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TITLE:

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

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RUNNING HEAD

Effect of Interval Walking on Type 2 Diabetics

BRIEF TITLE:

The InterWalk Trial

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ABSTRACT:

Introduction

Physical activity is a cornerstone in rehabilitation of Type 2 diabetes patients (T2D). Development of effective long-term and low cost strategies to keep these patients' physically active is needed. However, maintaining physical activity behaviour is difficult once formalised interventions end. One potentially effective strategy includes structured exercise training supported by mobile technology and remote feedback.

The aim is to investigate whether mobile health support using the InterWalk application for smartphones is effective in increasing the physical activity level in persons with T2D over time compared to standard care.

We investigate if a rehabilitation programme with interval walking training using the InterWalk app is superior to Danish municipality-based rehabilitation in increasing moderate-and-vigorous physical activity level in patients with T2D across 52 weeks. Secondary, we hypothesize that a motivational programme added from end of intervention to 52-weeks further increases level of physical activity in everyday life in patients with T2D.

Methods and analysis

The trial is a parallel-group, open-labelled, randomised controlled trial with 52-week follow-up including patients with T2D. The primary outcome is change in moderate-and-vigorous physical activity. The key secondary outcome includes motivation for physical

activity behaviour change. Exclusion criterion is medical contraindication to exercise. We include up to 246 patients and randomly allocate them into a control (standard group exercise) or an experimental group (8-12 weeks of interval walking training supported by the smartphone-based InterWalk application) in a 1:2 fashion. After intervention, the experimental group is randomly allocated into two follow-up conditions with unsupervised interval walking training with or without motivational support until 52-week follow-up. Data is analysed by the Intention-To-Treat principle.

Ethics and Dissemination

The local regional Research Ethics Committee in Denmark (H-1-2014-074) and the Danish Data Protection Agency (j.nr. 2014-54-0897) has approved the trial. Positive, negative or inconclusive results will be disseminated in scientific journals and conferences.

Trial registration: NCT02341690

Keywords: Type 2 diabetes, Rehabilitation, Interval walking Training, Physical activity, Behaviour maintenance

STREGTHS:

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

- The trial gives knowledge to the lacking evidence on pragmatic designed trials and secures directly implementable interventions in clinical practice
- The trial visualises the importance of individual motivation regarding behavioural change with physical activity when diagnosed with type 2 diabetes

LIMITS:

- We are aware that the design of the trial with a multi centre setup may cause variation in the testing situations were the performance can depend in the individual health professional. Accordingly, all results will be interpreted conservatively.

INTRODUCTION

Physical activity (PA) is a cornerstone in the clinical care of patients with type 2 diabetes (T2D).[1] PA activity has beneficial effect on glycaemic control and other key metabolic risk factors [2,3], as well as improvements in quality of life.[4,5] Furthermore, supervised long-term PA interventions have proven effective in improving glycaemic control.[2,6] However, experimental evidence does not support the efficiency of advice about physical activity alone.[7] As the number of patients with T2D is estimated to rise to 500 million by 2030 worldwide [8,9] the implementation of structured, long-term and supervised exercise regimes constitutes a large societal challenge and is not feasible. Thus, novel strategies to increase physical activity among patients with T2D are needed.

Smartphones have been used as a tool to register exercise, diet, weight and plasma glucose levels, but the evidence for using a smartphone as an exercise device and a self-management tool in the diabetes care is lacking.[10] However, emerging evidence suggest that eHealth solutions using information and communication technologies [11] can educate and engage patients with T2D in long-term self-management.[12–14] Due to the large ingress and ownership of smartphones, a smartphone-supported approach could prove feasible in increasing physical activity among patients with T2D and accommodate the increasing prevalence of T2D.

Efficiency of interval walking training (IWT) in patients with T2D has been established.[15] In the study by Karstoft and co-workers, IWT was administered and

monitored using a small exercise computer (JD-mate). IWT induced significant improvements in physical fitness level, body composition and glycaemic control and in adherence of more than 85% over a 16 weeks period.[15] The potential benefits of implementing eHealth solutions in T2D management and the apparent health benefits of and adherence to IWT gave rise to the development of the InterWalk application (InterWalk app) to deliver IWT.[16]

There is a lack of knowledge about the integration of PA in the everyday life of the patient following rehabilitation interventions.[17] It is, however, known that successful behavioural change depends on an on-going maintenance of individual motivation regarding the behaviour and behavioural change itself.[18] Furthermore, time since onset of diagnosis, unhealthy behaviour and own beliefs about the cause of the problem, together with the number of previous attempts to change and support from partners, peers and health professionals are of relevance.[18] This underlines the need for new interventions with a direct focus on motivational support and self-control regarding sustaining a newly acquired behavioural change with PA. To better target and structure manageable interventions related to patients with T2D, understanding patients' individual priorities and values are crucial. In this regard, knowledge of individual motivation and self-efficacy to initiate behavioural changes becomes essential to understand.[18]

This paper presents a detailed protocol for the InterWalk Randomised Controlled Trial and is described in accordance with the SPIRIT guidelines (Standard Protocol Items: Recommendations for Interventional Trials).[19] Results from the trial will

follow CONSORT guidelines (CONsolidated Standards Of Reporting Trials) for non-pharmacological interventions.[20]

Trial objective and hypothesis

The objective of the trial is to investigate whether mobile support using the InterWalk application for smartphones is effective in increasing the physical activity level in persons with type 2 diabetes over time compared with a standard care rehabilitation program.

We investigate the effectiveness of the implementation of interval walking training using the InterWalk application in the Danish municipality-based rehabilitation program and study whether the interval walking training is superior to standard care in increasing moderate-vigorous physical activity 52 after weeks. Furthermore, we expect that a motivational support program added from end of the intervention to 52-weeks, will increase the physical activity level in patients with type 2 diabetes and help maintaining a physically active everyday life long-term.

METHODS AND ANALYSIS

Trial design and setting

The trial is a 52-week parallel-arm, open-labelled, randomised controlled superiority trial. The participants are randomly allocated into two groups, 1) standard care or 2) experimental group with moderate-and-vigorous physical activity level, doing interval

walking facilitated by the InterWalk app. After an 8-12-week intervention period, patients in the experimental group are allocated to do interval walking using the InterWalk app with or without motivational support provided by the health professionals (see Figure 1).

[INSERT FIGURE 1 ABOUT HERE]

The intervention is conducted at the health promotion centres in Danish municipalities and hospitals that consecutively are included as cooperation partners. The municipality of Copenhagen is the first collaborator in the trial. Patients are referred to rehabilitation by their general practitioner (GP). Trained health professionals (physical therapists, nurses and staff with a master's degree) working at the health promotion centres recruit the patients, deliver the interventions and conduct all testing. The overall organization of health care in Denmark is fully tax-financed with universal access to health care services. The Danish model is described in detail elsewhere [21,22] and chronic disease care (including T2D) management is in Denmark based in the Chronic Care Model.[23]

Briefly, all patients diagnosed T2D can be referred to rehabilitation at either an out-patient clinic, municipality or hospital level in Denmark by their GP. The municipality based rehabilitation primarily includes non-complicated patients (~80% of all patients) referred from GPs.[21] If complications or co-morbidities are present, patients are referred to treatment at a specialized clinic at a hospital. Patients with a non-complicated

course of disease receive rehabilitation consisting of: 1) disease-specific patient education, 2) diet counseling, 3) smoking cessation and 4) exercise. The composition of the individual rehabilitation program depends however on disease progression and on the rehabilitation offered in the municipality-based program or at the hospital. The general focus is patient empowerment, disease-related self-care and prevention of a decay of the functional capacity of patients with T2D.

The Scientific Ethical Committee at the Capital Region of Denmark (H-1-2014-074), and the Danish Data Protection Agency (j.nr. 2014-54-0897) have approved the trial. The InterWalk application is approved by the Danish Data Protection Agency (2008-58-0035). The trial has been registered at http://www.clinicaltrials.org (NCT02341690) on January 9th, 2015. Amendments to the protocol will be approved by the Scientific Ethical Committee at the Capital Region of Denmark. Amendments will be reported to http://www.clinicaltrials.org. The trial is conducted in accordance with the Helsinki Declaration.

Participants

Eligibility

All non-complicated patients diagnosed with T2D (out-patients), referred to a health promotion centre or hospital in the participating municipalities by their GP, are eligible if more than 18 years of age. A flow chart of participants is presented in Figure 2.

[INSERT FIGURE 2 ABOUT HERE]

The exclusion criteria are medical contraindications to exercise e.g. chronic complications in the locomotive apparatus, painful osteoarthritis or heart conditions.[24] Information is collected through medical records and at a screening interview with a health professional at the health promotion centre. Furthermore, patients are excluded if they do not want to be physically active in the rehabilitation setting or are already participating in other intervention studies at a health promotion centre. The patients have to be able to talk, read and understand the Danish language (for overview over in- and exclusion criterion, see Table 1).

Table 1. ELIGIBILITY CRITERIA

Inclusion criteria
• Diagnosed with type 2 diabetes
• Referred by General practitioner to a health promoting center in participating municipality or hospital
Exclusion criteria
• < 18 years of age
• Medical contraindications to exercise
• Already participating in other exercise trials
• Does not talk and read Danish

If eligible, health professionals give oral and formalized written information with two days to consider participation in the trial. Written informed consent is obtained before any additional trial procedures. Enrolment was initiated in January 2015 and recruitment is terminated on December 15th 2016. Last-patient-last-visit is expected in December 2017.

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. The investigators (LSV, CB and HL) led four workshops (16 hours in total) with the health professionals during year 2014, in which the interventions of the study and work routines were discussed in detail. Furthermore, all participating health professionals underwent a thorough education program (15 hours in total) involving all procedures and manuals in the trial. This was done to ensure a standardization of all procedures throughout the trial. In addition, consecutive workshops were and are held from the start of the trial (January 2014) every second month to secure all routines and education level for all health professionals throughout the trial. The applicability of the trial results is hereby increased, as the interventions are already part of the rehabilitation programme offered to patients with T2D in the municipalities.

