Author’s response to reviews

Title: Intensification to injectable therapy in type 2 diabetes: mixed methods study (protocol)

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Author’s response to reviews:

Dear Members of the Review Panel,

Thank you for the helpful reviews and the opportunity to respond to reviewers’ comments. We feel these changes have significantly strengthened this manuscript.

We have attached:

(1) Authors’ response to each of the reviewers’ and editors’ comments.

(2) A revised manuscript with the changes highlighted and a further “clean copy” revised manuscript.

We have noticed that in one area, the video analysis, we gave scant details of how our analysis would be performed. We have strengthened this part of our study. We have also made some additional revisions throughout the manuscript to enhance its readability.
We greatly appreciate this opportunity and hope our revisions make the paper acceptable for publication. Please don’t hesitate to be in contact should you require any further information or clarification. Please also pass on our thanks to the reviewers for their efforts.

These amendments have been approved by all the authors.

Yours faithfully,

Simon de Lusignan

Editor Comments:

The Editor is aware that not all the comments from reviewer 2 are relevant (clearly there will not be any results for a protocol article). However, in addition to the points raised by reviewer 1, we kindly ask you to address the following points raised by reviewer 2:

- "As mentioned previously, the Polonsky (2018) international study that included the UK studied the patients’ and clinicians’ perceptions about the initiation of injectable therapies, which this study hoped to achieve. Since there is a larger, multi-national study on the horizon, this research may not be needed to further what is known in the literature."

- "Were you planning on conducting focus groups with patients and interviews with clinicians? This is unclear in sections"

- "Note, I wouldn't call them "dummy" patients but perhaps "standardized" patients or "example" patients."

- "The purpose of the consensus exercise is not clear. It appears as though you are using a Delphi approach, but this is complicated/not needed for the type of data you are planning to collect."

Authors’ response:>>

As requested by the Editor, we have only addressed the above points raised by reviewer 2, listed above. These are all set after our responses to peer reviewer 1.
Reviewer(s)' Comments to Author:

Reviewer 1

This paper is a protocol paper for a study about the perceptions of T2D (I got recently told that one now uses the abbreviation T2D and not T2DM anymore… personally I have no string feelings about either…) patients and primary care clinicians on initiation of injectable therapy (primarily insulin). This constitutes a considerable intensification of T2D treatment. In the paper's introduction there is made a case for starting on insulin for patients with bad glycemic control. However, given all these fine properties of injectable therapy, one wonders why delay of this therapy is a problem (especially since clinicians are nudged to initiate injectable therapy through targeted training and P4P). This is probably something that clinicians just know, but the paper should mention more explicitly some of the drawbacks of injectable therapy (I am not a clinician).

Authors’ response:>>

Concerning the use of T2D rather than T2DM the authors have amended the manuscript to reflect this suggestion.

We have increased the length of the introduction to improve the rationale for the study. This includes detail regarding the risk that suboptimal glycaemic control poses in terms of risk of associated complications such as stroke and renal disease (Background section, page 3, paragraph 1). We have also elaborated in terms of what we currently know about clinical inertia for the use injectable therapies, and why this study is needed to explore underlying issues that need to be addressed in order to improve glycaemic control in the T2DM population (Background section, page 5, paragraph 5). The updated text is shown below.

Type 2 diabetes (T2D) is a major problem for many health care systems [1-8]. The World Health Organisation (WHO) has estimated that there are approximately 422 million people in the world with T2D [1]. Following analyses of the Framingham study in the 1970s it became clear that T2D is a major risk factor for macrovascular disease (including myocardial infarction and stroke), and studies since have demonstrated that macrovascular risk increases with worsening glycaemic control [9, 10]. Diabetes is also associated with an increased risk of microvascular complications which includes diabetic retinopathy, neuropathy, and renal disease [11]. Several landmark trials have demonstrated that risk for both microvascular and macrovascular complications of diabetes can be reduced by improving blood glucose control [12-15].

National and international guidelines have provided targets for optimum glycaemic control, which have been established through observational evidence and clinical trials [16-22]. However, adequate glycaemic control is difficult to achieve for a significant proportion of people with T2D. In a large-scale European study, real-world diabetes care was compared against the glycaemic targets produced by the American Diabetes Association (ADA) and European
Association for the Study of Diabetes (EASD), and found that only 53.6% of people with T2D achieved adequate glycaemic control, with considerable variation between countries [23].

