PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol for the specialist supervised Individualized multifactorial treatment of new clinically diagnosed type 2 diabetes in general practice (IDA) – A prospective controlled multicenter open-label intervention study
AUTHORS	Stidsen, Jacob; Nielsen, Jens; Henriksen, Jan; Friborg, Søren; Thomsen, Reimar; Olesen, Thomas; Olsen, Michael; Beck-Nielsen, Henning

VERSION 1 – REVIEW

REVIEWER	Daisuke Yabe Kyoto University Graduate School of Medicine, Japan No Competing Interest
REVIEW RETURNED	14-Jun-2017

GENERAL COMMENTS	The manuscript entitled “Protocol for the specialist supervised Individualized multifactorial treatment of new clinically diagnosed type 2 diabetes in general practice (IDA) – A prospective controlled multicenter open-label intervention study” describes a protocol of IDA study to assess whether an individualized multifactorial intervention, based on pathophysiological phenotyping and individualized treatment goals, improves T2D outcomes, including improvement of QOL and reduction of T2D complications, with a manner requiring less medication and fewer resources. Reviewer finds this study will be a mile stone to establish T2D management based on a close cooperation between hospital-based diabetes specialists and general practitioners. The manuscript needs to be published after appropriate revisions. Specific comments: 1. The current protocol supposedly recruits Caucasian population in Denmark mostly. Since pathophysiology of diabetes may vary among various ethnic groups, the way to categorize T2DM in the current study protocol might not apply to other ethnic groups such as east Asian who are characterized by impaired insulin secretion in response to ingestions of glucose or mixed meals (e.g., Lancet Diabetes Endocrinology (2016) 4(1):2-3). The authors should discuss this point in the manuscript. 2. Along with my comment in 1, suitable treatment strategies also differ among ethnic groups such as that DPP-4 inhibitors expert greater HbA1c-lowering effects in east Asians and they are used as first line drug in this population (Journal of Diabetes Investigation, (2016) 7(Supple 1): 102-110). The authors can include this point in the manuscript.

	3. Use of pioglitazone has been a big debate not only in Europe, but also globally due to bladder cancer in addition to heart failure and bone fracture. The authors can make comments on this. 4. Recent emergence of PCSK9 allows further reduction of CV events in individuals with T2D. The authors should discuss possible use of this drug class during 10-year follow up period. 5. In Fig 3., directions of some arrows should be reverted to keep consistency.

REVIEWER	Jacek Kiljański Eli Lilly and Company, Global Medical Affairs, Poland
REVIEW RETURNED	03-Aug-2017

GENERAL COMMENTS	Very interesting and valuable research project, certainly worth of been published and discussed publicly. I congratulate the authors the idea addressing important knowledge gap in diabetes care. However the protocol is very complex, not easy to read and understand. I included a number of comments in the PDF choppy enclosed to facilitate revisions. The reviewer also provided a marked copy with additional comments. Please contact the publisher for full details.

VERSION 1 – AUTHOR RESPONSE

Reviewer Name: Daisuke Yabe
Institution and Country: Kyoto University Graduate School of Medicine, Japan
Please state any competing interests or state 'None declared': None

Specific comments:
1. The current protocol supposedly recruits Caucasian population in Denmark mostly. Since pathophysiology of diabetes may vary among various ethnic groups, the way to categorize T2DM in the current study protocol might not apply to other ethnic groups such as east Asian who are characterized by impaired insulin secretion in response to ingestions of glucose or mixed meals (e.g., Lancet Diabetes Endocrinology (2016) 4(1):2-3). The authors should discuss this point in the manuscript.

Answer: Good point. We have briefly added this point to the introduction (page 5, line 17)

2. Along with my comment in 1, suitable treatment strategies also differ among ethnic groups such as that DPP-4 inhibitors expert greater HbA1c-lowering effects in east Asians and they are used as first line drug in this population (Journal of Diabetes Investigation, (2016) 7(Supple 1): 102-110). The authors can include this point in the manuscript.