The interventions in the trial consist of two phases (Figure 1). In phase one (8-12 weeks), patients are randomised to either a standard care group (control intervention) or an experimental group doing IWT using the InterWalk app. The present trial uses the standard care programme as control intervention and is conducted directly in the clinical

setting. All patients receive supervision across phase one. In phase two (40-44 weeks), patients in the standard care group have no follow-up until 52 weeks post baseline. Patients in the experimental intervention group are in phase two randomly allocated to either IWT with or without motivational support (see section Experimental intervention – Interval Walking with the InterWalk application). Additional rehabilitation care (co-interventions) with disease-specific patient education, diet counseling and smoking cessation is offered to all patients across the intervention groups. The interventions are summarized in Table 2.

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

PHASE ONE	**STANDARD CARE (CONTROL INTERVENTION)**	
	Group based training at the health promotion center (Control intervention) (1/3)	• Group based sessions with 4-12 patients • Two sessions per week at the health promotion center • 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 center • 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 center (Control intervention) (1/3)	• No intervention at the health promotion center • Follow-up at 52-week
	EXPERIMENTAL INTERVENTION	
	IWTgroup (1/3)	• No intervention at the health promotion center • Follow-up at 52-weeks

	IWTsupport-group (1/3) **Motivational Support** ***1. Motivational interviews with individual goal setting***	• Four motivational interviews are scheduled in phase two: week 16, 20, 28, 40 • 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
	3. Interval Walking Ambassadors	• Educated patients with T2D do interval walking in local community near the health promotion centers • One session per week
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 counseling	Diabetes specific diet counseling - 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

Experimental intervention – Interval Walking with the InterWalk application

Patients allocated to the experimental intervention do interval walking after baseline test provided by health professionals (phase one). IWT is provided by health professionals to smaller groups of 3-12 patients. After the intervention period in phase two patients are allocated to either receive IWT without motivational support during follow-up (IWTgroup) or IWT with motivational support during follow-up (IWTsupport-group) (Figure 1). Trained health professionals conduct the IWT sessions (see below) and the motivational support in phase two. Table 2 gives an example of a typical week with interval walking in the experimental intervention group.

Interval Walking Training using The InterWalk Application

Interval walking training is performed using the InterWalk app, which works as a personal trainer as well as a monitoring unit allowing researchers to continuously and automatically monitor and store the physical activity level in a central database (Figure 3).[16]

Interval walking is personalized through a standardised eight-minute walking test, performed with the app before engaging in IWT.[25] The InterWalk app guides the user in IWT with repeated cycles of 3 minutes fast and 3 minutes slow walking. During Interval Walking Training (IWT) the InterWalk app provides the patient with continuous feedback on the walking speed. The patients are able to track exercise history and receive historic feedback on the quality of the IWT session using the app. The feedback system employs the

on-board accelerometer of the phone and GPS system to assess intensity and geographical location. Information on training intensity, total number of steps per day, IWT-data and data from the standardised walking test is stored in the smartphone or iPod and automatically transmitted to the central database at the Danish Strategic Research Centre for Type 2 Diabetes (DD2) when connected to Wi-Fi or mobile data network.[16]

[INSERT FIGURE/IMAGE 3 ABOUT HERE]

Experimental intervention, phase one

The patient receives a thorough introduction to the InterWalk app with follow-up instructions. The introduction consists of information and test of the app and the patient can ask clarifying questions if needed. A detailed manual regarding the InterWalk app is extradited to each patient. The health professional provides technical guidance and helps the patient to structure an everyday life with interval walking during phase one. Patients are encouraged to perform IWT using the InterWalk app (see section: InterWalk walking training using the InterWalk Application) as a minimum three times per week, 30 to 60 minutes per session, with two of the sessions taking place at the health promotion centre and the third is conducted in the patient's everyday life environment. The aim is that all patients are capable of continuing IWT using the InterWalk app at the end of phase one (Table 3).

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

Weekday	Intervention at the Health promotion center	Independent training in own environment	Notes to health professionals
Monday	Duration: 90 minutes 1. Warm-up: short walk to the walking point (either a park or an area near the center) 2. Interval walking: every patient do interval walking with the InterWalk app for a minimum of 30 minutes. The health professionals guide and facilitate the walking. 3. Group conversation: takes place at the health promotion center after doing interval walking with all participation patients. Here different focus areas are discussed in the group. 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)		• Make sure to encourage doing interval walking alone or together with other patients participating in interval walking at the health promotion center. • If some of the patients need to do a new walking test help should be given during the intervention.
Tuesday	Rest day		
Wednesday	Duration: 90 minutes 1. Warm-up: short walk to the walking point (either a park or an area near the center) 2. Interval walking: every patient do interval walking with the InterWalk app for a minimum of 30 minutes. The health professionals guide and facilitate the walking. 3. Group conversation: takes place at the health promotion center after doing interval walking with all participation patients. Here different focus areas are discussed in the group. 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)		
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 center in small groups of 3-12 patients. A third session is conducted in the patient's everyday life environment.

Experimental intervention, phase two

In phase two patients in the experimental intervention group are randomly allocated into two follow-up conditions: with unsupervised interval walking training without support (IWTgroup) or with motivational support (IWTsupport-group) following the intervention period until 52-week follow-up (see Figure 1).

Interval Walking Group without support (IWTgroup)

All patients in the Interval Walking Group (IWTgroup) are encouraged to continue to perform IWT with the InterWalk app three times a week, 30 to 60 minutes per session. The patients are not provided with any follow-up or support from health professionals from the end of the intervention period until follow-up at 52-weeks. However, patients are allowed to contact the health professionals at the health promotion centre at any time if necessary.

Interval Walking Group with support (IWTsupport-group)

Patients in the Interval Walking Group with support (IWTsupport-group) are also encouraged to do IWT with the InterWalk app three times per week. All patients in the IWTsupport-group receive additional motivational support by the health professionals at the promotion centre (see below for information regarding the motivational support).

Motivational support (phase two)

The motivational support is summarised in Table 4. The motivational intervention consists of four motivational interviews with individual goal setting and weekly Short Message

Service via the mobile phone (a SMS-track), (see Figure 5 and 6). Furthermore, patients have the opportunity to participate in IWT at predefined timeslots with an Interval Walking Ambassador in the local community near the health promotion centre (see Figure 1).

Motivational interview and goal setting: The Motivational interview is used to structure the communication between the patient and the health professional. The interview works as a partnership were focused and detailed questions reveal and visualize the patients motivation and barriers towards behaviour change and acknowledgement of patient autonomy.[26] Four motivational interviews are scheduled for each patient in the IWT support-group. See Table 4 for more detail. The interviews seek to help the patients reflect on their physically active habits and to set individual motivating goals related to everyday life.[27] The goal setting is based on the S.M.A.R.T.-principle derived from the Goal Setting Theory developed by Edwin Locke.[28] S stands for Specific (e.g. what do I want to accomplish?), M for Measurable (e.g. specific and measurable), A for achievable (realistic), R for relevant (individual goals) and T for timely (not too big to achieve in a short period).[29]

Table 4. MOTIVATIONAL INTERVIEWS WITH INDIVIDUAL GOAL SETTING PHASE TWO, IWTsupport-group

Four motivational interviews with individual goal setting,	The interviews aim at helping the patient to reflect on why and how physical activity can be incorporated in everyday life o Make informed choices regarding behavioral changes regarding physical activity o Relate to own everyday life o Clarify barriers and facilitators of importance for the individual Two to three individual goals are set at all interviews

The goals is based on need in the individual everyday life
A short resume with the individual goal setting is written after all interviews in the database. The written text is prospectively incorporated in the following interviews with the patient at the health promotion center

The interviews are placed in Week 16, 20, 28, 40 post baseline-test. Goal setting in the interviews are based on the *the S.M.A.R.T.- principle derived from the Goal Setting Theory developed by Edwin Locke.*[28]

Short Message Service (henceforth referred to as text message) enables inexpensive and possibly effective interaction between patients and health professionals at any time or place.[30,31] Communication as well as feedback is believed to enhance motivation through feelings of competence and relatedness [32], which may positively affect adherence to treatment. Text messages have shown positive effect on various health outcomes including diabetes self-management when used in behavior change interventions. Further, a higher effectiveness and lower attrition rate has been observed when customized and tailored messages is used.[30] In the present study, the patient receives two types of text messages during phase two (see Figure 4 and 5). The first type is a weekly and interactive text message consisting of questions regarding the amount of IWT performed during the past week (see Figure 4). The patients are required to give feedback by returning a text message with one of the three response options provided. If the patient does not reply for two consecutive weeks, or if the patient answers that she/he has not been walking, a personal phone call to the patient is conducted from a health professional from the local health promotion centre. The aim of the call is to encourage and help the patient to plan IWT to fit the individual life of the patient. The second type of text message is sent every fourth week,

encouraging the patients to perform the walking test using the InterWalk app without a requirement of feedback (see Figure 5).

[INSERT FIGURE 4 AND 5 ABOUT HERE]

Interval Walking Ambassadors: Using peers to educate other patients with T2D has shown effective in providing ongoing support over a longer period.[33,34] In this study, volunteer patients with T2D are recruited through the Danish Diabetes Association, where a consultant contacts possible patients via e-mail. The Interval Walking Ambassadors do IWT locally in phase two with patients from the IWTsupport group. The Interval Walking Ambassadors receives a two-day training programme in the participating municipality by researchers from the InterWalk research group. At any time during phase two, patients can attend IWT at predefined timeslots with an Interval Walking Ambassador (see Table 2).

Adherence to interventions

To prevent patients from dropping out during phase one of the trial, patients are contacted by phone by a trained health professional if they fail to appear at the planned training sessions. Up to five attempts are made to contact the patient. In phase two only patients allocated to the IWTsupport-group are monitored by SMS-track and supervised during the

phase until week 52. Patients in IWTgroup have no contact with the health professionals until 52-weeks follow-up (see Figure 1).

Control intervention – Standard care

Patients in the control group receive the standard rehabilitation treatment offered to patients with T2D in Denmark in a multimodal setting including physical activity (phase one, Figure 1). The duration of rehabilitation treatment differs between participating municipalities, but may not be shorter than eight weeks during phase one. At the end of the standard care rehabilitation program in the municipalities there is no follow-up on the exercise intervention, which is the normal procedure in Danish municipalities (phase two, Figure 1).[35]

The participating municipalities offer group exercise twice a week at the health promotion centres with 6-15 patients participating depending on the population size in the participating municipality. The content of the group exercise period is based on clinical guidelines in Denmark. A typical session is structured with first a short warm-up session followed by a strength and cardio part and finished with a cool-down period with strengthening (See Table 2). Furthermore, it is recommended that the patients have regularly consultation at the general practitioner every third month.

