration MUST be provided for this manuscript to be at least informative.</p> <p>Abstract: The abstract employed a lot of big terms, including integrated, service provider empowering, hierarchical model, contracting... all required further elaboration in the main text where I only found repeats of these terms. Also, subject inclusions (who are studied) the randomization (2:1 ratio)/comparison arm (what to compare with) or statistical analysis plan were not mentioned in the methods section.</p> <p>Article summary: point 3 and 4 are quite similar. It's worthwhile to discuss some limitation of the study, such as who were excluded</p> <p>English: needs some improvement. Generally very long sentences with multiple breaks were hard to understand. Some spelling and grammatical mistakes.</p> <p>Introduction: The introduction was rather brief and did not provide readers with much information / insights on what is the intervention being tested, and why was it developed in this way.</p>
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While the burden of T2DM was adequately described in the introduction, the reasons for suboptimal glycaemic / ABC control in China (i.e. where are the gaps) were not elaborated or discussed. This piece of information would be essential for readers to appreciate how the ROADMAP intervention could possible address those gaps. Also, addition background information on the proven effectiveness of the different components of this complex intervention would be necessary to support that such intervention will likely be effective in improving glycaemic control of T2DM patients. Although the current health care service structure in China was presented in the supplementary appendix, a brief description in the introduction section would be very helpful.

Methods: As I am a clinician without much statistical training, I would not be able to comment much on the cluster selection or sampling method of this cluster RCT. In general, I think Figure 1 should be enhanced with case definitions, including how to define "less developed area", urban or rural area so that readers could appreciate how the cluster sampling were representative of the China population. Also, the authors should support with reference why 2:1 intervention / control ratio was employed in the study, but not other ratio. Also, for subject selection criteria, it was stated that "patients with any situation deemed to be inadequate to continue by any investigators" should be excluded. If the authors failed to explain what would be the potential situations, the patient selection deemed too biased and would severely affect the robustness of any findings from this study.

On the other hand, I would like to know more about the current USUAL primary care services in China, including the number / qualification of staff at each village clinic or community healthcare service station, what types of services are routinely provided by whom and how frequent, whether there were any existing medical record system or not, paper or electronic. Such essential information of the comparison group must be included to allow fair assessment of the impact of the intervention of interest. In addition to the supplementary appendix, these important points should be brief stated in the relevant section.

Regarding the intervention, perhaps the content of the training session should be made available at least in the supplementary material. When little was known about the areas of deficiency (as stated above), the readers could not differentiate whether the training provided could address the knowledge gaps of the service providers. As for the contracted standardized services, a figure outlining the types of services and particularly when to refer MUST be included in the protocol paper. Also, prescription of anti-diabetic drugs was not mentioned at all in the services, which was surprising. Most importantly, the service providers would be paid a substantial amount for caring for patients enrolled in the intervention but NOTHING for the control group. This probably SEVERELY affect motivation / quality of care of providers. If this is the case, I don't think if the intervention / usual care groups were at all comparable, not to mention the reliability of the planned process evaluation (I can't find much description on what will be done).

Several apps / websites were listed as part of the intervention. However, some of them were simply developed to facilitate study operation and should not be considered as part of the intervention. For example, the app used for randomization or managing subject list should not have anything to do with outcomes of T2DM patients. Conversely, there were little description of the 2

	<p>INTERVENTION app to enhance patient care. It's very hard to guess how the "Your Doctor" app helped T2DM given the very short description.</p> <p>Discussion: Although the ROADMAP was packaged as an innovative complex intervention, little was known about how it would work unless the authors provide much more information on both the intervention itself and the comparison group. I came across a few statements in the discussion section about the potential advantages of the ROADMAP, e.g. "unique opportunity to assess epidemiology of T2D...", "unified, portable centrally assessed, instrument for managing HbA1c, thus avoiding measurement error..." which were not previously mentioned / supported with any points through the manuscript and was hard to understand.</p>
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REVIEWER	Janet McGill, MD Washington University School of Medicine St. Louis, MO USA
REVIEW RETURNED	27-Aug-2019