Answer: Good point. The algorithm is based on Caucasians and cannot readily be extrapolated to other ethnicities (added at page 14).

3. Use of pioglitazone has been a big debate not only in Europe, but also globally due to bladder cancer in addition to heart failure and bone fracture. The authors can make comments on this.

Answer: We agree that the issue of bladder cancer should be addressed and we have updated this point in the treatment algorithm and the supplemental material

4. Recent emergence of PCSK9 allows further reduction of CV events in individuals with T2D. The authors should discuss possible use of this drug class during 10-year follow up period.

Answer: The supplemental material has been updated with a discussion of this subject. With the present evidence on hard endpoints we do not advocate combination therapy with lipid-lowering medication.

5. In Fig 3., directions of some arrows should be reverted to keep consistency.

Answer: We agree that there is some inconsistency in the figure. Therefor we have divided it in to a part A and B. In part A the pre-trial flow is outlined whereas the trial flow is outlined in part B. We hope this have improved interpretation of the figure.

Reviewer: 2
Reviewer Name: Jacek Kiljański
Institution and Country: Eli Lilly and Company, Global Medical Affairs, Poland
Please state any competing interests or state 'None declared': none declared

Comment: Is there any role for patients preference for specific treatments? What if the patient for whatever reason does not want to follow the advice and prefers some other effective treatment?

Answer: We have added: "The suggested individualized treatment in the intervention group is made available to the treating GP, but the actual treatment is chosen at the discretion of the GP after due process with the patient. The intervention is designed to mimic the actual real life effect of specialist treatment suggestions and patients who do not follow the proposed algorithm are therefore not discontinued". On page 11 we have added "The GP will report the goal of the treatment and reasons for protocol deviations annually." very complex composite endpoint, inclusion of cancer not well explained/justified in the introduction.

Comment: Will the composites be adjudicated?

Answer: We have made a paragraph about cancer in the introduction. The endpoint could be seen as a contemporary version of "any diabetes related endpoint" known from UKPDS.
No the composite will not be adjudicated

Comment: It would be very important to consider health economics aspects of the treatments. Is it planned to be analysed?

Answer: Yes "socioeconomic cost"(page 21) is a secondary outcome (biobank) what for? Study assessments? I believe that the trial will provide an extremely interesting and unique material for genomic evaluation of responders vs. non-responders to therapies etc.

Comment: Is this sample collection considered, maybe as an addendum?

Answer: Yes this is considered. We have shortly added information regarding this and added a reference to the published paper that describes the biobank

Comment: will there be information on outcomes in specific subgroups and phenotypes in a control arm? It would be very important to have it and fully characterize both groups, not just one.

Answer: Yes the concept is that all basic information is available from the nationwide Danish registries or the DD2 study. Surrogate markers of cardiovascular disease that require special examinations will only be measured in the intervention group due to the overall design. See the added table 1 for overview

Comment: I assume the examinations will be performed also in the comparatory arm. If not, why?

Answer: No. The initial phase of the study revealed that it was not possible to recruit sufficient GPs to the control arm. Therefore we made the current set up with a dormant control group. As a consequence we are not able to do study measurements on the control group, but most rely upon clinical data stored registered in the Danish health registries.

Comment: (Age of type 1 diabetes) Is it the age at diagnosis?

Answer: No, at the time of DD2 enrollment where the Gad-ab is measured. We have added this in the manuscript

Comment: about what? Being randomized to the control group? Maybe I misunderstood the protocol but I assume that GPs will be involved in therapeutic decisions so they should be aware. Or will they simply continue whatever specialist prescribe without any decision power?

Answer:The control group is only followed via registries as part of their participation in the DD2-cohort. As a consequence they are not informed that they act as a control in the IDA-study. They will therefore receive clinical control at their general practitioner as all other patients with type 2 diabetes. As stated on page 8 and 9

Comment: A little bit more detailed information about what DD2 is would be helpful.Are standards of care in different regions of Denmark similar? Is there a possibility of biasing the study by use patients from different regions in the two arms?