Additional rehabilitation care (Co-interventions)

All patients receiving rehabilitation at either a health promotion centre or at the hospital receives an offer of specific disease related patient education, diet counselling and smoking cessation.[35] It is optional whether the patient participate in one or all additional offers.

Disease specific patient education includes a section focused on behaviour modification and self-management and a specific part on diseases were the patients get knowledge regarding sequelae. *Diet counselling* regarding nutritional advice when living with T2D is handled by a dietitian. *Smoking cessation* is either group based or in individual process and is handled by smoking cessation counsellors.

Trial endpoints and Assessments

Data on the primary and secondary outcomes are obtained at baseline, post intervention (after 8-12 weeks) and 52 weeks after enrolment (Table 5). To standardize all measurements between health professionals and participating centres, all health professionals uses standardised protocols crafted for the trial regarding procedures and measurements. All data are entered directly in an online database (see section: Data management and quality control).

Table 5, SUMMARY OF DATA COLLECTION AND MEASURES

Measurements		Description	Baseline	8-12 weeks	52 weeks
Demographic†‡*					
	Age (median)	Obtained using self report	x	-	-
	Women		x	-	-
	Marital status		x	-	-
	Diabetes duration		x	-	-
	Education level		x	-	-
	Height, weight, body mass index	Obtained using standard procedures	x	x	x
Medical history†‡*		Obtained using medical records			
	History of Heart disease		x	x	x
	Hypertension		x	x	x
	Kidney disease		x	x	x
	Chronic Obstructive Pulmonary Disease (COPD)	Defined by FEV1<70%	x	x	x
Medicine†*					
	Self-reported use of medication		x	x	x
	Register-data use of medicine		x	x	x
*Physical fitness**					
	Moderate-to-Vigorous-intensity	Accelerometer (Axivity AX3, Newcastle, UK), worn for seven consecutive days, 3 times	x	x	x
	Total physical activity	InterWalk - Walking test performed using an iPod touch or IPhone	x	x	x
*Strength**	Lower extremities	Sit-To-Stand	x	x	x
*Patient Reported Outcomes (PROs)**					
	Behavioral Regulation in Exercise	*Obtained using BREQ-2,* Behavioral Regulation in Exercise Questionnaire	x	x	x

Physical Activity	*Obtained using R-PAQ*, Resent Physical Activity Questionnaire	x	x	x
Health related quality of life	*Obtained using SF-12*, Short Form - Health Related Quality of life Questionnaire	x	x	x
Automaticity of behavior	The Self-Report Habit Index		x	x
Personality traits†	*Obtained using NEO-FFI,* Neuroticism, Extroversion and Openness – Five Factor Inventory (Personality traits)	x	-	-
Risk behavior†	*Obtained using SES,* Sensation Seeking Scale (risk behavior)	x	x	x
*Adherence to interventions**				
Attendance registration	From baseline to 8-12 weeks	x	x	x
Log in the InterWalk app	Measured by the electronic log in the InterWalk-app	x	x	x
Registry data assessment‡*				
Mortality, cause of death	Obtained using medical records	-	x	x
Hospitalization		-	x	x
Contract with general practitioner		-	x	x

* Article 1: The effectiveness of smartphone delivered Interval Walking Training on moderate-and-vigorous physical activity versus standard care in patients with type 2 diabetes: a parallel group single-blinded randomized controlled trial.
†Article 2: Baseline characteristics and personality traits in patients with type 2 diabetes: descriptive study of all participants
‡Article 3: Nay Sayers – Characteristics of patients who does not want to be part of a physical activity study related to everyday life; all patients referred to the health promotion centers in the municipalities participating in the randomized controlled trial.
§Article 4: Effectiveness of smartphone delivered Interval Walking Training versus standard care in patients with type 2 diabetes on HbA1c and HDL, high-density lipoprotein; LDL, low-density lipoprotein: A sub-study to the randomized controlled trial (The InterWalk Trial, article 1), measured in a sub-sample (n=40).

Primary outcome

The primary outcome is change in moderate-to-vigorous-intensity physical activity from baseline to 52-week follow-up.

Secondary outcomes

The key secondary outcome changes in motivation for sustaining a behavioural change with physical activity in everyday life at 52-week follow-up.

Other secondary outcomes of interest are changes in patients' fitness level measured as VO_2-peak by the standardised walking test (part of the InterWalk application) and health-related quality of life. Strength in the lower extremities, adherence to intervention and impact of personality traits on physical activity in everyday life are also considered exploratory secondary outcomes. All outcomes are measured at baseline, after intervention and at 52-week follow-up (see Figure 2).

Data collection

Level of daily moderate-to-vigorous-intensity physical activity

It is important to gain knowledge into physical activity in everyday life. To determine level of daily moderate-to-vigorous-intensity physical activity a hip-mounted physical activity monitor (Axivity AX3, Newcastle, UK) is worn for seven consecutive days, at three time periods during the trial period; after baseline-test, after the intervention period and again at

52-weeks follow-up. The monitor is fixed using adhesive tape (Leukomed T, BSN medical, Germany) on right side the lumbar spine. Additionally, a monitor is fixed on on the lateral side of the right thigh (Leukomed T, BSN medical, Germany) for supporting information about posture.[25] The patients are instructed not to remove the physical activity monitor at any time during the three time periods. If de-attached, the participants are trained in fixing the monitors correctly and are instructed to note the incident. If the patients need help in fixing the monitors correctly the health professionals at the health promotion centre are educated to help.

Physical activity diary

In order to validate the physical activity level during the seven days with physical activity monitors we ask the patient to complete a seven-day diary to report number of work- and sleep hours, bicycling and strength training sessions at the three time periods on a daily basis. The physical activity monitor and the diary are returned free-of-charge via mail. The patient is contacted by phone after within one week if the physical activity monitors are not returned as expected.

Motivation for behaviour change with physical activity

Changes in motivation for sustaining a behavioural change with physical activity in everyday life is measured with the Behavioural Regulation of Exercise Questionnaire

(BREQ-2) which measures individual motivation for physical activity. The questionnaire consists of 19 questions in a 0-4 Likert format.[36] In addition to the questionnaire, patients are asked to answer four questions in a 0-4 Likert format, regarding motivation for physical activity after being diagnosed with T2D.

Health Related Quality of Life

The patients Health Related Quality of Life is very important to maintain after being diagnosed with T2D.[37] To gain knowledge into the individual perception of quality of life on a physical and mental level we use the Short-Form Health Survey (SF-12). The questionnaire consists of 12 questions and uses a Likert scale of 1-3 for the physical function items; 1-5 for the bodily pain, social function, and general health perceptions items; 1-6 for the vitality and mental health; and a dichotomous scale of yes/no for the presence of role function limitations. The higher score, the higher level of health or functioning.[38]

Maintenance of behaviour change with physical activity

Automaticity of behaviour is essential when new habits become present in the everyday life.[39] To measure if the patient has adopted new habits as a result of the intervention we ask the patient to answer four questions from The Self-Report Habit Index. The Index uses a 0-4 Likert format and the four questions to be answered measures automatic activation, frequency of behaviour and relevance to self-identity related to physical activity.[40]

VO_2-peak

Incorporated in the InterWalk app is a standardised walking test consisting of 5 stages; 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). The test is performed with an iPod placed in the pocket at the hip and the instructions are delivered from the app through earphones. To ensure the right walking intensity in the intervention period, the patients are asked to perform the test every 4th week.[16]

Strength in the lower extremities

The sit-to-stand test (30 seconds) measures the lower body strength and will be administered using a chair without arms. The patient is encouraged to complete as many full stands as possible within a 30-sec time limit.[41]

Adherence to the intervention

Adherence is determined by an evaluation and quantification of the electronic log of data from the InterWalk app to the central database of all uploaded data.

S*elf-rated physical activity*

The "Recent Physical Activity Questionnaire" (RPAQ) has 9 main questions, which covers 4 domains of physical activity: domestic life, work, recreation and transport. Physical Activity is estimated in MET's (Metabolic Equivalent). In answering the questions in the questionnaire, the patient will answer in regards to the last four weeks with physical activity in the everyday life.[42]

Personality traits

The NEO-Five Factor Inventory (NEO-FFI) [43] consists of 60 questions in a 0-4 Likert format constructed by selecting 2 items from each of the six facets characterizing each of the five personality traits (Neuroticism, Extraversion, Openness, Agreeableness, Conscientiousness) assessed by NEO-PI-R. The Sensation Seeking Scale (SES) [44] is a 40 items self-administered questionnaire consisting of 40 questions designed to test the tendency towards varied, novel and intense sensations.

Demographic, social economic and anthropometry measures

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. Relevant national registers will be used to obtain information regarding hospitalization, co-morbidities, medical history, use of medicine and mortality.

Height measurement is conducted using a portable altimeter (Tanita Stadiometer). The measurement is done without shoes and is repeated two times with each measure to nearest 0,1 cm. If the two measures are dissimilar with more than 0,5 cm, then the measurement is repeated. *Weigh* is measured in kilograms (kg) using an electronic weight. The measure is repeated two times with each measure to nearest 0,1 cm. If the two measures are dissimilar with more than 0,5 kg, then the measurement is repeated a third time. The patient is weighed fully dressed and one kilo is subtracted from each measure. *Hip circumference* is measured on the skin on the crest of the hipbone. The patient is asked to place a finger in the belly bottom and the measure is done with a tape measure (2 meters) placed on the upper side of the patients' finger. If the two measures are dissimilar with more than 0,5 cm, then the measurement is repeated a third time.

Safety criteria and adverse events

Patients are informed that performing the InterWalk walking test may cause some degree of breathlessness as patients are expected to reach 80-85% of VO_2max during the walking test. All other measurements are not associated with any known risk or discomfort. Injuries linked to the intervention are registered, if informed to the health professionals at the health promotion centres, during the trial period. In case of severe adverse events, the Scientific Ethical Committee of the Capital Region of Demark is informed.

Sample size considerations

The minimum difference of interest (MDI) is 10 minutes per day. Based on existing experimental evidence, we expect the standard deviation (SD) of the change in moderate-and-vigorous physical activity from baseline to 12 month follow up to be between 1.2 – 2.3 times the effect size.[45,46] Therefore, SD twice the MDI (20 min of moderate-and-vigorous physical activity) per day was applied in the sample size calculations. After applying Bonferroni adjustment due to multiple comparisons in the three group trial a total of 190 participants are needed to obtain a statistical power (1-β) of 80% with an α of 0.017 (two-tailed). Allowing for an attrition rate of 30%, 272 patients (91 in the control group and 181 in experimental group) are recruited. The setting enables recruitment until December 15st 2016. The sample size is truncated at 272 participants or the N reached at the end of recruitment period - whatever is reached first (see section 'Participants').