GENERAL COMMENTS	<p>This paper introduces the diabetes readership to the ROADMAP study, which will be completed in the near future. The ROADMAP study is an ambitious, multifaceted approach to providing community doctors with support in their efforts to treat diabetes. Major efforts are being undertaken to apply an intervention that is potentially scalable to the health service in China. I find the paper to be well written and descriptive, which is the purpose of the protocol/baseline paper. Concerns about intervention fidelity and workforce discrepancies are appropriate, but could use a bit more elaboration. If ROADMAP is successful, how will learnings from different provinces or communities with different staffing models be affected and how will they be treated? Does the intervention circumvent these issues?</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: #1

In this protocol paper, the authors described the design of an ongoing (almost completed by now – August 2019) large-scale cluster randomized controlled trial that evaluates the short-term effect of a complex intervention involving 4 different components and different stakeholders in improving glycaemic control of patients with type 2 diabetes mellitus in the current Chinese primary care system. It was impressive that this RCT study could involve 24 provinces and over 18,000 patients, and new electronic platforms had been established to facilitate study operation.

1. However, the paper at present has not allowed readers to clearly understand the actual design of the intervention, and how this intervention work to promote glycaemic control.

Response:

Thank you for your insightful comments. Indeed, this is a complex project dealing with both intervention and implementation. Regarding the intervention, we have now provided explanations in

the context, and added a table (Table 2) to compare the services provided in intervention and control arms. In brief, we aimed to promote glycaemic control through: (1) Capacity building for primary care providers through standard training. (2) Improving the patients' acknowledgement of the service provider team and the referral pathway by signing a service contract with all the care providers at different levels. (3) Facilitating the service delivery by the "Graded ROADMAP" app, mainly including mandatory monitoring of blood glucose (BG) at least twice per month and blood pressure (BP) measurement at least once per month. Medical referrals provided when patients were not well-controlled to target level or complications were suspected. (4) Reasonable reimbursement as "pay for performance". In summary, the key and fundamental intervention in our study was to offer the patients with access to more frequent BG and BP monitoring services, followed by corresponding consultations on lifestyle and medication guidance.

We prepared for about two years to develop and pilot the intervention as well as mobile application-based project management and data management system which were really helpful in performing a standard quality trial in primary care settings in China. In order 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 during the year. This explanation has also been added in the Discussion part in the revised MS.

2. Also, the comparability of usual care to the intervention was not stated. Further elaboration MUST be provided for this manuscript to be at least informative.

Response: As mentioned above, we added Table 2 to elaborate the differences between usual care and intervention. In addition, we also added a small paragraph "Usual care" following the Interventions part to briefly introduce the other related services included in Essential Public Health Services (EPHS).

Abstract:

3. The abstract employed a lot of big terms, including integrated, service provider empowering, hierarchical model, contracting... all required further elaboration in the main text where I only found repeats of these terms.

Response: Thank you for your comments. We have rewritten the abstract using more straightforward expression (mHealth-based, and three-tiered care team engaged diabetes management system), instead of the ambiguous adjectives. Those big terms (integrated, service provider empowering, hierarchical model, contracting) have been elaborated in the Intervention section under the corresponding subtitle. Relevant supporting documents including a list of contracted services have been added as supplementary appendix.

4. Also, subject inclusions (who are studied) the randomization (2:1 ratio)/comparison arm (what to compare with) or statistical analysis plan were not mentioned in the methods section.

Response: Subject inclusion was included in Table 1 (after the eligibility descriptions of study sites). Now we have taken them out from the table and placed them in the Study sites selection and participants section to make it easy to read. The reason of randomization with 2:1 ration is explained below (Comment 9). The intervention effect is compared to the usual care (routine services offered by the EPHS package), which has been explained above and added in the MS. A brief description on statistical analysis principal, primary analysis and pre-specified subgroup has been updated in the Outcome analysis section.

5. Article summary: point 3 and 4 are quite similar. It's worthwhile to discuss some limitation of the study, such as who were excluded.

Response: We agree with your comment here and comment 16 below, where you mentioned the site management apps we used should not have anything to do with the outcomes of T2DM patients. Therefore, we removed the point 4 in the Article summary. In addition, we reminded our readers in point 5 and the Discussion section that our study population was those registered EPHS recipients. Undiagnosed and diagnosed T2D patients who haven't registered for receiving EPHS were not included in our study.

