PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Head-to-Head comparison of intensive lifestyle intervention (U-TURN) vs. conventional multi-factorial care in patients with type 2 diabetes: Protocol and rationale for an assessor-blinded, parallel group, randomised trial
AUTHORS	Ried-Larsen, Mathias; Christensen, Robin; Hansen, Katrine; Johansen, Mette; Pedersen, Maria; Zacho, Morten; Hansen, Louise; Kofoed, Katja; Thomsen, Katja; Jensen, Mette; Nielsen, Rasmus; MacDonald, Chris; Langberg, Henning; Vaag, Allan; Pedersen, Bente; Karstoft, Kristian

VERSION 1 - REVIEW

REVIEWER	Giuseppe Pugliese Department of Clinical and Molecular Medicine, “La Sapienza” University, Rome, Italy
REVIEW RETURNED	10-Sep-2015

GENERAL COMMENTS	The Authors present the protocol for an assessor-blinded, parallel group one year randomised trial comparing an intensive lifestyle intervention (U-TURN) with conventional multi-factorial care in patients with type 2 diabetes (T2D). The primary outcome is change in glycaemic control (HbA1c), with the key secondary outcome being reductions in anti-diabetic medication. The study is interesting, as it test the hypothesis that intensive lifestyle changes is equally effective as standard diabetes care including pharmacological treatment in maintaining glycaemic control when implemented relatively early in T2D patients. However, it is not clear from the abstract that the intervention group will continue pharmacological treatment with the aim of reducing or discontinuing it. Another limitation is the assessment of physical activity based on a questionnaire.

REVIEWER	Cynthia Fritschi University of Illinois at Chicago, USA
REVIEW RETURNED	15-Sep-2015

GENERAL COMMENTS	This is a very ambitious and important trial and I commend the authors for their efforts. There are a few areas that were unclear and need more detail. 1. Since the intervention will comprise more exercise than standard recommendations, we need more detail regarding the activity portion

	of U-TURN. Specifically: How will dose and amount be determined for each subject? You give a broad range for minutes on page 9, but no explanation of how you will determine that number for each subject. Also-will all the subjects be exercising at a facility under supervision? How are you going to provide supervision if each of the group members chooses a different activity? This section is muddy-we need a lot more detail. 2. Self-reported adherence should be listed as a potential weakness. The use of daily, emailed diaries is a good idea since many subjects get bored with diaries, stop completing them, or fill them out only when they are meeting with the investigators. Will you be calling subjects who do not complete their diaries by a certain time each day? 3. Regarding medication titration: Why are you choosing NPH as the basal insulin to be used to lower FBS? Insulin glargine is a safer and better choice for bedtime insulin and there is less risk of nocturnal hypoglycemia. 4. This is a very complex study and goes beyond the lifestyle intervention used by the DPP. Please give more details about the exercise and diet portions of the intervention, as this is very exciting and would be helpful to anyone wanting to replicate the study in a different population. Additionally, the authors may want to publish their findings about what did and did not work with their intervention and subject adherence.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dear Dr. Pugliese. Thank you for your encouraging comments. The comments are answered point-by-point below.

Comment: However, it is not clear from the abstract that the intervention group will continue pharmacological treatment with the aim of reducing or discontinuing it.
Answer: We have specified this in the abstract.
Correction; “Both groups will be exposed to the same standardised, blinded, target driven pharmacological treatment and can thus maintain, increase, reduce or discontinue the pharmacological treatment. The decision is based upon the standardized algorithm.”

Comment: Another limitation is the assessment of physical activity based on a questionnaire.
Answer: We agree that this is a limitation and this have been mentioned in the discussion. The following text has been added to the ‘Ethics and dissemination’ section;
“Furthermore, the inclusion of self-reported physical activity and adherence pose a potential information bias, limiting the interpretation of the effects of the single intervention components on HbA1c.”

Reviewer: 2

Dear Dr. Fritschi. Thank you for the encouraging comments. We have responded to the comments point-by-point below.

Comment 1. Since the intervention will comprise more exercise than standard recommendations, we need more detail regarding the activity portion of U-TURN. Specifically: How will dose and amount be

determined for each subject? You give a broad range for minutes on page 9, but no explanation of how you will determine that number for each subject. Also-will all the subjects be exercising at a facility under supervision? How are you going to provide supervision if each of the group members chooses a different activity? This section is muddy-we need a lot more detail.
Answer: We have elaborated on intervention component 1(training) and included an example of a weekly training program (Table 2). Briefly, the intervention coordination center delivers a training program to the coaches every week. This program specifies the duration and intensity for all participants. However, the exact exercise modality (e.g. power walking, cycling etc.) is decided by the coaches to match the participants' preferences and to comply with injuries (e.g. in case of an injury in the arm, a modality using the legs is preferred). However, the intensity and volume is not altered.

Comment 2. Self-reported adherence should be listed as a potential weakness. The use of daily, emailed diaries is a good idea since many subjects get bored with diaries, stop completing them, or fill them out only when they are meeting with the investigators. Will you be calling subjects who do not complete their diaries by a certain time each day?
Answer: We have included self-reported adherence as a potential weakness. In relation to non-compliance with the questionnaire we have specified that the participant will be contacted by email or phone if they do no fill in the questionnaire three consecutive times. The following text has been added to the 'Ethics and dissemination' section
"Furthermore, the inclusion of self-reported physical activity and adherence pose a potential information bias, limiting the interpretation of the effects of the single intervention components on HbA1c."

Comment 3. Regarding medication titration: Why are you choosing NPH as the basal insulin to be used to lower FBS? Insulin glargine is a safer and better choice for bedtime insulin and there is less risk of nocturnal hypoglycemia.
Answer: The patients known to be at highest risk of developing hypoglycemic events are elderly with long diabetes duration and comorbidity such as nephropathy and cardiac disease. Also treatment combination with sulfonylurea and insulin increases risk of hypoglycemia. None of these risk factors are present in the UTURN patient group. However, we recognize that NPH insulin could result in increased risk of developing hypoglycemia. So, therefore we have decided to change the basal insulin from NPH to Abasaglar (insulin glargine biosimilar). Enrollment of patients have started, but so far no patients involved in the study have started insulin. We have corrected the type of insulin in the treatment algorithm and article.

Comment 4. This is a very complex study and goes beyond the lifestyle intervention used by the DPP. Please give more details about the exercise and diet portions of the intervention, as this is very exciting and would be helpful to anyone wanting to replicate the study in a different population. Additionally, the authors may want to publish their findings about what did and did not work with their intervention and subject adherence.
Answer: We agree that the intervention should be described in such detail that replication is possible. Thus, we have elaborated on the intervention components 1 and 2 (exercise and diet). For the exercise component please see the replay for your comment 1. For the elaboration on the diet component we have included a table (Table 3) describing the principles of the formation of the meal plans prepared by our dieticians. Furthermore we have included a paragraph about the timing of the main meals and snack meals in relation to exercise to minimize the risk of subjective hypoglycemia (please see description of the diet component below – changes are marked in yellow for your convenience). We do agree that a publication of 'best practice' is important following our study.