Randomisation, sequence generation and allocation concealment

After returning the physical activity monitors patients are randomised to either standard care or experimental group after baseline test (phase one). Allocation to either IWTgroup or IWTsupport-group on patients allocated to the experimental group is concealed until after the post intervention test (phase two). A health professional associated with the trial, telephones the patient and inform about random allocation after returning the PA monitors to either IWT-group or IWTsupport-group. The patients are stratified by gender to ensure an

equal number across all groups. The allocation sequence is generated through a standardised computer program by an independent researcher (RC). The allocation sequence is concealed until the trial arms are assigned. A Flow of patients is depicted in Figure 2.

Blinding

The scientific staff is blinded to patient allocation from baseline to the 52-week follow-up is completed for all patients. The health professionals at the promotion centre are not blinded to allocation to either standard care or experimental groups.

Statistical methods

All analyses will be conducted according to the Intention-To-Treat principle. Continuous endpoints will be analysed using repeated measures analysis of covariance in a mixed linear model. Categorical and dichotomous end points will be analysed with the use of logistic regression. The model will include with group, and sex as fixed effects, with the baseline value as a covariate.

All patients randomised to one treatment, will be analysed according to the treatment to which the patient was allocated, irrespective of whether they received this or some other treatment, or no treatment at all. The ITT population will be handled all patients randomised to the three treatment arms, and the dataset is equal to the "all patients randomized set" (APRS). Missing values due to patients' absence from follow-ups or withdrawal from the study are to be expected in clinical trials. Several approaches are

described for handling missing data in the ITT analysis, and among them "baseline observation carried forward" (BOCF: i.e., a null-responder imputation, where the level at baseline is also considered the last). 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. Exploratory analyses of the treatment effects will be performed on the secondary outcomes.

Data management and quality control

All data are entered in an SSL-secured, online-based database developed by the Danish Stakeholder Help2Run (CVR: 34801088). The online-based database logistically handles the data gathered at baseline, after intervention in phase one, and during follow-up (phase two) and after 52 weeks. Data on demography, measurements, tests and questionnaires are entered directly in the database available via a project-specific homepage (http://www.runsafe.dk/mtd/login/admin-signihttps://www.runsafe.dk/mtd/login/admin-signin). A protected back-end system (https://www.runsafe.dk/mtd/admin) is used to logistically handle information on demography, measurements, tests and questionnaires on each participant in the trial (for information on interval walking training using the InterWalk app see '*Interval Walking*

Training using The InterWalk Application'). The system was approved in 2014 after an inspection by the Danish Data Protection Agency. Access to personalized data from the InterWalk participants is only possible using a personalized username and password. Only specified researchers are allowed to administrate the back-end system and each researcher and project member with access to the back-end has a unique username and personal password for the back-end system. All activities, including changing data and downloading data, in the back-end system are logged in accordance with the rules and regulations from the Danish Data Protection Agency. A unique subject ID number will be subscribed to all patients in order to anonymize data. The identification key (ID to personal information) will be encrypted and stored securely and separately from the unique ID number on a secure database.

Ethics and Dissemination

The InterWalk trial contributes with important knowledge on different treatment approaches in the rehabilitation of patients with T2D. Physical activity and exercise have beneficial effect on patients with T2D when the interventions are conducted in well-designed efficacy studies.[2,4,6] However, little is known on whether this effect also is present in effectiveness studies or "real-world setting" studies. These studies are of great importance and relevance regarding evidence-based medicine highlighting the importance of the InterWalk trial.

The InterWalk trial has a pragmatic design that allows for different intervention periods in the participating municipalities. Furthermore, the interventions are

conducted directly in the clinical setting giving a more reliable frame of the experienced challenges in a population with T2D. We believe that the implementation of the study results will have a smoother implementation phase, as the health professionals already are familiar with the preceding's.

The trial gives valuable insight into the impact of different motivational and supportive tools as well as knowledge about individual motivation and the impact on sustaining a newly acquired behaviour change regarding physical activity in everyday life.

Interval Walking Training is expected to be a suitable and effective way of providing moderate-vigorous physical activity for at large group of patients with T2D. IWT can be done at any time and anywhere and is thus integrated and tailored to fit individual everyday life. The overall objective is to promote lifelong physical activity for the individual and we believe that experiences from the present trial can help when planning future interventions with IWT to patients with various lifestyle diseases e.g. coronary heart diseases.

It is a major advantage that the trial is designed as a randomised controlled trial in a "real-world setting" with a study population representing patients with T2D referred to rehabilitation. Furthermore, data and results are collected consecutively and directly in the clinical setting in which the interventions are to be used after the trial. Together with the very limited number of inclusion and exclusion criteria and a stratification of patients on

gender secures external validity of the trial and thus will add important information to the current body of evidence on T2D treatment.

All data from eHealth solutions as the InterWalk app are electronically monitored. The patient is not dependent on opening hours at the health promotion centre as the InterWalk is either installed on an iPhone or an iPod. This gives a unique possibility for the patient to be physically active whenever it fits in their everyday life.

We acknowledge that physical activity only has effect when adherence is high, which is why we first compare standard care with interval walking for a shorter period (phase one) followed by a re-allocation of patients in the experimental group to either interval walking with or without motivational support (phase two). All groups have a 52-week follow-up. The trial design enables us to investigate if patients are able to maintain a newly acquired behaviour change with physical activity in everyday life with or without motivational support for a longer period.

All personalized data and measures are stored on a central online-based database developed to logistically handle all data collected at baseline and during follow-up. The backend system (https://www.runsafe.dk/mtd/admin/) secures all information from each patient. The construction of the database with personalized usernames, passwords, and specific permissions to all health professionals and administering permissions to scientific staff in the backend secures all data. Furthermore, all activities are logged.

All outcomes measures are assessed blinded to allocation at baseline and the primary outcome is assessed blinded to intervention in the experimental group after the intervention period. All measures are conducted by the health professionals at the health promotion centres and are blinded for allocation after intervention in the experimental group with IWT until after return of the physical activity monitors by the patient. All statistical analyses are blinded to researchers, reducing the risk of detection and interpretation bias.[47–49] All secondary outcomes, but VO_2-peak and the Sit to Stand Test are self-reported and by nature likely to be biased. The patients answer questionnaires independently of the health professionals at the health promotion centres.

The secondary outcomes of motivation for physical activity and behaviour change are of highly importance as knowledge concerning motivational support and maintenance of effect (new habits with physical activity) to our knowledge is lacking in patients with T2D. This knowledge will help health professionals to better tailor the treatment and herby potentially achieve a higher adherence to the programme following the supervised intervention.

The limitations in this trial are similar to those of other exercise trials where physical testing and time-of-day and day-to-day variation constitute a challenge. We have standardised all testing protocols for all procedures to reduce the variation and run a routine program of on-going calibration and training of the health professionals.

The trial is conducted in accordance with the Helsinki Declaration II.[50] All eligible patients receive written and oral informed consent prior to inclusion before any additional trial procedures. Data on all screened patients are registered in order to report characteristics of in-eligible patients and written informed consent is also obtained from these patients. The patients can withdraw from the trial at all times during the trial period. This has no consequence for any other future treatment. If patients discontinue the trial intervention, standard care is offered for the rest of the intervention period. All results from the trial, negative, positive or inconclusive results, are disseminated in international peer-reviewed scientific papers and at national and international conferences. We follow the guidelines from the International Committee of Medical Journal Editors when authorship is determined. The results will be reported when all long-term data become accessible.

Furthermore, all results are shared with the participating municipalities and participating health professionals and are used to develop future intervention and implementation strategies in the Danish municipalities.

Trial status

The inclusion period started in January 2015 and is scheduled to finish in December 2017 with a 52-week follow-up. To ensure enrolment of patients in the trial we are open for collaborations with new municipalities during the trial period. So far the trial has resulted in collaboration with both rural and urban municipalities in Denmark. The inclusion rate is

carefully monitored every week by the research team. In July 2016, 210 patients had been enrolled in the trial.

Contributors LSV, MR-L and HL drafted the manuscript. All authors made substantial contributions to conception and design, and revised the manuscripts critically for important intellectual content. All authors have given their approval for the manuscript to be published.

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Ethics approval

The local regional Research Ethics Committee in Denmark (H-1-2014-074) and the Danish Data Protection Agency (j.nr. 2014-54-0897) has approved the trial.

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Competing interests statement

We have read and understood The BMJ policy on declaration of interests and declare no competing interests.

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FIGURE LEGENDS

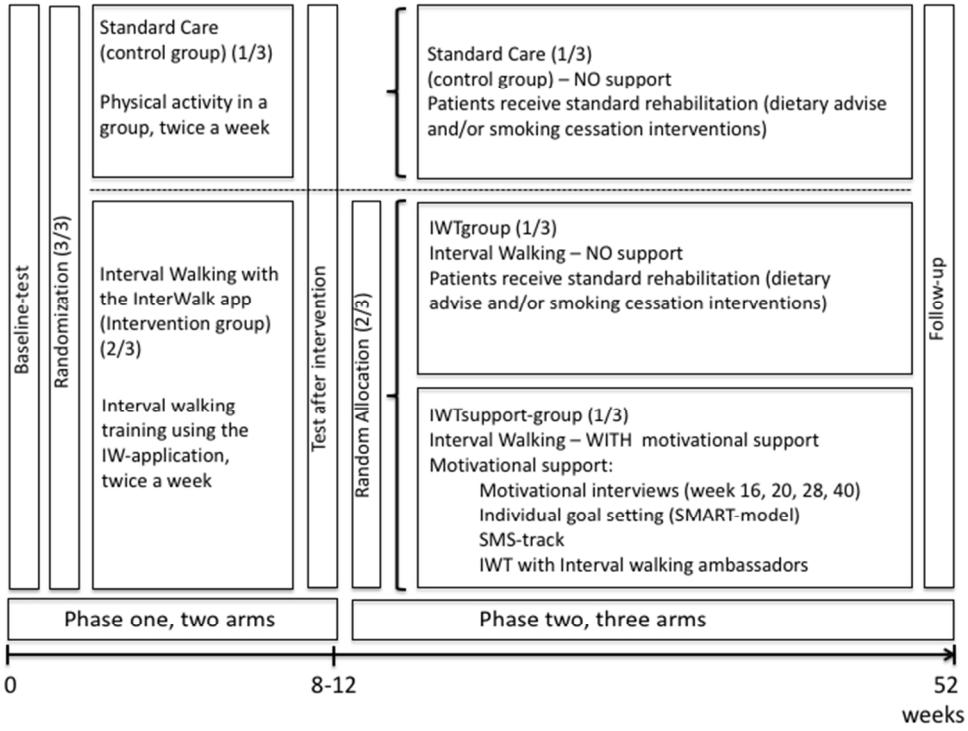
Figure 1. Timeline and overview of interventions in the InterWalk trial
Phase one shows baseline-test, randomization, intervention and test after intervention. Phase two shows the re-allocation of patients in the experimental group who do interval walking training (IWT with the InterWalk app to either IWT with or without motivational support form a health professional. All patients are tested at baseline, after intervention and again at follow-up at 52 weeks

