PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The long-term effect of smartphone-delivered Interval Walking Training on physical activity in patients with type 2 diabetes: protocol for a parallel group single-blinded randomized controlled trial
AUTHORS	Valentiner, Laura; Ried-Larsen, Mathias; Karstoft, Kristian; Brinkløv, Cecilie; Brøns, Charlotte; Nielsen, Rasmus; Christensen, Robin; Nielsen, Jens; Vaag, Allan; Pedersen, Bente; Langberg, Henning

VERSION 1 - REVIEW

REVIEWER	Kirsty Winkley King's College London & Institute of Psychiatry, Psychology & Neuroscience, UK
REVIEW RETURNED	26-Sep-201

GENERAL COMMENTS	Originality This is a protocol paper for a randomised controlled trial (RCT) of a smartphone-delivered Interval Walking Training (IWT) intervention which aims to improve physical activity in people with Type 2 diabetes (T2DM). There is a need to develop cost-effective interventions to improve health outcomes in people with T2DM and this intervention has the potential to provide benefits to many people if it is shown to be effective. The authors have previously demonstrated the feasibility of IWT in this population (Karstoft et al, 2013) and increasing physical activity is known to have a beneficial effect on glycaemic control in T2DM (Snowling et al, 2006). However, there is little focus on T2DM in terms of selection of outcome variables. There is no measure of glycaemic control nor blood pressure. Research questions The authors seek to answer 2 research questions following this trial: 1. to determine whether integrating IWT into usual rehabilitation care for this population is more effective than standard care at 12 months (phase 1); and 2. to determine whether adding in a motivational support program will increase physical activity following the intervention (rehabilitation care and IWT) compared with no motivational support at 12 months (phase 2). Study design This is a RCT and therefore appropriate to test the effectiveness of this intervention. Participants are eligible if they are 18 years or more and have T2DM and have been referred to rehabilitation by their GP. Therefore there may be variation/bias in terms of who GPs refer to rehabilitation from different sites. For example, it seems likely they will not refer people with mental health problems as this is not listed as an exclusion criterion. The interventions are described, page 13 onwards. It is not that clear as to who delivers the IWT, whether it is the health professionals already providing rehabilitation, or study employees. I did not understand sentence 5 and 6 in the first

	paragraph on page 13. In terms of the motivational interviewing component there is no information as to how treatment fidelity will be ensured, is this component questionnaire based or semi-structured, if the latter are sessions audio-taped and do the interventionists receive specific psychological skills training? The main outcome is well-described and concerns change in moderate-to-vigorous intensity physical activity measured using a physical activity monitor. This has been used to calculate sample size. The randomisation will be 2-stage as in phase 2 intervention participants will be randomised to receive motivational support or no motivational support. Randomisation will be stratified by gender and conducted by an independent researcher using a computer program. Outcome assessors are blinded to allocation status. Statistical analysis is Intention-To-Treat and there is plan for missing data. The study has been approved by an appropriate ethics committee. There is no information as to whether a process evaluation will be conducted. There is also no detail of any planned economic evaluation. Key messages Strengths and weaknesses section needs editing. The statements are not clear. Figures These are clearly presented Tables Table 2: IWT (p15) unclear, i.e. 'Three times per week, 60 minutes per session, twice a week at a health promotion center' IWT support/group, motivational support: not sure if these sessions are 1-to-1 or how long they are. Should participants receive everything on this list? Table 3: Notes to professionals, text not clear Checklist The SPIRIT checklist has been included.

REVIEWER	Neal Kaufman, MD MPH Canary Health UCLA Los Angeles CA
REVIEW RETURNED	04-Nov-2016

GENERAL COMMENTS	Very well done. Only question is would the study be more likely to show results if it was limited to individuals who currently aren't active?

REVIEWER	Steven K. Malin University of Virginia, United States
REVIEW RETURNED	07-Dec-2016

GENERAL COMMENTS	Overall the goal of this work is to assess the impact of a smartphone app on increasing/maintaining physical activity in people with type 2 diabetes. Behavior is the primary outcome. Secondary measures will include some clinical demographics. There are some minor points that warrant attention. Abstract: Intro reads a bit long. Also, are clinical health measures being assessed to show long-term care? Good to include here.