Additional updated text is shown below.

QOF remuneration targets for T2D include optimising the number of people below set glycaemic thresholds. CMR based interventions are known to generally improve care [25] and the introduction of these P4P targets appear to have improved glycaemic control and reduced inequalities in T2D management [26, 27]. However, it is difficult to disentangle these effects from other quality improvement initiatives.

One component of suboptimal management is delay in intensification of therapy. Delays in intensification occur at each stage of treatment: from diagnosis to first oral medication, to second and third oral medications, to the initiation of injectable therapies and escalation of injectable therapies once initiated [28]. These delays termed “therapeutic inertia” or, more commonly “clinical inertia” [29], are associated with impaired glycaemic control and concomitant complications including microvascular (e.g. retinopathy, chronic kidney disease) and macrovascular diseases (e.g. heart failure, stroke) [30]. Despite improved glycaemic control following the use of injectable therapy, drawbacks of insulin include weight gain, and severe hypoglycaemia and increased risk of death [31, 32], whilst glucagon-like peptide 1 receptor agonists (GLP-1 RAs) have been linked to gastrointestinal symptoms such as nausea, vomiting, and diarrhoea [33], which may deter people from using them. Other barriers to starting injectable therapy include the individual struggling to acknowledge that their diabetes has progressed, anxiety and fear of pain from injecting, the need to regularly test blood glucose levels, and the difficulty incorporating injecting during working hours [34-36].

Clinician, patient, and health service factors have been identified as contributing to clinical inertia [37-44]. However, an improved understanding of the specific patient, clinician, and health service factors that influence clinical inertia is urgently needed to facilitate improved glycaemic control and health outcomes in people with T2D.

Reviewer 1

The study is characterized as a "mixed methods study", but the focus is (to me) clearly on the qualitative part. This is probably also where the expertise of the authors lies. I am a statistician, and do not know a lot of qualitative research (although I have quite some qualitative colleagues and it is contagious…). However, on the topic of planning qualitative studies, I have to point out the paper by Malterud et al 2016: Sample size in Qualitative interview studies: guided by information power, Qualitative Health Research, 26, 1753-1760 (Yes, the paper is applicable to
qualitative studies broader than only interview studies, and deals with more than only sample size: it suggests some information elements to report so as others can gauge the "information power" in the study). I applaud the authors to state the number of informants to be included in the focus groups already here in the protocol paper and to avoid using the saturation principle.

Authors’ response:>>

We agree with the reviewer’s observation that the type of research in this study appeared to be predominantly qualitative. However, given that some components of the study will require quantitative analysis (e.g. the video data, survey), we feel it more appropriate to describe this as a mixed methods study.

We have added more detail to the Data Analysis subsection in the Methods section to describe how this data will be analysed quantitatively (page 10). The qualitative aspects of this study (focus groups and interviews) will inform the quantitative component (simulated surgery and survey) of the study, and we’ll use the sequential exploratory design as a basis for this process (“Integration of the data from each study phase”, page 10).

We appreciate the reviewer’s acknowledgement that we have included the number of participants we intend to include in each phase of the study. We have tried to be pragmatic in our approach, and based on the literature, we believe these sample sizes to be realistic to achieve in terms of recruitment, and in acquiring the data that we need.

Reviewer 1

On the topic of sample selection, I read that all T2D patients (adult, etc.) are eligible for interviews and focus groups, but wouldn't you want a narrower group, e.g. T2D patients that have suboptimal glycemic control and with some of them already on injectable therapy (or maybe specifically not on injectable therapy yet)?

Authors’ response:>>

We agree with the reviewer’s observation that patients with T2D should be separated into two separate focus groups: those that are naïve to injectable therapy, and those with none. We will ask patients slightly differently worded questions, depending on their exposure to injectable therapy. It is likely that the perceptions of injectable experienced patients will have changed over time, and differ from the naïve patients. The details have now been added to the manuscript (“Data collection” - subsection of Methods, page 7). We don’t intend to separate patients according to their glycaemic control as we feel this may limit our sample size too much when it comes to recruiting patients to the study, and alienate patients as “poor performers” with regard to their diabetes.
Reviewer 1

There will be three simulated surgeries shown to the clinicians in connection with the focus groups, or are they performed by the clinicians in the focus groups? It is a bit unclear. Data will be generated in the videos of the simulated surgeries, but this is still part of the qualitative part of the study I figure. Some schematic of when and where what will take place (some timeline?) could be helpful.