6. English: needs some improvement. Generally very long sentences with multiple breaks were hard to understand. Some spelling and grammatical mistakes.

Response: Thank you for your suggestion. We have asked our native English speaker colleague to complete the proofread. We tried our best to shorten some long sentences and corrected the spelling and grammar errors identified. The assistance by our colleague is recognized in the Acknowledgement section.

Introduction:

7. (1) The introduction was rather brief and did not provide readers with much information / insights on what is the intervention being tested, and why was it developed in this way. (2) While the burden of T2DM was adequately described in the introduction, the reasons for suboptimal glycaemic / ABC control in China (i.e. where are the gaps) were not elaborated or discussed. This piece of information would be essential for readers to appreciate how the ROADMAP intervention could possible address those gaps. (3) Also, addition background information on the proven effectiveness of the different components of this complex intervention would be necessary to support that such intervention will likely be effective in improving glycaemic control of T2DM patients. (4) Although the current health care service structure in China was presented in the supplementary appendix, a brief description in the introduction section would be very helpful.

Response: (1) The reasons for why the intervention have been addressed in the Intervention section, which was designed to tackle the deficiency in primary care and also based on proved effective strategies. (2) We have added the reasons for suboptimal glycaemic / ABC control in China, and (3) proven effectiveness of the key components (mHealth-based diabetes management intervention¹, intervention with deliver system design 【moving from a reactive to a proactive care delivery system where planned visits are coordinated through a team-based approach】^{2,3}, frequent clinic visit⁴, service contract⁵ and doctor-patient communication^{6,7}) of our complex intervention, and (4) the current health care service structure in China in the Introduction section. We believe these will be much easier for readers to understand as background of the supposed intervention of our study.

1. Johnston L, Zemanek J, Reeve M, Grills N. The evidence for using mHealth technologies for diabetes management in low- and middle-income countries. *Journal of Hospital Management and Health Policy*. 2018;2:35-35.

2. Reynolds R, Dennis S, Hasan I, Slewa J, Chen W, Tian D et al. A systematic review of chronic disease management interventions in primary care. *BMC Family Practice*. 2018;19(1).

3. Mitchell G, Burrige L, Zhang J, Donald M, Scott I, Dart J et al. Systematic review of integrated models of health care delivered at the primary–secondary interface: how effective is it and what determines effectiveness?. *Australian Journal of Primary Health*. 2015;21(4):391.

4. Morrison F. Encounter Frequency and Serum Glucose Level, Blood Pressure, and Cholesterol Level Control in Patients With Diabetes Mellitus. *Archives of Internal Medicine*. 2011;171(17):1542.

5. Coupe N, Peters S, Rhodes S, Cotterill S. The effect of commitment-making on weight loss and behaviour change in adults with obesity/overweight; a systematic review. *BMC Public Health*. 2019;19(1).

6. Ralston JD, Rutter CM, Carrell D, et al. Patient use of secure electronic messaging within a shared medical record: a cross-sectional study, *J Gen Intern Med*, 2009, vol. 24. (pg.349-355)

7. Bredfeldt C, Compton-Phillips A, Snyder M. Effects of between visit physician-patient communication on Diabetes Recognition Program scores. *International Journal for Quality in Health Care*. 2011;23(6):664-673.

Methods:

8. As I am a clinician without much statistical training, I would not be able to comment much on the cluster selection or sampling method of this cluster RCT. In general, I think Figure 1 should be enhanced with case definitions, including how to define “less developed area”, urban or rural area so that readers could appreciate how the cluster sampling were representative of the China population.

Response: We have added footnotes to Figure 1 to explain the classification basis for “developed or less developed area”, “urban or rural area”.

9. Also, the authors should support with reference why 2:1 intervention / control ratio was employed in the study, but not other ratio.