Figure 2. Flow-chart, The InterWalk-RCT Trial

Figure 3. The InterWalk front page (A), Protocol for the fitness test in the application (B), The start page for interval walking showing smileys as direct feedback to the user (C) (translated from Danish).[16]

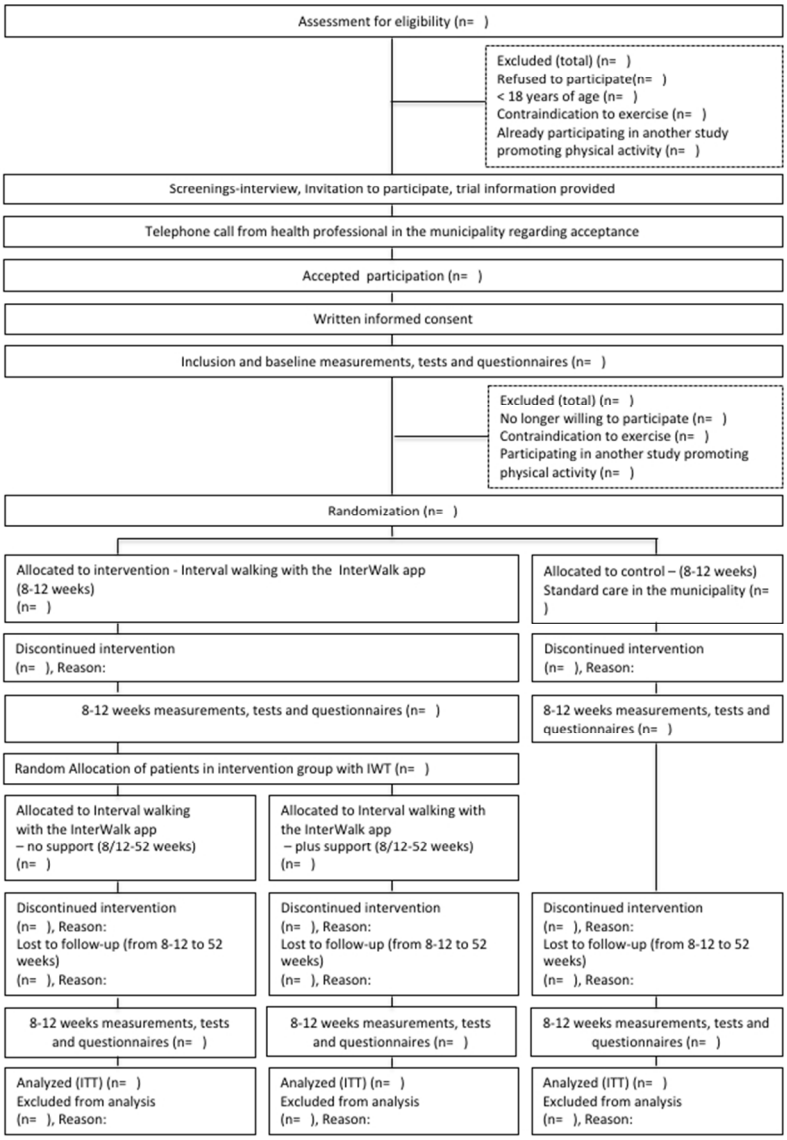
Figure 4. Short Message Service (SMS), send every Sunday to patients in the IWTsupport-group

Figure 5. Short Message Service (SMS), Standardized walking test in the InterWalk application, send every fourth week to patients in the IWTsupport-group



Timeline and overview of interventions in the InterWalk trial
Phase one shows baseline-test, randomizations, intervention and test after intervention. Phase two shows the re-allocation of patients in the experimental group who do interval walking training (IWT with the InterWalk app to either IWT with or without motivational support form a health professional. All patients are tested at baseline, after intervention and again at follow-up at 52 weeks

Figure 1
254x190mm (72 x 72 DPI)

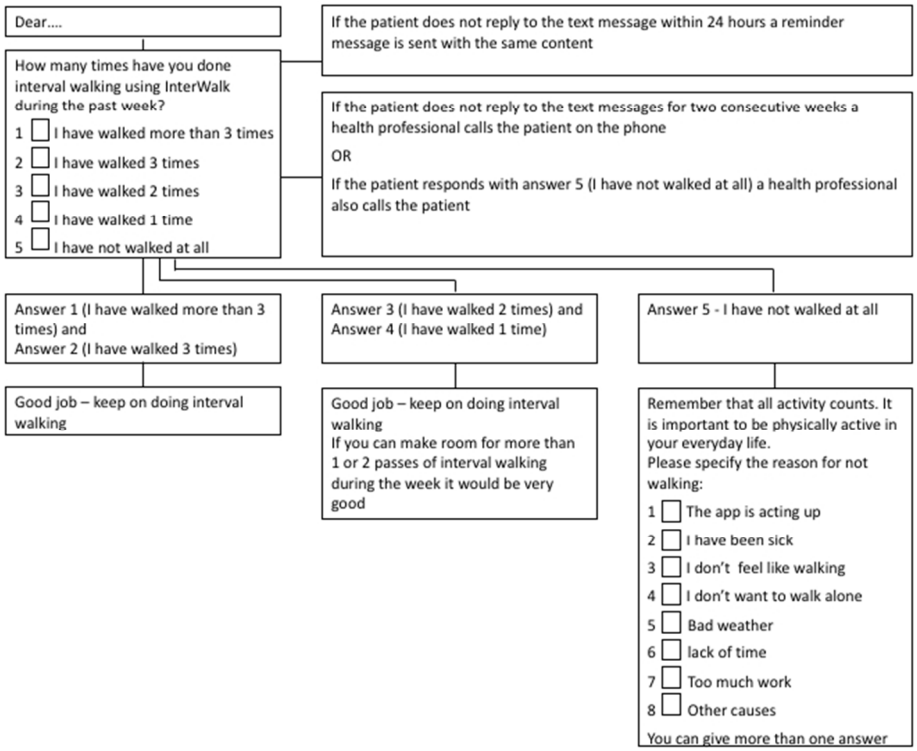


Flow-chart, The InterWalk-RCT Trial

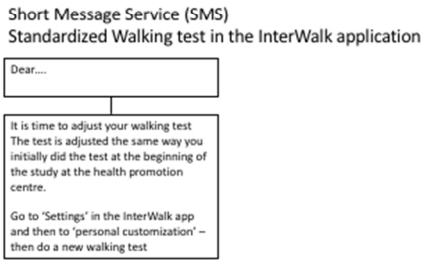
Figure 2
190x254mm (96 x 96 DPI)

The InterWalk front page (A), Protocol for the fitness test in the application (B), The start page for interval walking showing smileys as direct feedback to the user (C) (translated from Danish).[16]

Figure 3
112x68mm (72 x 72 DPI)



Short Message Service (SMS), send every Sunday to patients in the IWTsupport-group
Figure 4
254x190mm (72 x 72 DPI)



Short Message Service (SMS), Standardized walking test in the InterWalk application, send every fourth week to patients in the IWTsupport-group
Figure 5
338x190mm (54 x 54 DPI)

DANISH CENTRE FOR STRATEGIC RESEARCH IN TYPE 2 DIABETES

To BMJ Open

As the senior author of the published paper "*Implementation of interval walking training in patients with type 2 diabetes in Denmark: rationale, design, and baseline characteristics*" I herby approve the use figure A, B and C in paper "*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*" submitted to BMJ Open by Laura Valentiner.

Original publication of the figures:

"*Implementation of interval walking training in patients with type 2 diabetes in Denmark: rationale, design, and baseline characteristics.* Ried-Larsen M, Thomsen RW, Berencsi K, Brinkløv CF, Brøns C, Valentiner LS, Karstoft K, Langberg H, Vaag AA, Pedersen BK, Nielsen JS. Clin Epidemiol. 2016 Jun 8;8:201-9. doi: 10.2147/CLEP.S97303. eCollection 2016."

Kind regards

PhD Jens Steen Nielsen

2016-08-17

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	
Administrative information			**Page**
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2 & 5
	2b	All items from the World Health Organization Trial Registration Data Set	4, 31, 1, 5, 7-22, 6, 26, 23
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	33
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	33
	5b	Name and contact information for the trial sponsor	N/A
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	7, 16, 17, 31
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3, 7-22
	6b	Explanation for choice of comparators	4, 16, 29
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5, 6

Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-22
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	14, 21
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12, 14
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	14
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	23
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5, 24, 27
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	25
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	4
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	27
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	27
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	27
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	28
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	21
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	24
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	22
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	31
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	28
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	31
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	21, 31
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	5
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	5
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	32
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	31

Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	33
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	31
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	31
	31b	Authorship eligibility guidelines and any intended use of professional writers	31
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	32

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

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

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Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Diabetes and endocrinology, Sports and exercise medicine, Rehabilitation medicine, Evidence based practice
Keywords:	Type 2 diabetes, Rehabilitation, Interval Walking Training, Physical Activity, Behaviour maintenance

TITLE:

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

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RUNNING HEAD

Effect of Interval Walking on Type 2 Diabetics

BRIEF TITLE:

The InterWalk Trial

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TOTAL NUMBER OF WORDS:

6785

ABSTRACT:

Introduction

Physical activity is a cornerstone in Type 2 diabetes (T2D) rehabilitation. Effective long-term and low-cost strategies to keep these patients' physically active are needed. However, maintaining physical activity behaviour is difficult once formalised interventions end. Structured exercise training supported by mobile technology and remote feedback is potentially an effective strategy.