Authors’ response:>>

We have improved Figure 1 to make the sequence easier to follow.

The study will be completed in three phases in the following order:

1) Focus groups will be conducted first. These will be with T2D patients and primary care clinicians;

2) Simulated surgeries of diabetes consultations, will take place next. These simulated surgeries be conducted with actors acting out three different scenarios of simulated patients with T2D, where initiation of an injectable therapy might be necessary, to six different clinicians (general practitioners (GPs) in rotation. There will be a follow-up focus group to discuss the different patient scenarios, which will give the GPs an opportunity to explain how they made clinical decisions (e.g. initiate insulin or a GLP-1 receptor agonist therapy) based on the fictional patients’ medical history. These diabetes experts will also be invited to provide feedback on a number of consensus statements generated from feedback from the focus groups and interviews. The consensus statements will then be revised further according to this feedback for circulation to a wider audience, as described in phase 3.

3) The consensus exercise is the final phase. A consensus exercise, whereby experts will be asked to review their previous responses, and explain the extent to which they agree or disagree with statements about injectable therapy in T2DM. The equivalent statements will be presented to clinicians in the wider RCGP RSC network to gauge consensus with the statements.

Reviewer 1

The quantitative part of the study takes the form of a survey where the statements from the qualitative part are assessed by a representative sample of patients and clinicians: 40-50 participants in all (or is it 40-50 patients and 40-50 clinicians?). It is not so clear what the purpose is of this “consensus exercise". As I read it, this survey assesses the prevalence of the perceptions that correspond to the statements in the population (of patients and/or clinicians). For
example, if the theme "fear of needles" appeared in the qualitative part of the study, a statement could be "I am afraid of needles" and if 40 out of 50 patients agreed with this, we could claim that this is a highly prevalent experience and worthy to take into consideration when injection therapy has to be initiated; notably because we have a representative sample. Maybe such example could be written into the paper? But what is written in the paper is that some agreement is sought and it is not clear why there should be agreement and what this will tell us. How do the authors imagine a representative sample (of patients) is gathered, and representative of what underlying population? Hence, for the quantitative part of the study I would like to see planned an analysis that assesses whether the sample can be viewed as representative, and a report of the prevalence of the generated statements (that will correspond to the themes found in the qualitative part). Here one could even do a formal power calculation to validate your "40-50": how many respondents are necessary to get a 5 percentage point error margin on the prevalence estimate?

Authors’ response:>>

We are sorry the description provided is not clear. This part of the study would be better described as a consensus exercise where the quantitative measure will be either that there is agreement with a statement, disagreement or equivocation. This approach is commonly used in Delphi studies, of which the group has conducted many. What this will tell us is whether there is consensus or a spread of views. We think this is a reasonable check of the themes that emerge in the course of the study.

Reviewer 1

Do you think that a 9-point Likert scale is not too fine? What about a five-point scale? How many statements are you planning to put in the survey? Will there be multiple statements per theme found in the qualitative part? In summary, I had a hard time figuring out the quantitative part of the study, this has to be described clearer.

Authors’ response:>>

In light of this suggestion, we have compromised and have reduced the survey to a seven-point scale. We feel that some respondents will have strong feelings on the subject matter that a five-point scale might not allow them to express as they wish. The survey will be designed to last between 5 and 10 minutes. This is considered a suitable amount of time to complete a survey with a reasonable response rate, though we decided not to include financial incentives. Our plan is to include between 10 and 15 statements with some added open ended questions.
We have broken down each section of the phases to make these clearer, and provided more detail as to how the quantitative components of the study will be performed (“Data collection” - subsection of Methods, pages 7-9).

Reviewer 2

OBJECTIVE - Full research articles: is there a clear objective that addresses a testable research question(s) (brief or other article types: is there a clear objective)?

Yes - there is a clear objective

DESIGN - Is the current approach (including controls and analysis protocols) appropriate for the objective?

Yes - the approach is appropriate

EXECUTION - Are the experiments and analyses performed with technical rigor to allow confidence in the results?

N/A - no experiments or analyses

Statistics - Is the use of statistics in the manuscript appropriate?

N/A - there are no statistics in this study

INTERPRETATION - Is the current interpretation/discussion of the results reasonable and not overstated?

N/A - no results to interpret

OVERALL MANUSCRIPT POTENTIAL - Is the current version of this work technically sound? If not, can revisions be made to make the work technically sound?