	Strengths: What do the authors mean by “visualizes”. Reads awkward. Introduction: none Methods: Is the word “superiority” needed on page 9, line 46? Why 8-12 weeks of intervention (page 10, line 9)? This seems like it would promote variation is learned behavior. Eligibility criteria does not make mention of depression or mental health status. Given the study is designed to assess behavior and/or compliance with the device, is the mental health status of concern here when assess psychology of these patients? Are food logs being assessed for nutritional change? This could impact body weight. Medication change may also be a part of lifestyle modification. Is this being documented? Will patients being insulin dependent at all and are patients to have cardiovascular disease? How will this be accounted for? Data collected appear to not list any information on fasting glucose and HbA1c. Is this correct? If so, how will the study inform people of glycemic control aside from medication only? Table 5 does not show VO2peak. Is this being done at pre, post and follow up? What method is used to test VO2peak and is it on the treadmill? Page 32, line 13 suggests a submaximal prediction test is used. This should be clarified as it is unclear if indirect calorimetry is being used to measure O2 or if this is simplybeing predicted from an equation. How will cardiovascular health be assessed if at all? No BP records or lipid measures? While behavior may change it would strengthen the finding to relate back to clinical outcomes (e.g. metabolic syndrome). Table 5 gives no insight. Where will waist circumference be measured? Will this be standardized? Page 34, line 40 “VO2max” replaced with “VO2peak”? Page 38, line 9; typo with “)” and page 39 “preceeding’s”? grammatical error. Will weight loss be adjusted for statistically? This may be important

	as diet could impact behavior, not exercise. Also, age, race, smoking, etc? This appears missing from the statistical section. Figure 1: Spelling errors “advice”; check others. Figure 2 and 3 are difficult to read Discussion: There is no discussion of the potential for sex differences or potential for drug-to-exercise interaction, which could impact interpretation of results. Can the authors comment?

VERSION 1 – AUTHOR RESPONSE

Reviewer #1

Originality

This is a protocol paper for a randomised controlled trial (RCT) of a smartphone-delivered Interval Walking Training (IWT) intervention which aims to improve physical activity in people with Type 2 diabetes (T2DM). There is a need to develop cost-effective interventions to improve health outcomes in people with T2DM and this intervention has the potential to provide benefits to many people if it is shown to be effective.

The authors have previously demonstrated the feasibility of IWT in this population (Karstoft et al, 2013) and increasing physical activity is known to have a beneficial effect on glycaemic control in T2DM (Snowling et al, 2006). However, there is little focus on T2DM in terms of selection of outcome variables. There is no measure of glycaemic control nor blood pressure.

Thank you for your comment regarding measurement of glycaemic control and blood pressure. We agree with the reviewer that it could have been a strength to address both outcomes in this trial. As previous studies have shown that physical activity influences glycaemic control and moreover, several studies have found that medication and dietary interventions in the patients with T2D improves glycaemic control and reduces disease related complications, we have chosen the primary outcome in the InterWalk trial to be physical activity in relation to everyday life. The secondary outcomes reflect patients’ adherence and motivation to a physically active daily life in terms of long-term follow-up at 52-weeks. We have clarified this in the text.

“Trial endpoints and Assessments

Previous studies have established that physical activity influences glycaemic control [36] and Karstoft and colleagues (2013) has shown that physical activity with Interval Walking Training had effect on glycaemic control in patients with T2D. [15] Moreover, medication and dietary interventions have also proven to improve glycaemic control and reduce disease related complications.[37–39] In the present trial the primary outcome focus on physical activity in relation to everyday life (end of page 26, section Trial endpoints and Assessments)”

Research questions

The authors seek to answer 2 research questions following this trial:

1. to determine whether integrating IWT into usual rehabilitation care for this population is more effective than standard care at 12 months (phase 1); and 2. to determine whether adding in a motivational support program will increase physical activity following the intervention (rehabilitation care and IWT) compared with no motivational support at 12 months (phase 2).