The objective of the trial is to investigate whether mobile health support using the InterWalk application for smartphones is effective in increasing physical activity levels in persons with T2D over time compared to standard care.

We investigate whether Interval Walking Training (IWT) using the InterWalk application is superior to Danish municipality-based rehabilitation in increasing moderate-and-vigorous physical activity levels in patients with T2D across 52 weeks. Secondary, we hypothesize that a motivational programme added from end of intervention to 52-weeks further increases level of physical activity in everyday life in patients with T2D.

Methods and analysis

The trial is a parallel-group, open-labelled, randomised controlled trial with long-term follow-up at 52-week including patients with T2D. The primary outcome is change in moderate-and-vigorous physical activity. The key secondary outcome includes motivation for physical activity behaviour change. Other secondary outcomes are VO_2-peak, strength in

the lower extremities. Exclusion criterion is medical contraindication to exercise. We include up to 246 patients and randomly allocate them into a control (standard group) or an experimental group (8-12 weeks of IWT supported by the smartphone-based InterWalk application) in a 1:2 fashion. After intervention, the experimental group is randomly allocated into two follow-up conditions with unsupervised IWT with or without motivational support until 52-week follow-up. The Intention-To-Treat principle is applied.

Ethics and Dissemination

The local regional Research Ethics Committee in Denmark (H-1-2014-074) and the Danish Data Protection Agency (j.nr. 2014-54-0897) have approved the trial. Positive, negative or inconclusive results will be disseminated in scientific journals and conferences.

Trial registration: NCT02341690

Keywords: Type 2 diabetes, Rehabilitation, Interval Walking Training, Physical activity, Behaviour maintenance

STREGTHS:

- 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.
- The efficiency of Interval Walking Training on e.g. glycaemic control has previously been demonstrated.
- The trial has a long-term follow-up period of 52-weeks from baseline.

- 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.

LIMITS:

- The trial has several collaborators in the setup which may cause variation in the testing procedures.
- Lack of clinical endpoints e.g. depression and mental health
- The length of the intervention periods varies between the three collaborating municipalities may influence the results of the trial.
- There may be a risk of contamination in the control group as the InterWalk application can be downloaded in App Store.

INTRODUCTION

Physical activity (PA) is a cornerstone in the clinical care of patients with type 2 diabetes (T2D).[1] PA activity has beneficial effect on glycaemic control and other key metabolic risk factors [2,3], as well as improvements in quality of life.[4,5] Furthermore, supervised long-term PA interventions have proven effective in improving glycaemic control.[2,6] However, experimental evidence does not support the efficiency of advice about physical activity alone.[7] As the number of patients with T2D is estimated to rise to 500 million by 2030 worldwide [8,9] the implementation of structured, long-term and supervised exercise regimes constitutes a large societal challenge and is not feasible. Thus, novel strategies to increase physical activity among patients with T2D are needed.

Smartphones have been used as a tool to register exercise, diet, weight and plasma glucose levels, but the evidence for using a smartphone as an exercise device and a self-management tool in the diabetes care is lacking.[10] However, emerging evidence suggest that eHealth solutions using information and communication technologies [11] can educate and engage patients with T2D in long-term self-management.[12–14] Due to the large ingress and ownership of smartphones, a smartphone-supported approach could prove feasible in increasing physical activity among patients with T2D and accommodate the increasing prevalence of T2D.

Efficiency of Interval Walking Training (IWT) in patients with T2D has been established.[15] In the study by Karstoft and co-workers, IWT was administered and

monitored using a small exercise computer (JD-mate). IWT induced significant improvements in physical fitness level, body composition and glycaemic control and in adherence of more than 85% over a 16 weeks period.[15] The potential benefits of implementing eHealth solutions in T2D management and the apparent health benefits of and adherence to IWT gave rise to the development of the InterWalk application (InterWalk app) to deliver IWT.[16]

There is a lack of knowledge about the integration of PA in the everyday life of the patient following rehabilitation interventions.[17] It is, however, known that successful behavioural change depends on an on-going maintenance of individual motivation regarding the behaviour and behavioural change itself.[18] Furthermore, time since onset of diagnosis, unhealthy behaviour and own beliefs about the cause of the problem, together with the number of previous attempts to change and support from partners, peers and health professionals are of relevance.[18] This underlines the need for new interventions with a direct focus on motivational support and self-control regarding sustaining a newly acquired behavioural change with PA. To better target and structure manageable interventions related to patients with T2D, understanding patients' individual priorities and values are crucial. In this regard, knowledge of individual motivation and self-efficacy to initiate behavioural changes becomes essential to understand.[18]

This paper presents a detailed protocol for the InterWalk Randomised Controlled Trial and is described in accordance with the SPIRIT guidelines (Standard Protocol Items: Recommendations for Interventional Trials).[19] Results from the trial will

follow CONSORT guidelines (CONsolidated Standards Of Reporting Trials) for non-pharmacological interventions.[20]

Trial objective and hypothesis

The objective of the trial is to investigate whether mobile support using the InterWalk application for smartphones is effective in increasing physical activity levels in persons with type 2 diabetes over time compared with a standard care rehabilitation program.

We investigate the effectiveness of the implementation of Interval Walking Training using the InterWalk application in the Danish municipality-based rehabilitation program and study whether the Interval Walking Training is superior to standard care in increasing moderate-vigorous physical activity 52 after weeks. Furthermore, we expect that a motivational support program added from end of the intervention to 52-weeks, will increase the physical activity level in patients with type 2 diabetes and help maintaining a physically active everyday life long-term.

METHODS AND ANALYSIS

Trial design and setting

The trial is a 52-week parallel-arm, open-labelled, randomised controlled trial. The participants are randomly allocated into two groups, 1) standard care or 2) experimental group with moderate-and-vigorous physical activity level, doing interval walking

facilitated by the InterWalk app. After an 8-12-week intervention period, patients in the experimental group are allocated to do interval walking using the InterWalk app with or without motivational support provided by the health professionals (see Figure 1).

[INSERT FIGURE 1 ABOUT HERE]

The intervention is conducted at the health promotion centres in Danish municipalities and hospitals that consecutively are included as cooperation partners. The municipality of Copenhagen is the first collaborator in the trial. Patients are referred to rehabilitation by their general practitioner (GP). Trained health professionals (physical therapists, nurses and staff with a master's degree) working at the health promotion centres recruit the patients, deliver the interventions and conduct all testing. The overall organization of health care in Denmark is fully tax-financed with universal access to health care services. The Danish model is described in detail elsewhere [21,22] and chronic disease care (including T2D) management is in Denmark based in the Chronic Care Model.[23]

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. Patients with a non-complicated course of disease receive rehabilitation consisting of: 1) disease-specific patient education, 2) diet counseling, 3) smoking cessation and 4) exercise. The composition of the individual rehabilitation program depends however on disease progression and on the rehabilitation offered in the municipality-based program or at the hospital. The general focus is patient empowerment, disease-related self-care and prevention of a decay of the functional capacity of patients with T2D.

The Scientific Ethical Committee at the Capital Region of Denmark (H-1-2014-074), and the Danish Data Protection Agency (j.nr. 2014-54-0897) have approved the trial. The InterWalk application is approved by the Danish Data Protection Agency (2008-58-0035). The trial has been registered at http://www.clinicaltrials.org (NCT02341690) on January 9th, 2015. Amendments to the protocol will be approved by the Scientific Ethical Committee at the Capital Region of Denmark. Amendments will be reported to http://www.clinicaltrials.org. The trial is conducted in accordance with the Helsinki Declaration.

Participants

Eligibility

All non-complicated patients diagnosed with T2D (out-patients), referred to a health promotion centre or hospital in the participating municipalities by their GP, are eligible if more than 18 years of age. A flow chart of participants is presented in Figure 2.

[INSERT FIGURE 2 ABOUT HERE]

The exclusion criteria are medical contraindications to exercise e.g. chronic complications in the locomotive apparatus, painful osteoarthritis or heart conditions.[24] Information is collected through medical records and at a screening interview with a health professional at the health promotion centre. Furthermore, patients are excluded if they do not want to be physically active in the rehabilitation setting or are already participating in other intervention studies at a health promotion centre. The patients have to be able to talk, read and understand the Danish language (for overview over in- and exclusion criterion, see Table 1).

Table 1. ELIGIBILITY CRITERIA

Inclusion criteria
• Diagnosed with type 2 diabetes
• Referred by General practitioner to a health promoting centre in participating municipality or hospital
Exclusion criteria
• < 18 years of age
• Medical contraindications to exercise
• Already participating in other exercise trials
• Does not talk and read Danish

If eligible, health professionals give oral and formalized written information with two days to consider participation in the trial. Written informed consent is obtained before any additional trial procedures. Enrolment was initiated in January 2015 and recruitment is terminated on December 15th 2016. Last-patient-last-visit is expected in December 2017.

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. The investigators (LSV, CB and HL) led four workshops (16 hours in total) with the health professionals during year 2014, in which the interventions of the study and work routines were discussed in detail. Furthermore, all participating health professionals underwent a thorough education program (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. The applicability of the trial results is hereby

increased, as the interventions are already part of the rehabilitation programme offered to patients with T2D in the municipalities.

The interventions in the trial consist of two phases (Figure 1). In phase one (8-12 weeks), patients are randomised to either a standard care group (control intervention) or an experimental group doing IWT using the InterWalk app. The present trial uses the standard care programme as control intervention and is conducted directly in the clinical setting. All patients receive supervision across phase one. In phase two (40-44 weeks), patients in the standard care group have no follow-up until 52 weeks post baseline. Patients in the experimental intervention group are in phase two randomly allocated to either IWT with or without motivational support (see section Experimental intervention – Interval Walking with the InterWalk application). Additional rehabilitation care (co-interventions) with disease-specific patient education, diet counseling and smoking cessation is offered to all patients across the intervention groups. The interventions are summarized in Table 2.