Answer: The basic concept of the DD2-cohort is described on page 7: “Newly diagnosed T2D patients are enrolled prospectively in the population-based DD2 cohort. At baseline, the DD2 project collects interview data and biobanks blood and urine samples [28 29]. Following enrolment, each participant is followed over time using data in nationwide registries [30]. This study is one of several planned studies drawing on the cohort”. In its essence DD2 is nothing more than this. The data secured in DD2 is available for use in projects found eligible.
Denmark consists of 5 regions and standards of care does not differ much (https://www.sundhed.dk/content/cms/87/4687_diabetes-2016.pdf). There might be minor intraregional differences in standards of care and maybe more importantly inter- and intraregional differences in the socioeconomical characteristics of the population. So using patients from different regions in the two arms together with a range of other variables might bring bias into the study as it is non-randomized. This concern is summarized in page 8: “The selection process for patients in the two groups will be different and adjustment for differences in prognostic factors at baseline is therefore warranted as described in the statistical section”

Comment: are these centralized measurments or to be done in the local labs?

Answer: These measurements are done in local labs, as they are “everyday” clinical measurements. See the added table 1.

Comment: Wearing these accelerometers for 10 days may provide very valuable data but it is a burden for patients, i expect high non-compliance, missing data and maybe even discontinuations. Are the authors considering this risk and how are they planning to mitigate it

Answer: In our study accelerometers are fitted to the skin of the patient with adhesive tape to ensure 24 h wear time and a high compliance. In a recent study where accelerometers were fitted to the skin using a method as in the present study and furthermore aimed to be carried for up to 10 consecutive day, compliance to 24 h wear time for >7 days was 65%. (Schneller MB et al, Medicine and science in sports and exercise 2017:49(6)). Furthermore, Schneller instructed users not to reattach accelerometers if they detached – in the present study we instruct patients to re-attaché accelerometers in case it falls off, thus we believe we will achieve a high compliance to accelerometer wear time

Comment: (daily physical activity) is this information only collected for intervention group or also control group?

Answer: Only in the intervention group due to the overall design of the study. See the added table

Comment: (cardiovascular surrogate markers) Will they be collected in both study arms?

Answer: Only in the intervention group due to the overall design of the study. See the added table

Comment: what happens if the patient does not respond well to the therapy prescribed according to the phenotyping? Are rescue medications allowed?

Answer: Inefficient therapy is addressed in page 19:
“Termination of inefficient medication
The effect of a specific anti-diabetic, antihypertensive, or cholesterol-lowering treatment will be measured. The following efficacy requirements after titration to the full tolerable dose will need to be met:
1) Decline in Hba1c exceeding 0.5 % within 3 months.
2) Decline in systolic blood pressure exceeding 5 mmHg within 1 month.
3) Decline in LDL-cholesterol exceeding 0.5 mM within 1 month.
If the target is not met, the specific treatment should be terminated and replaced by another drug according to the algorithm. The missing effect on blood pressure should be validated by home blood pressure measurements according to national guidelines. For anti-hypertensive medication, another drug within the same class can be tried.”
As described in the added paragraph in page 13: “The suggested individualized treatment in the intervention group is made available to the treating GP, but the actual treatment is chosen at the discretion of the GP together with the patient. The intervention is designed to mimic the actual real life effect of specialist treatment suggestions and patients who do not follow the proposed algorithm are therefore not discontinued.”
The treating general practitioner therefore always has the final call on which medication to choose. In that sense rescue medication is allowed.

Comment: I assume that A,B, C etc is a consecutive order of medications used line after line for a given phenotype, correct? Or maybe it is a choice and the investigators might choose whatever fits best the patients needs?

Answer: Yes A, B, C,.. is additive. We have made a clarifying remark in the manuscript

Comment: Why SGLT-2s are not considered in these patients?

Answer: As the reduction of mortality with SGLT-2 inhibitors has only been shown in patients with prior cardiovascular disease, we have chosen to only include SGLT-2 inhibitors in patients with prior CVD. This has been added to the supplemental material.