Study design

This is a RCT and therefore appropriate to test the effectiveness of this intervention. Participants are eligible if they are 18 years or more and have T2DM and have been referred to rehabilitation by their GP. Therefore, there may be variation/bias in terms of who GPs refer to rehabilitation from different sites. For example, it seems likely they will not refer people with mental health problems as this is not listed as an exclusion criterion.

We acknowledge that this is a valid point to make. However, the trial is designed to take place directly in the clinical setting to reflect patients with T2D referred to rehabilitation in the municipality. There is no formal collaboration with the general practitioners (GP) in the participating municipalities and the GPs are not familiar with the InterWalk trial. As such they do not prioritize patients referred to rehabilitation in the municipalities. The screening, recruitment and inclusion is conducted by the health professionals at health promotion centres. We have clarified the procedures in the text.

"Briefly, GPs refer patients diagnosed with T2D to rehabilitation at either an out-patient clinic, within a municipality or at the hospital level in Denmark. The setting depends on stage of the disease, presence of complications and co-morbidities e.g. severe heart conditions, depression or mental illness. The municipality based rehabilitation primarily includes non-complicated patients (~80% of all patients).[21] If complications or co-morbidities are present, patients are referred to treatment at a specialized clinic at a hospital. (METHODS AND ANALYSIS, *Trial design and setting, last section page 10)"*

The interventions are described, page 13 onwards.

It is not that clear as to who delivers the IWT, whether it is the health professionals already providing rehabilitation, or study employees. I did not understand sentence 5 and 6 in the first paragraph on page 13.

We apologize for the confusion on who delivers the IWT intervention and sentence 5 and 6 in the first paragraph. We have clarified the sections in the text (page 13).

(IWT intervention)

"Interventions

The trial is developed in collaboration with the health professionals from the municipality of Copenhagen in Denmark. The interventions are designed to reflect the clinical rehabilitation settings in Denmark in order to increase the likelihood of implementation of the programme following this trial, if proven superior. Health professionals from the municipalities already providing the rehabilitation delivers all interventions in both the control and experimental groups during the trial period"

….

(sentence 5 and 6, page 13)

…"Furthermore, all participating health professionals underwent a thorough education programme (15 hours in total) involving all procedures and manuals in the trial. *This was done to ensure standardization of all procedures throughout the trial. In addition, workshops were held from the start of the trial (January 2014) and hereafter every second month. This is done to secure that the health professionals follow all procedures and prepared manuals throughout the trial"*

In terms of the motivational interviewing component there is no information as to how treatment fidelity will be ensured, is this component questionnaire based or semi-structured, if the latter are sessions audio-taped and do the interventionists receive specific psychological skills training?

Thank you for pointing this out. Motivational interviewing in the InterWalk trial is conducted using a semi-structured approach. All health professionals involved in the trial have been well educated in conduction the motivational interview ***(page 22, first paragraph).***

"Motivational interview and goal setting: All health professionals from the municipalities are well-educated in conducting the motivational interview with patients. All health professionals working in a health promotion centre in Denmark are obligated to participate in formalised motivational interviewing courses conducted by educators with psychological background"

Treatment fidelity is important and the text in the manuscript has been revised

…"The motivational interview seek to help the patients reflect on their physically active habits and to set individual motivating goals related to everyday life.[27] The health professional secures all notes and reflections from the interview in the InterWalk database. As more than one interview is conducted over the trial period fidelity may be ensured when the health professional uses the patient's reflections from the former interview to help reflect upon motivation and barriers towards changes in the next motivational interview"

The main outcome is well-described and concerns change in moderate-to-vigorous intensity physical activity measured using a physical activity monitor. This has been used to calculate sample size. The randomisation will be 2-stage as in phase 2 intervention participants will be randomised to receive motivational support or no motivational support. Randomisation will be stratified by gender and conducted by an independent researcher using a computer program. Outcome assessors are blinded to allocation status. Statistical analysis is Intention-To-Treat and there is plan for missing data. The study has been approved by an appropriate ethics committee.