Response: The reason for 2:1 intervention/control ratio is that we expect not only to compare the difference on effectiveness between intervention and control arm, but also want to know if intensive intervention (basic + “Your Doctor” app) is better than basic intervention. It was hard to determine who can use the app and the extent of utility during patient recruitment. We assumed half of the patients in the intervention arm would receive intensive intervention, and the other half receive basic intervention, which was mentioned and defined in the Sample size estimation section.

10. Also, for subject selection criteria, it was stated that “patients with any situation deemed to be inadequate to continue by any investigators” should be excluded. If the authors failed to explain what would be the potential situations, the patient selection deemed too biased and would severely affect the robustness of any findings from this study.

Response: In implementation, patients were excluded only when presented with severe physical or psychological problems. The reasons for exclusion had been recorded in our “ROADMAP Assistant” and “mEDC” system. The exclusion criteria has been rewritten as “Patients with severe physical or psychological problems and unable to attend the site visit or answer questions properly, women in the process of, or plan for, pregnancy or breastfeeding, and those who have participated in any other clinical trials within 6 months.”

11. On the other hand, I would like to know more about the current USUAL primary care services in China, including the number / qualification of staff at each village clinic or community healthcare service station, what types of services are routinely provided by whom and how frequent, whether there were any existing medical record system or not, paper or electronic. Such essential information of the comparison group must be included to allow fair assessment of the impact of the intervention of interest. In addition to the supplementary appendix, these important points should be brief stated in the relevant section.

Response: We have added the information you suggested in the Introduction section and Method part (following the Intervention section). Usual care for community patients with chronic disease continue receiving packaged services covered by the Essential Public Healthcare Service, including developing personal health records, updating health records after follow-ups, and health education. Patients with T2D have access to blood glucose monitoring and regular follow-up (at least four free blood glucose tests), as well as lifestyle advice. The description for current primary care system (organisational

structure, service provision, workforce qualification) have been stated in the Introduction section. Due to the word limit, the detailed 2017 workforce statistics has been added in the Supplementary section.

Intervention:

12. Regarding the intervention, perhaps the content of the training session should be made available at least in the supplementary material. When little was known about the areas of deficiency (as stated above), the readers could not differentiate whether the training provided could address the knowledge gaps of the service providers.

Response: The contents of the training material has been outlined in the Intervention section. We also added the areas of deficiencies (low capacity of primary healthcare providers, inefficient resource utilization, most importantly, fragmented delivery of care) as you suggested. In this way, the audience could be more informed about the intervention rationale.

13. As for the contracted standardized services, a figure outlining the types of services and particularly when to refer MUST be included in the protocol paper.

Response: We have listed the services and their required frequency in Table 2 in the Intervention section, instead of a figure. The referral will be initiated in two manners: urgent referral and routine referral. The urgent referral will be initiated under the detection of diabetic ketosis or ketoacidosis; diabetic nonketotic hyperosmolar syndrome; and hypoglycaemia. Routine referral will be suggested under the circumstances such as blood glucose remain uncontrolled after treatment or complications suspected. Because nearly all of the referral are due to the chronic situations, so we did not include the urgent referral criteria in Table 2.

14. Also, prescription of anti-diabetic drugs was not mentioned at all in the services, which was surprising.

Response: Medication instruction had already been included as the most important part in the training, but the algorithm on how to use medication were not included in the "Graded ROADMAP" app. The strategy of the intervention is to strengthen the patients' lifestyle change and medication through improved the capacity of providers' by training, providing more frequent BG and BP monitoring, and enhancing doctors' support via mhealth-supported referral. The adjustment of medication has been/will be collected from each patient at baseline and end-of-study assessments, and the improvement and impact on BG control will be analysed later in papers of study results.

15. Most importantly, the service providers would be paid a substantial amount for caring for patients enrolled in the intervention but NOTHING for the control group. This probably SEVERELY affect motivation / quality of care of providers. If this is the case, I don't think if the intervention / usual care groups were at all comparable, not to mention the reliability of the planned process evaluation (I can't find much description on what will be done).