No - manuscript has some fundamental flaw(s)
PEER REVIEWER COMMENTS:

GENERAL COMMENTS: Although this is a well-designed study, no work has been completed; it is a future intervention and this paper simply describes the protocol. Therefore, it would not be recommended for publication until data are collected and the study results are available. Also, there is a mixed methods study currently (Polonsky, 2018, epub ahead of print) that is international (including the UK) and includes the facilitators to insulin initiation. Much literature already exists on the barriers to insulin initiation, so this study may not contribute much further to what is already known about this subject. The authors should submit a publication reporting the "real world" lessons for clinical practice, but this paper is premature.

REQUESTED REVISIONS:

As mentioned previously, the Polonsky (2018) international study that included the UK studied the patients' and clinicians' perceptions about the initiation of injectable therapies, which this study hoped to achieve. Since there is a larger, multi-national study on the horizon, this research may not be needed to further what is known in the literature.

Authors’ response:

Thanks for this. We are not certain we have found the right study. William H Polonsky is a prolific, highly cited, and expert diabetes author. We have searched Medline and the web for relevant contributions. Including his ResearchGate papers page:

https://www.researchgate.net/scientific-contributions/2110747116_William_H_Polonsky

The most relevant first author paper we can find is:


Another we found that fitted the description of the reviewer was:

Both of these papers include important information about experts’ views of key issues, and how to respond to them; and patient and practice characteristics that might predict escalation or change in insulin, respectively. We could not find any work that supplanted the need for our study. We plan to focus on the context in which the decision to escalate therapy is taken. In the UK this is on where nearly all primary care consultations are computer mediated and contextualised by pay-for-performance indicators that don’t precisely match to national evidence-based guidance. We feel our UK exploration of this context will add to the literature and potentially become generalisable as other health services move to computer mediated consultations.

Reviewer 2

Were you planning on conducting focus groups with patients and interviews with clinicians? This is unclear in sections. It just strikes me that the work on barriers has been done before, and the work on facilitators has recently been published.

Authors’ response:>>

Focus groups will be conducted separately with patients and clinicians. Interviews will be performed with patients and clinicians in the instances that they are willing to participate in the research but are unable (e.g. the participant can’t attend a focus group on a specific date) or uncomfortable with participating in focus groups.

Reviewer 2

Note, I wouldn't call them "dummy" patients but perhaps "standardized" patients or "example" patients.

Authors’ response:>>

We agree that the term “dummy” is inappropriate, and have therefore described the patients as simulated patients, so it’s still clear to the reader that the records aren’t those of real patients and will be created specifically for this study.

Reviewer 2

The purpose of the consensus exercise is not clear. It appears as though you are using a Delphi approach, but this is complicated/not needed for the type of data you are planning to collect.

Authors’ response:>>
The purpose of the consensus exercise is to draw together the findings from the study as a whole and to see if there was agreement, disagreement or equivocation about these.

Additional changes made:

We realised that the protocol was light on details about the video analysis, we have therefore added the following (“Data analysis” - subsection of Methods, page 10):

**Assessment of the consultation quality using the Calgary-Cambridge model**

The Calgary-Cambridge consultation model [53] will be used to appraise the primary care clinicians’ consultation skills from the simulated surgeries. This enables us to assess if there has been shared understanding and decision-making [80-83]. The Calgary-Cambridge consultation model has five steps: (1) initiating the session; (2) gathering information; (3) building the relationship; (4) explanation and planning; and (5) closing the session. The Global Consultation Rating Scale, based on the Calgary-Cambridge will be used to assess the quality of communication [84].

**Assessment of the interaction between the GP and the simulated patient**

A checklist will be developed for each simulated surgery to enable us to:

1) Highlight key prompts/triggers for action either in the patient’s history or the simulated medical record;

2) Note whether these were stated or accessed during the consultation;

3) Whether the prompts / triggers resulted in action;

4) To determine whether the outcome of the consultation which would be anticipated if guidelines were followed.

This will be carried out using expert reviewers. These reviewers will first identify key triggers in the records or history from the simulated patient which should trigger action, in this case intensification of T2D therapy. These will be identified by two expert reviewers, and any differences discussed. The videos will then be independently reviewed by two experts to see if these triggers were recognised, discussed, and actioned. This peer approach will mirror similar methods used to assess multidisciplinary team meetings [85].