Comment: (DDP4 sep ved insulin initiering) Why is that so?

Answer: See the added paragraph in the supplemental section

Comment: The study is very long and I expect that many patients might need reassessment of the treatment goals for a variety of factors not listed here. E.g. if the patient life expectancy drops dramatically due to the diagnosis of cancer, if the patient develops severe renal failure, severe stroke, if the social status changes dramatically (being alone with no family support) etc. Is there a way to allow such modifications? How are they going to be handled in the final analysis?

Answer: It is part of the intervention that the goal of the patient should be reassessed with time. And as we have written, the GP is free to chose the goal, of course with special focus on the conditions mentioned in the protocol. We have made a clarifying adjustment to the manuscript. As reassessment of the goal is a part of the intervention there will not be adjusted for this in the final analysis.

Comment: While I can only complement thoughtfulness of the protocol and a variety of treatment scenarios to provide solutions to a variety of clinical problems the complexity of the protocol makes it difficult for investigators. I expect therapeutic inertia (no decision taken despite of the need, delaying decisions, no intensification of insufficient therapy, no dose adjustments etc.) described in other trials adopting similar approach. How the study team is going to prevent this inertia and ensure that investigators and patients following the protocol? Assessing compliance with the treatment protocol is a fundamental step in evaluating further outcomes including primary. How compliance is going to be measured/analyzed?

Answer: Yes this is of great concern. At baseline the relevant information of the patient is gathered centrally to allow for a correct phenotyping. The part of the protocol relevant for the specific patient is written down, with an easy accessible resume at the beginning. The patient specific protocol recommendations is sent electronically to the electronic health record at the general practitioner. This process is iterated after 2 and 4 years. At follow-up it is also assessed whether the last recommendation have been followed. If not, it is possible to explore the reason for this. Furthermore the treating physicians will receive education regarding the protocol during the study

Comment: My comment above pertains even more to the lifestyle interventions. I understand that the objectives might not be fulfilled but the complexity of interventions, monitoring of a lifestyle makes the study very challenging for patients. The study team might expect missing data and high dropout. There is a high likelihood that only most motivated and disciplined patients remain in the trial which may bias the overall study results and make conclusions difficult to extrapolate.

Answer: Yes lifestyle modification is difficult to facilitate. The study tries to mimic clinical reality and therefore we do not expect 100% adherence to the lifestyle intervention. Our aim is to increase the prevalence of patients that adhere fully to the recommendations and to increase the prevalence of patients that partly adhere to the lifestyle intervention with simple means. As stated in the updated manuscript patients are not discontinued if they don’t follow the algorithm, including the lifestyle intervention. Adherence to individualized interval walking is automatically recorded centrally as all use of the app is recorded at a central server (Ried-Larsen et al 2016).

Use of the internet and smartphone platform is registrered through a personalized login and adherence is estimated through the login. Shortly, the intervention is an offer which is endorsed, with automatic and simple monitoring. We don't think this is a bias but a strength of the study. Mechanistic studies of lifestyle intervention might prove a concept. But until date these have not proved its worth in reality. What is of interest is, in this study, what works in reality. We test a comprehensive multifactorial intervention under real life setting, with feasible realistic interventions. Therefore we believe our data will be more simple to extrapolate to a real world setting compared to standardized and very controlled studies.

Comment: (Diet) Are these recommendations modifiable because of individual patients needs/preferences?

These recommendations forms the basis of the recipes that are available to the patients. All evidence on dietary modification is heavily depend upon massive support and in addition the effect fades over time as support is eased of. Such massive support is not feasible in a clinical reality which we aim to mimic. Therefore we have no illusion of 100% (or anything near) adherence to these recommendations. Our aim is to increase the prevalence of patients that adhere fully to the recommendations and to increase the prevalence of patients that have one or more low-carb meals on a regular basis. This is done by trying to make the implementation of the meals easy and available at all times.

What happens if the primary endpoint is driven by one single category e.g. hypo requiring hospitalization? Are you planning an analysis of time to the CV composite without hypo and cancer considered? It would be of interest.