There is no information as to whether a process evaluation will be conducted. There is also no detail of any planned economic evaluation.

This is a very valid point. Economic evaluation is not something that we have planned to do so far. It however a very good idea and when the trial is finished we will collaborate with the participating municipalities regarding evaluation of the trial both in concern of the economical aspect and regarding implementation of the findings in the clinical rehabilitation context.

Key messages
Strengths and weaknesses section needs editing. The statements are not clear.

Thank you for pointing this out. Please see the response to the editor on page 2.

Table 2: IWT (p15) unclear, i.e. 'Three times per week, 60 minutes per session, twice a week at a health promotion centre'
IWT support/group, motivational support: not sure if these sessions are 1-to-1 or how long they are. Should participants receive everything on this list?

We apologise for the confusion in table 2 regarding IWT and IWT support. The text has been revised in the table with red font, see below (the corrections have been revised in the manuscript, pages 15-16)

Table 2. INTERVENTIONS IN THE TRIAL DURING PHASE ONE AND TWO

PHASE ONE	**STANDARD CARE (CONTROL INTERVENTION)**	
	Group based training at the health promotion centre **(Control intervention)** **(1/3)**	• Group based sessions with 4-12 patients • Two sessions per week at the health promotion centre • Warm-up exercises • Cardio-respiratory exercises • Resistance training • Cool down period
	EXPERIMENTAL INTERVENTION	
	Interval Waling Training **(IWT) (2/3)**	• Group based Interval Walking Training (IWT) using the InterWalk app • Introduction to the InterWalk app • Follow-up instructions and guidance • IWT using the InterWalk app • *Three times per week, 60 minutes per session - twice a week at a health promotion centre in a group and one time alone in everyday life* • End of phase one: preparation to continue IWT with IW app in the end of the intervention period, through a transition program
PHASE TWO	**STANDARD CARE (CONTROL INTERVENTION)**	
	Group based training at the health promotion centre **(Control intervention) (1/3)**	• No intervention at the health promotion centre • Follow-up at 52-week

EXPERIMENTAL INTERVENTION

IWTgroup (1/3)

- No intervention at the health promotion centre
- Follow-up at 52-weeks

IWTsupport-group (1/3)

Motivational Support

1. ***Individual Motivational interviews with individual goal setting (semi-structured)***

- *Four semi-structured individual motivational interviews are scheduled in phase two: week 16, 20, 28, 40*
- *Each interview is scheduled to last 30 minutes*
- Individual goal setting related to everyday life following the SMART-principle.
- The aim of goal setting is to help the patient reflect on their physical activity habits

2. ***Short Message Service (SMS)***
One weekly SMS and one SMS every forth week

- Weekly SMS
- The reply indicates amount of IWT during the past week (none, 1-2 or 3 or more)
- If no reply for two consecutive weeks, or if the reply indicates none-walking, then the patient is contacted by phone by a health professional
- SMS every forth week
- Encourages the patient to make a new walking test using the InterWalk app

- Educated patients with T2D do interval walking in local community near the health promotion centres
- One session per week

	3. Interval Walking Ambassadors	
Co-interventions **(Across phase one and two)**	**ADDITIONAL REHABILITATION CARE (CO-INTERVENTIONS) WITH SPECIFIC FOCUS AREAS**	
	Patient education	Disease related education regarding living with type 2 diabetes, empowerment and self-management and medication handled by either medical doctor, a nurse, physical therapist or dietitian and another patient with type 2 diabetes - group based or individually handled
	Diet counselling	Diabetes specific diet counselling - group based or individually handled by a dietitian
	Smoking Cessation	Smoking cessation courses is handled by smoking cessation counselors The course lasts 10-12 hours and can be either individually or group based

Table 3: Notes to professionals, text not clear

Thank you for pointing this out. We have revised the text regarding the health professionals in table 3 (see next page)