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
	3. Interval Walking Ambassadors	• Educated patients with T2D do interval walking in local community near the health promotion centres • One session per week
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 counsellors The course lasts 10-12 hours and can be either individually or group based

Experimental intervention – Interval Walking Training with the InterWalk application

Patients allocated to the experimental intervention do interval walking after baseline test provided by health professionals (phase one). IWT is provided by health professionals to smaller groups of 3-12 patients. After the intervention period in phase two patients are allocated to either receive IWT without motivational support during follow-up (IWTgroup) or IWT with motivational support during follow-up (IWTsupport-group) (Figure 1). Trained health professionals conduct the IWT sessions (see below) and the motivational support in phase two. Table 2 gives an example of a typical week with interval walking in the experimental intervention group.

Interval Walking Training using The InterWalk Application

Interval Walking Training is performed using the InterWalk app, which works as a personal trainer as well as a monitoring unit allowing researchers to continuously and automatically monitor and store the physical activity level in a central database (Figure 3).[16]

Interval Walking Training is personalized through a standardised eight-minute walking test, performed with the app before engaging in IWT.[25] The InterWalk app guides the user in IWT with repeated cycles of 3 minutes fast and 3 minutes slow walking. During Interval Walking Training (IWT) the InterWalk app provides the patient with continuous feedback on the walking speed. The patients are able to track exercise history and receive historic feedback on the quality of the IWT session using the app. The feedback system

employs the on-board accelerometer of the phone and GPS system to assess intensity and geographical location. Information on training intensity, total number of steps per day, IWT-data and data from the standardised walking test is stored in the smartphone or iPod and automatically transmitted to the central database at the Danish Strategic Research Centre for Type 2 Diabetes (DD2) when connected to Wi-Fi or mobile data network.[16]

[INSERT FIGURE/IMAGE 3 ABOUT HERE]

Experimental intervention, phase one

The patient receives a thorough introduction to the InterWalk app with follow-up instructions. The introduction consists of information and test of the app and the patient can ask clarifying questions if needed. A detailed manual regarding the InterWalk app is extradited to each patient. The health professional provides technical guidance and helps the patient to structure an everyday life with IWT during phase one. Patients are encouraged to perform IWT using the InterWalk app (see section: InterWalk Walking Training using the InterWalk Application) as a minimum three times per week, 30 to 60 minutes per session, with two of the sessions taking place at the health promotion centre and the third is conducted in the patient's everyday life environment. The aim is that all patients are capable of continuing IWT using the InterWalk app at the end of phase one (Table 3).

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		

	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.

Experimental intervention, phase two

In phase two patients in the experimental intervention group are randomly allocated into two follow-up conditions: with unsupervised Interval Walking Training without support (IWTgroup) or with motivational support (IWTsupport-group) following the intervention period until 52-week follow-up (see Figure 1).

Interval Walking Group without support (IWTgroup)

All patients in the Interval Walking Group (IWTgroup) are encouraged to continue to perform IWT with the InterWalk app three times a week, 30 to 60 minutes per session. The patients are not provided with any follow-up or support from health professionals from the end of the intervention period until follow-up at 52-weeks. However, patients are allowed to contact the health professionals at the health promotion centre at any time if necessary.

Interval Walking Group with support (IWTsupport-group)

Patients in the Interval Walking Group with support (IWTsupport-group) are also encouraged to do IWT with the InterWalk app three times per week. All patients in the IWTsupport-group receive additional motivational support by the health professionals at the promotion centre (see below for information regarding the motivational support).

Motivational support (phase two)

The motivational support is summarised in Table 4. The motivational intervention consists of four motivational interviews with individual goal setting and weekly Short Message

Service via the mobile phone (a SMS-track), (see Figure 5 and 6). Furthermore, patients have the opportunity to participate in IWT at predefined timeslots with an Interval Walking Ambassador in the local community near the health promotion centre (see Figure 1).

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. The Motivational interview is a semi-structured interview used to structure the communication between the patient and the health professional. The interview works as a partnership were focused and detailed questions reveal and visualize the patients motivation and barriers towards behaviour change and acknowledgement of patient autonomy.[26] Four motivational interviews are scheduled for each patient in the IWT support-group. See Table 4 for more detail. 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 that 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 goal setting is based on the S.M.A.R.T.-principle derived from the Goal Setting Theory developed by Edwin Locke.[28] S stands for Specific

(e.g. what do I want to accomplish?), M for Measurable (e.g. specific and measurable), A for achievable (realistic), R for relevant (individual goals) and T for timely (not too big to achieve in a short period).[29]

Table 4. MOTIVATIONAL INTERVIEWS WITH INDIVIDUAL GOAL SETTING PHASE TWO, IWTsupport-group

Four semi-structured motivational interviews with individual goal setting,	○ The interviews aim at helping the patient to reflect on why and how physical activity can be incorporated in everyday life ○ Make informed choices regarding behavioral changes regarding physical activity ○ Relate to own everyday life ○ Clarify barriers and facilitators of importance for the individual ○ Two to three individual goals are set at all interviews ○ The goals is based on need in the individual everyday life
A short resume with the individual goal setting is written after all interviews in the database. The written text is prospectively incorporated in the following interviews with the patient at the health promotion centre	

The interviews are placed in Week 16, 20, 28, 40 post baseline-test. Goal setting in the interviews are based on the *the S.M.A.R.T.- principle derived from the Goal Setting Theory developed by Edwin Locke.*[28]

Short Message Service (henceforth referred to as text message) enables inexpensive and possibly effective interaction between patients and health professionals at any time or place.[30,31] Communication as well as feedback is believed to enhance motivation through feelings of competence and relatedness [32], which may positively affect adherence to treatment. Text messages have shown positive effect on various health outcomes including diabetes self-management when used in behavior change interventions. Further, a higher effectiveness and lower attrition rate has been observed when customized and tailored messages is used.[30] In the present study, the patient receives two types of text messages during phase two (see Figure 4 and 5). The first type is a weekly and interactive

text message consisting of questions regarding the amount of IWT performed during the past week (see Figure 4). The patients are required to give feedback by returning a text message with one of the three response options provided. If the patient does not reply for two consecutive weeks, or if the patient answers that she/he has not been walking, a personal phone call to the patient is conducted from a health professional from the local health promotion centre. The aim of the call is to encourage and help the patient to plan IWT to fit the individual life of the patient. The second type of text message is sent every fourth week, encouraging the patients to perform the walking test using the InterWalk app without a requirement of feedback (see Figure 5).

[INSERT FIGURE 4 AND 5 ABOUT HERE]

Interval Walking Ambassadors: Using peers to educate other patients with T2D has shown effective in providing ongoing support over a longer period.[33,34] In this study, volunteer patients with T2D are recruited through the Danish Diabetes Association, where a consultant contacts possible patients via e-mail. The Interval Walking Ambassadors do IWT locally in phase two with patients from the IWTsupport group. The Interval Walking Ambassadors receives a two-day training programme in the participating municipality by researchers from the InterWalk research group. At any time during phase

two, patients can attend IWT at predefined timeslots with an Interval Walking Ambassador (see Table 2).

Adherence to interventions

To prevent patients from dropping out during phase one of the trial, patients are contacted by phone by a trained health professional if they fail to appear at the planned training sessions. Up to five attempts are made to contact the patient. In phase two only patients allocated to the IWTsupport-group are monitored by SMS-track and supervised during the phase until week 52. Patients in IWTgroup have no contact with the health professionals until 52-weeks follow-up (see Figure 1).

Control intervention – Standard care

Patients in the control group receive the standard rehabilitation treatment offered to patients with T2D in Denmark in a multimodal setting including physical activity (phase one, Figure 1). The duration of rehabilitation treatment differs between participating municipalities, but may not be shorter than eight weeks during phase one. At the end of the standard care rehabilitation program in the municipalities there is no follow-up on the exercise intervention, which is the normal procedure in Danish municipalities (phase two, Figure 1).[35]

The participating municipalities offer group exercise twice a week at the health promotion centres with 6-15 patients participating depending on the population size in the participating municipality. The content of the group exercise period is based on clinical guidelines in Denmark. A typical session is structured with first a short warm-up session followed by a strength and cardio part and finished with a cool-down period with strengthening (See Table 2). Furthermore, it is recommended that the patients have regularly consultation at the general practitioner every third month.

Additional rehabilitation care (Co-interventions)

All patients receiving rehabilitation at either a health promotion centre or at the hospital receives an offer of specific disease related patient education, diet counselling and smoking cessation.[35] It is optional whether the patient participate in one or all additional offers.

Disease specific patient education includes a section focused on behaviour modification and self-management and a specific part on diseases were the patients get knowledge regarding sequelae. *Diet counselling* regarding nutritional advice when living with T2D is handled by a dietitian. *Smoking cessation* is either group based or in individual process and is handled by smoking cessation counsellors.

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.

Data on the primary and secondary outcomes are obtained at baseline, post intervention (after 8-12 weeks) and 52 weeks after enrolment (Table 5). To standardize all measurements between health professionals and participating centres, all health professionals uses standardised protocols crafted for the trial regarding procedures and measurements. All data are entered directly in an online database (see section: Data management and quality control).

Effect of Interval walking on type 2 diabetics

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Table 5, SUMMARY OF DATA COLLECTION AND MEASURES

Measurements		Description	Baseline	8-12 weeks	52 weeks
Demographic†‡*					
	Age (median)	Obtained using self report	x	-	-
	Women		x	-	-
	Marital status		x	-	-
	Diabetes duration		x	-	-
	Education level		x	-	-
	Height, weight, body mass index	Obtained using standard procedures	x	x	x
Medical history†‡*		Obtained using medical records			
	History of Heart disease		x	x	x
	Hypertension		x	x	x
	Kidney disease		x	x	x
	Chronic Obstructive Pulmonary Disease (COPD)	Defined by FEV1<70%	x	x	x
Medicine†*					
	Self-reported use of medication		x	x	x
	Register-data use of medicine		x	x	x
*Physical fitness**					
	Moderate-to-Vigorous-intensity	Accelerometer (Axivity AX3, Newcastle, UK), worn for seven consecutive days, 3 times	x	x	x
	Total physical activity (VO_2-peak)	InterWalk - Walking test performed using an iPod touch or IPhone	x	x	x
*Strength**	Lower extremities	Sit-To-Stand	x	x	x
*Patient Reported Outcomes (PROs)**					
	Behavioural Regulation in Exercise	*Obtained using BREQ-2,* Behavioural Regulation in Exercise Questionnaire	x	x	x

Physical Activity	*Obtained using R-PAQ*, Resent Physical Activity Questionnaire	x	x	x
Health related quality of life	*Obtained using SF-12*, Short Form - Health Related Quality of life Questionnaire	x	x	x
Automaticity of behaviour	The Self-Report Habit Index		x	x
Personality traits†	*Obtained using NEO-FFI,* Neuroticism, Extroversion and Openness – Five Factor Inventory (Personality traits)	x	-	-
Risk behaviour†	*Obtained using SES,* Sensation Seeking Scale (risk behaviour)	x	x	x
*Adherence to interventions**				
Attendance registration	From baseline to 8-12 weeks	x	x	x
Log in the InterWalk app	Measured by the electronic log in the InterWalk-app	x	x	x
Registry data assessment‡*				
Mortality, cause of death	Obtained using medical records	-	x	x
Hospitalization		-	x	x
Contract with general practitioner		-	x	x

* Article 1: The effectiveness of smartphone delivered Interval Walking Training on moderate-and-vigorous physical activity versus standard care in patients with type 2 diabetes: a parallel group single-blinded randomized controlled trial.
†Article 2: Baseline characteristics and personality traits in patients with type 2 diabetes: descriptive study of all participants
‡Article 3: Nay Sayers – Characteristics of patients who does not want to be part of a physical activity study related to everyday life; all patients referred to the health promotion centre in the municipalities participating in the randomized controlled trial.
§Article 4: Effectiveness of smartphone delivered Interval Walking Training versus standard care in patients with type 2 diabetes on HbA1c and HDL, high-density lipoprotein; LDL, low-density lipoprotein: A sub-study to the randomized controlled trial (The InterWalk Trial, article 1), measured in a sub-sample (n=40).