Response: We agree with your comments on the reimbursement, and we also agree "This probably SEVERELY affect motivation / quality of care of providers" if the reimbursement is only given to the intervention group. However, the purpose of pay for performance here is to evaluate the impact of the additional incentive, so that we can suggest the government if it deserves more financial input based on cost-effectiveness analysis. During project implementation, whether or not the reimbursements would be given was determined according to the decisions of local medical centres, and the cap amount was determined by the study working group, so that such incentives are scalable and acceptable by government if it is cost-effective. Regardless of the impact, the reimbursement will be recorded if it ever takes place, and will be included in the health economics analysis in the end.

16. Several apps / websites were listed as part of the intervention. However, some of them were simply developed to facilitate study operation and should not be considered as part of the

intervention. For example, the app used for randomization or managing subject list should not have anything to do with outcomes of T2DM patients. Conversely, there were little description of the 2 INTERVENTION app to enhance patient care. It's very hard to guess how the "Your Doctor" app helped T2DM given the very short description.

Response: We have removed most introduction of "ROADMAP Assistant" and "mEDC" in the main text, only leave them in a few sentences regarding data collection and management as well as in the discussion related to challenges of project implementation. The features of the 2 INTERVENTION apps have been described in detail in the Intervention section in main text. And the Graded ROADMAP App user-interface and the exemplars of Your Doctor messages' titles have been presented in supplementary appendixes. We agree this is really important.

Discussion:

17. Although the ROADMAP was packaged as an innovative complex intervention, little was known about how it would work unless the authors provide much more information on both the intervention itself and the comparison group.

Response: The intervention and the usual care have been further described in detail in the Intervention and Usual care sections. This is also as a response to your previous comments (comment1, 2 and 11)

18. I came across a few statements in the discussion section about the potential advantages of the ROADMAP, e.g. "unique opportunity to assess epidemiology of T2D...", which were not previously mentioned / supported with any points through the manuscript and was hard to understand.

Response: In response to the statement "unique opportunity to assess epidemiology of T2D..." in the Discussion part, we do think that the large scale study (baseline data) gives us a good opportunity to assess the distribution of patients with established T2D and the proportion of diabetic complications in China. But considering this is not the key purpose of the study as a clinical trial, we removed this sentence. We also noted that the sentence "unified, portable centrally assessed, instrument for managing HbA1c, thus avoiding measurement error..." was not clear and had a typo. We rewritten it as "To address the inconvenience and huge cost for centralized laboratory tests, we adopted a unified, portable, proven accurate instrument for measuring HbA1c".

Reviewer: #2

This paper introduces the diabetes readership to the ROADMAP study, which will be completed in the near future. The ROADMAP study is an ambitious, multifaceted approach to providing community doctors with support in their efforts to treat diabetes. Major efforts are being undertaken to apply an intervention that is potentially scalable to the health service in China. I find the paper to be well written and descriptive, which is the purpose of the protocol/baseline paper.

1. Concerns about intervention fidelity and workforce discrepancies are appropriate, but could use a bit more elaboration.

Response: Thanks for your comments, and as a response to the similar comments of the other reviewer, we have elaborated these two aspects in the Discussion section.

2. If ROADMAP is successful, how will learnings from different provinces or communities with different staffing models be affected and how will they be treated? Does the intervention circumvent these issues?

Response: Even if the study were successful, we anticipate that the effect may vary in different study areas, that's why we sampled the participants from four strata (developed urban, developed rural, under-developed urban and under-developed rural). The difference on effect of the intervention may also be good evidence to help government to set priority on where should be scaled up first. Regarding to the potential impact from different staffing models, a process evaluation has been planned to be conducted in different areas to see what staffing model using which components of the complex intervention will be having more impact on improvement of diabetes control. This can be a clue to indicate which part of the intervention is worth more input in a certain area during scaling up. The staff information has also been collected at the stage of site selection. We hope this data can also help us to conclude what kind of staff are more suitable to use this kind of intervention. Considering the audience may also have this query, we included these explanations in the discussion part and reconfirmed in the Process evaluation part.

VERSION 2 – REVIEW

REVIEWER	Janet McGill, MD Washington University School of Medicine, St. Louis, MO
REVIEW RETURNED	24-Nov-2019
GENERAL COMMENTS	Revisions are acknowledged. The paper adequately describes a very complex public health intervention aimed at improving care of persons with diabetes in China.