Table 3, EXAMPLE OF EXPERIMENTAL INTERVENTION FOR ONE WEEK IN PHASE ONE

Weekday	Intervention at the Health promotion centre	Independent training in own environment	Notes to health professionals
Monday	Duration: 90 minutes 1. Warm-up: short walk in a group to the walking point (either a park or an area near the health promotion centre) 2. Interval Walking Training: every patient does Interval Walking Training with the InterWalk app for a minimum of 30 minutes. Every patient does the Interval Walking Training by themselves so that the app instructions during the session can be followed. The health professionals guide and facilitate the individual patient if necessary. After the Interval Walking Training everyone goes back to the health promotion centre 3. Group conversation at the health promotion centre after doing interval walking with all participating patients. Different focus areas are discussed in the group. Everyone sits on a chair and the health professional participates as a facilitators in the group conversation (examples of focus areas: weather conditions, motivation for exercise, social needs when waking, motivation for a physically active everyday life)		Remember to encourage and guide every patient to do Interval Walking Training three times a week either by themselves or together with other patients. Make sure that everyone are active during the walking sessions. If a patient needs to do a new walking test then it is the health professional who should help during the intervention period. Every patient need a new test every forth week.
Tuesday	Rest day		
Wednesday	Duration: 90 minutes 1. Warm-up: short walk in a group to the walking point (either a park or an area near the health promotion centre) 2. Interval Walking Training: every patient does Interval Walking Training with the InterWalk app for a minimum of 30 minutes. Every patient does the Interval Walking Training by themselves so that the app instructions during the session can be followed. The health professionals guide and facilitate individual patient if necessary. After the Interval Walking Training everyone goes back to the health promotion centre. 3. Group conversation at the health promotion centre after doing interval walking with all participating patients. Different focus areas are discussed in the group. Everyone sits on a chair and the health		

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	professional participates as a facilitators in the group conversation (examples of focus areas: weather conditions, motivation for exercise, social needs when waking, motivation for a physically active everyday life)		
Thursday	Rest day		
Friday	Rest day		
Saturday		Interval walking using the InterWalk application for 30-60 minutes. Can be done alone or together with other patients.	
Sunday	Rest day		

Patients allocated to the experimental intervention do interval walking twice a week, 30 to 60 minutes per session during phase one at the health promotion centre in small groups of 3-12 patients. A third session is conducted in the patient's everyday life environment.

Reviewer #2

Very well done. Only question is would the study be more likely to show results if it was limited to individuals who currently aren't active?

Thank you. We agree with the reviewer that effect of the intervention in the trial is more likely to show results with a non-active population of patient with T2D. However, many patients with T2D referred to rehabilitation in the municipal setting by the general practitioner do not follow international recommendations regarding daily physical activity and as such the trial with its primary and secondary endpoints is still relevant.

Reviewer #3

Overall the goal of this work is to assess the impact of a smartphone app on increasing/ maintaining physical activity in people with type 2 diabetes. Behavior is the primary outcome. Secondary measures will include some clinical demographics. There are some minor points that warrant attention.

Abstract:

Intro reads a bit long.

Thank you for pointing this out. We have shortened the abstract including the introduction paragraph (pages 4-5)

Also, are clinical health measures being assessed to show long-term care? Good to include here.

We agree that the long-term follow-up at 52-weeks could be more clear in the manuscript. Clinical health outcomes are now mentioned in the abstract in the 'Methods' section and we revised the text to also include clinical outcomes (page 4-5)

Other secondary outcomes VO_2-peak and strength in the lower extremities.

Strengths:
What do the authors mean by "visualizes". Reads awkward.

Thank you for pointing this out. Please see the response to the editor on page 1.

Methods:
Is the word "superiority" needed on page 9, line 46?

We have removed the word "superiority" from the first sentence in the 'Trial design and setting' section

Why 8-12 weeks of intervention (page 10, line 9)? This seems like it would promote variation is learned behavior.

We agree that the different intervention periods in phase I in the trial may cause a variation in learned behaviour. However, the trial has a pragmatic design that adapts and emphasizes how the real clinical setting is structured relative to the participating municipalities. Moreover, the applicability of the trial results is increased, as the interventions are already part of the rehabilitation programme

offered to patients with T2D in the individual municipality. We will adjust for the difference in intervention length between municipalities in the statistical analysis.