Answer: we acknowledge the difficulty in putting equal weight in the single measures of the composite endpoint. We have added any microvascular and any macrovascular endpoint as tertiary endpoints in order to illustrate the separate effect of these.

Comment: Inclusion of cancer triggers some questions. Why is it included in this composite endpoint? Is any type of cancer considered? Are patients with preexisting cancer or cancer history excluded? How the diagnosis is going to be confirmed etc

Answer: See answer at an earlier comment. Yes any type of cancer is considered, except basocellular carcinoma as stated in table 1. A clarification has been added. The inclusion criteria are as stated in page 9. Some patients with cancer will probably be excluded due to a life expectancy below 2 years. But patients with cancer or prior cancer is not excluded per se. The diagnosis as other endpoints will be available from high quality Danish registries.

Comment: I understand that the outcomes will not be adjudicated which might be a significant limitation of this study.

Answer: Yes this is a limitation to the study as noted under limitations. Adjudication requires study contact with the control group. The registration in the Danish national patient registry has since 2002 been the basis of payment to Danish hospitals making the registration in the registries of very high quality, although limitations is still present (Schmidt M et al, clinical epidemiology 2015: 7)

Comment: Only one specific subcategory of severe hypoglycemia will be included. cases requiring third party assistance but not hospitalization will not be included which is a limitation.

Answer: yes this is a limitation, but is a consequence of the overall design. Hypoglycemia requiring hospitalization is available in registries and is therefore available in both the intervention group and the control group.

Comment: how exactly is it going to be defined? 100% reimbursement? Is there any drug accountability considered?

Answer: Drug adherence=total yearly reimbursed dose*100%/(intended daily dose*365days). No drug accountability is considered as patients will not receive medication from the study, but purchase medication without consideration of the study.

Comment: It might be interesting to look at proportions of patients reaching HbA1c and BP goals

Answer: Yes, an addition has been made

Comment: I am wondering if any other safety information is to be recorded and analyzed. I believe that AEs reporting and analysis although very complex, should be considered, at least the most relevant categories of hypoglycemia.

Answer: Yes we would very much like to have such data but the overall design does not make it possible. In the intervention group such data is collected at visits and through questionnaires every 3 month

Comment: What is an expected age of patients to be enrolled? If you do, do you consider some functional characterization of these patients? In general interpretation of treatment results in older patients without considering their functional status is difficult.

Answer: In DD2 among 5813 patients the median age was 62 year(IQR 53-69 years). Due to the design we cannot do any measurements of functionality in the control group and this is therefore not considered in the intervention group. We will have measures of social support which to some degree will have a relation to the functionality of the patients.

Comment: Based on the study timeline chart, 1Jan2018 cannot be end of study. Should it be 1Jan2028?

Answer: Yes this has been changed

Comment: not sure if the authors can claim this - the internvetion group will require input from specialists as well as dieticians - so more resources needed at least at study entry. The hypothesis is that there may be less healthcare resource use by end of the study.

Answer: A more precise description is added

Comment: is this an event-driven study or will all patients be followed for 10 years?

Answer: All patients will be followed for 10 years

VERSION 2 – REVIEW

REVIEWER	Daisuke Yabe Kyoto University Graduate School of Medicine, Japan No Competing Interest
REVIEW RETURNED	08-Sep-2017

GENERAL COMMENTS	The manuscript has been revised successfully based on comments by Reviewer.

REVIEWER	Jacek Kiljański Eli Lilly and Company, Global Medical Affairs, Warsaw, Poland
REVIEW RETURNED	02-Oct-2017

GENERAL COMMENTS	Thank you very much for considering my comments. The authors' responses and more importantly the edits made to the manuscript made the protocol clearer and more understandable. Some of concerns regarding the protocol and its execution remain (e.g. regarding avoidance of therapeutic inertia) but I understand why it is difficult to address them with the design of the study. Therefore I recommend acceptance of this paper and wish the authors success in the project which might potentially bring relevant information to the clinical and research community.