Eligibility criteria does not make mention of depression or mental health status. Given the study is designed to assess behavior and/or compliance with the device, is the mental health status of concern here when assess psychology of these patients?

We acknowledge that this is a valid point to make. All patients are screened for depression and mental illness before starting rehabilitation in the municipalities. If however, there are patients that are referred anaway all health professionals (physical therapists, nurses and staff with a master's degree) are as part of their job trained to deal with patients that experiences psychological challenges with depression or mental illness during their rehabilitation period. If a patient experiences more severe problems then the patient will be referred to a trained psychologist working in the municipality.

Are food logs being assessed for nutritional change? This could impact body weight.

We agree that a nutritional change could impact body weight. We do not collect data regarding diet and nutritional intake. However, this is not a primary outcome but it is part of the explorative outcomes in the trial. The section '*Demographic, social economic and anthropometry measures'* describes the procedures, the text has been rephrased (pages 34-35)

Information on height, weight, waist and hip circumference is collected before inclusion through an electronic questionnaire at the first formal meeting at the health promotion centre and after the intervention period and again at 52-week follow-up. Waist circumference is measured at the point between the top of the iliac crest and the bottom of the costae regardless of the placement of the umbilicus. A Tanita stadiometer is used to measure height and an electronic weight to measure weight. ***Relevant national registers will be used to obtain information regarding hospitalization, co-morbidities, medical history, use of medicine and mortality.***

Medication change may also be a part of lifestyle modification. Is this being documented? Will patients being insulin dependent at all and are patients to have cardiovascular disease? How will this be accounted for?

Thank you for pointing this out. Table 5 gives a summary of data collection and measures. As part of the table data on self-reported and register data on medication use is collected at baseline, after the intervention and again at long-term follow-up at 52-weeks. We have clarified this point in the text in the '*Demographic, social economic and anthropometry measures'* describes the procedures, the text has been rephrased (pages 34-35)

Data on self-reported information together with ***relevant national registers will be used to obtain information regarding hospitalization, co-morbidities, medical history, use of medicine and mortality.***

Data collected appear to not list any information on fasting glucose and HbA1c. Is this correct? If so, how will the study inform people of glycemic control aside from medication only?

It is correct that the trial does not list any information on fasting glucose and HbA1c. In Denmark all patients are controlled by their GP every 3. month and as such the trial and the health professionals do not inform people of glycaemic control apart from the information from the GP.

Table 5 does not show VO2peak. Is this being done at pre, post and follow up? What method is used to test VO2peak and is it on the treadmill? Page 32, line 13 suggests a submaximal prediction test is used. This should be clarified as it is unclear if indirect calorimetry is being used to measure O2 or if this is simply being predicted from an equation.

Thank you for pointing this out. VO2-peak is measured by a validated and standardised walking test consisting of 5 stages incorporated in the InterWalk app and is measured at baseline, after the intervention and again at long-term follow-up at 52-weeks. The text has been rephrased (page 33, section VO2-peak)

VO_2-peak is measured by a validated and standardised walking test consisting of 5 stages incorporated in the InterWalk app; 1) 30 sec. of standing still, 2) 2 min. of slow walking 3) 2 min. of walking at moderate intensity 4) 2 min. walking at high intensity 5) 1 min. walking at highest intensity possible. The four paces are self-selected (See, Figure 3 and 4).[25]

Table 5 has been corrected (page 28)

How will cardiovascular health be assessed if at all? No BP records or lipid measures? While behavior may change it would strengthen the finding to relate back to clinical outcomes (e.g. metabolic syndrome). Table 5 gives no insight.

We acknowledge that cardiovascular health and BT and lipid measures is important in patients with T2D. However, in this trial the main focus is on physical activity and the clinical setting in which the interventions takes place. Control measures regarding lipids and glycaemic control is conducted by the GP. It is the health professionals that recruit, include, tests and conduct the intervention in the trial. There are no GP's working at the health promotion centres in the Danish municipalities and we want the findings in the trial to reflect the real rehabilitation setting in Denmark.

Where will waist circumference be measured? Will this be standardized?

We apologize for the confusion regarding standardization of waist circumference. We have clarified this in the text (page 34-35).

Waist circumference is measured at the point between the top of the iliac crest and the bottom of the costae regardless of the placement of the umbilicus. A Tanita stadiometer is used to measure height and an electronic weight to measure weight.

Page 34, line 40 "VO2max" replaced with "VO2peak"?

Thank you for pointing this out. The text has been rephrased (page 35)

Page 38, line 9; typo with ")" and page 39 "preceeding's"? grammatical error.

Thank you for pointing this out. The text has been corrected.

Will weight loss be adjusted for statistically? This may be important as diet could impact behavior, not exercise. Also, age, race, smoking, etc? This appears missing from the statistical section.

The statistical analysis section now state (page 38)

"A linear mixed model analysis includes all patients with a baseline assessment, and includes both fixed and random factors. Thus, repeated linear mixed model method is chosen for the primary analyses in this trial (i.e., no data imputation), whereas the BOCF imputation, as well as the 'Per Protocol' population will be applied for the purpose of sensitivity analysis. Also, we will explore whether potentially important covariates such as age, sex, disease duration, degree of overweight (using BMI), and smoking status at enrollment/baseline could potentially confound the results from the primary analyses (ie, an extra prespecified sensitivity analysis). Exploratory analyses of the treatment effects will be performed on some of the secondary outcomes"

Figure 1: Spelling errors "advice"; check others.

Thank you for pointing this out. The spelling errors have been corrected in Figure 1

Figure 2 and 3 are difficult to read

Figure 2 and 3 have been corrected

Discussion:
There is no discussion of the potential for sex differences or potential for drug-to-exercise interaction, which could impact interpretation of results. Can the authors comment?

Thank you for bringing this up. The discussion of the potential for sex differences or potential for drug-to-exercise interaction is a very interesting point. It is not a discussion that we will bring into the protocol paper. We will however, address this when all data are collected and the paper on primary endpoint is written.

VERSION 2 – REVIEW

REVIEWER	Kirsty Winkley, PhD King's College London & Institute of Psychiatry UK
REVIEW RETURNED	20-Jan-2017

GENERAL COMMENTS	Thank you for your careful and thorough revision and for addressing the points I and the other reviewers made. I think the manuscript is much improved. The only other suggestion I would have is to remove from the 'Strengths' section the point about the association between physical activity and HbA1c as you are not testing it here.

REVIEWER	Neal Kaufman, MD MPH UCLA schools of Medicine and Public Health USA
REVIEW RETURNED	03-Feb-2017

GENERAL COMMENTS	Well done research protocol

REVIEWER	Steven K. Malin University of Virginia and United States of America
REVIEW RETURNED	31-Jan-2017

GENERAL COMMENTS	Concerns have been addressed.

VERSION 2 – AUTHOR RESPONSE

Reviewer #1

Thank you for your careful and thorough revision and for addressing the points I and

the other reviewers made. I think the manuscript is much improved. The only other

suggestion I would have is to remove from the 'Strengths' section the point about the association between physical activity and HbA1c as you are not testing it here.

Thank you for your comment on the ‘Strengths’ section regarding “The efficiency of Interval Walking Training on e.g. glycaemic control has previously been demonstrated”. It is true that we are not testing this in this trial and we have therefor removed this point from the ‘Strengths’ section. The section now reads:

STREGTHS:

o The trial is the largest of its kind, and meets the criteria for high quality randomized controlled trials with central randomization and use of valid and reliable measures.

o The trial has a long-term follow-up period of 52-weeks from baseline.

o The trial has high external validity with relevance for the clinical setting as it is performed within clinical practice and includes a limited use of inclusion/exclusion criteria’s.

Reviewer #2

Well done research protocol

Thank you for you comment.

Reviewer #3

Concerns have been addressed

Thank you for you comment.