Primary outcome

The primary outcome is change in moderate-to-vigorous-intensity physical activity from baseline to 52-week follow-up.

Secondary outcomes

The key secondary outcome changes in motivation for sustaining a behavioural change with physical activity in everyday life at 52-week follow-up.

Other secondary outcomes of interest are changes in patients' fitness level measured as VO_2-peak by the standardised walking test (part of the InterWalk application) and health-related quality of life. Strength in the lower extremities, adherence to intervention and impact of personality traits on physical activity in everyday life are also considered exploratory secondary outcomes. All outcomes are measured at baseline, after intervention and at 52-week follow-up (see Figure 2).

Data collection

Level of daily moderate-to-vigorous-intensity physical activity

It is important to gain knowledge into physical activity in everyday life. To determine level of daily moderate-to-vigorous-intensity physical activity a hip-mounted physical activity monitor (Axivity AX3, Newcastle, UK) is worn for seven consecutive days, at three time periods during the trial period; after baseline-test, after the intervention period and again at

52-weeks follow-up. The monitor is fixed using adhesive tape (Leukomed T, BSN medical, Germany) on right side the lumbar spine. Additionally, a monitor is fixed on on the lateral side of the right thigh (Leukomed T, BSN medical, Germany) for supporting information about posture.[25] The patients are instructed not to remove the physical activity monitor at any time during the three time periods. If de-attached, the participants are trained in fixing the monitors correctly and are instructed to note the incident. If the patients need help in fixing the monitors correctly the health professionals at the health promotion centre are educated to help.

Physical activity diary

In order to validate the physical activity level during the seven days with physical activity monitors we ask the patient to complete a seven-day diary to report number of work- and sleep hours, bicycling and strength training sessions at the three time periods on a daily basis. The physical activity monitor and the diary are returned free-of-charge via mail. The patient is contacted by phone after within one week if the physical activity monitors are not returned as expected.

Motivation for behaviour change with physical activity

Changes in motivation for sustaining a behavioural change with physical activity in everyday life is measured with the Behavioural Regulation of Exercise Questionnaire

(BREQ-2) which measures individual motivation for physical activity. The questionnaire consists of 19 questions in a 0-4 Likert format.[40] In addition to the questionnaire, patients are asked to answer four questions in a 0-4 Likert format, regarding motivation for physical activity after being diagnosed with T2D.

Health Related Quality of Life

The patients Health Related Quality of Life is very important to maintain after being diagnosed with T2D.[41] To gain knowledge into the individual perception of quality of life on a physical and mental level we use the Short-Form Health Survey (SF-12). The questionnaire consists of 12 questions and uses a Likert scale of 1-3 for the physical function items; 1-5 for the bodily pain, social function, and general health perceptions items; 1-6 for the vitality and mental health; and a dichotomous scale of yes/no for the presence of role function limitations. The higher score, the higher level of health or functioning.[42]

Maintenance of behaviour change with physical activity

Automaticity of behaviour is essential when new habits become present in the everyday life.[43] To measure if the patient has adopted new habits as a result of the intervention we ask the patient to answer four questions from The Self-Report Habit Index. The Index uses a 0-4 Likert format and the four questions to be answered measures automatic activation, frequency of behaviour and relevance to self-identity related to physical activity.[44]

VO_2-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] The test is performed with an iPod placed in the pocket at the hip and the instructions are delivered from the app through earphones. To ensure the right walking intensity in the intervention period, the patients are asked to perform the test every 4th week.[16]

Strength in the lower extremities

The sit-to-stand test (30 seconds) measures the lower body strength and will be administered using a chair without arms. The patient is encouraged to complete as many full stands as possible within a 30-sec time limit.[45]

Adherence to the intervention

Adherence is determined by an evaluation and quantification of the electronic log of data from the InterWalk app to the central database of all uploaded data.

S*elf-rated physical activity*

The "Recent Physical Activity Questionnaire" (RPAQ) has 9 main questions, which covers 4 domains of physical activity: domestic life, work, recreation and transport. Physical Activity is estimated in MET's (Metabolic Equivalent). In answering the questions in the questionnaire, the patient will answer in regards to the last four weeks with physical activity in the everyday life.[46]

Personality traits

The NEO-Five Factor Inventory (NEO-FFI) [47] consists of 60 questions in a 0-4 Likert format constructed by selecting 2 items from each of the six facets characterizing each of the five personality traits (Neuroticism, Extraversion, Openness, Agreeableness, Conscientiousness) assessed by NEO-PI-R. The Sensation Seeking Scale (SES) [48] is a 40 items self-administered questionnaire consisting of 40 questions designed to test the tendency towards varied, novel and intense sensations.

Demographic, social economic and anthropometry measures

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. 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.

Height measurement is conducted using a portable altimeter (Tanita Stadiometer). The measurement is done without shoes and is repeated two times with each measure to nearest 0,1 cm. If the two measures are dissimilar with more than 0,5 cm, then the measurement is repeated. *Weigh* is measured in kilograms (kg) using an electronic weight. The measure is repeated two times with each measure to nearest 0,1 cm. If the two measures are dissimilar with more than 0,5 kg, then the measurement is repeated a third time. The patient is weighed fully dressed and one kilo is subtracted from each measure. *Hip circumference* is measured on the skin on the crest of the hipbone. The patient is asked to place a finger in the belly bottom and the measure is done with a tape measure (2 meters) placed on the upper side of the patients' finger. If the two measures are dissimilar with more than 0,5 cm, then the measurement is repeated a third time.

Safety criteria and adverse events

Patients are informed that performing the InterWalk walking test may cause some degree of breathlessness as patients are expected to reach 80-85% of VO_2-peak during the walking test. All other measurements are not associated with any known risk or discomfort. Injuries linked to the intervention are registered, if informed to the health professionals at the health

promotion centres, during the trial period. In case of severe adverse events, the Scientific Ethical Committee of the Capital Region of Demark is informed.

Sample size considerations

The minimum difference of interest (MDI) is 10 minutes per day. Based on existing experimental evidence, we expect the standard deviation (SD) of the change in moderate-and-vigorous physical activity from baseline to 12 month follow up to be between 1.2 – 2.3 times the effect size.[49,50] Therefore, SD twice the MDI (20 min of moderate-and-vigorous physical activity) per day was applied in the sample size calculations. After applying Bonferroni adjustment due to multiple comparisons in the three group trial a total of 190 participants are needed to obtain a statistical power (1-β) of 80% with an α of 0.017 (two-tailed). Allowing for an attrition rate of 30%, 272 patients (91 in the control group and 181 in experimental group) are recruited. The setting enables recruitment until December 15st 2016. The sample size is truncated at 272 participants or the N reached at the end of recruitment period - whatever is reached first (see section 'Participants').

Randomisation, sequence generation and allocation concealment

After returning the physical activity monitors patients are randomised to either standard care or experimental group after baseline test (phase one). Allocation to either IWTgroup or IWTsupport-group on patients allocated to the experimental group is concealed until after

the post intervention test (phase two). A health professional associated with the trial, telephones the patient and inform about random allocation after returning the PA monitors to either IWT-group or IWTsupport-group. The patients are stratified by gender to ensure an equal number across all groups. The allocation sequence is generated through a standardised computer program by an independent researcher (RC). The allocation sequence is concealed until the trial arms are assigned. A Flow of patients is depicted in Figure 2.

Blinding

The scientific staff is blinded to patient allocation from baseline to the 52-week follow-up is completed for all patients. The health professionals at the promotion centre are not blinded to allocation to either standard care or experimental groups.

Statistical methods

All analyses will be conducted according to the Intention-To-Treat principle. Continuous endpoints will be analysed using repeated measures analysis of covariance in a mixed linear model. Categorical and dichotomous end points will be analysed with the use of logistic regression. The model will include with group, and sex as fixed effects, with the baseline value as a covariate.

All patients randomised to one treatment, will be analysed according to the treatment to which the patient was allocated, irrespective of whether they received this or some other treatment, or no treatment at all. The ITT population will be handled all patients randomised

to the three treatment arms, and the dataset is equal to the "all patients randomized set" (APRS). Missing values due to patients' absence from follow-ups or withdrawal from the study are to be expected in clinical trials. Several approaches are described for handling missing data in the ITT analysis, and among them "baseline observation carried forward" (BOCF: i.e., a null-responder imputation, where the level at baseline is also considered the last). 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 (i.e. an extra pre-specified sensitivity analysis). Exploratory analyses of the treatment effects will be performed on some the secondary outcomes.

Data management and quality control

All data are entered in an SSL-secured, online-based database developed by the Danish Stakeholder Help2Run (CVR: 34801088). The online-based database logistically handles the data gathered at baseline, after intervention in phase one, and during follow-up (phase two) and after 52 weeks. Data on demography, measurements, tests and questionnaires are

entered directly in the database available via a project-specific homepage (http://www.runsafe.dk/mtd/login/admin-signihttps://www.runsafe.dk/mtd/login/admin-signin). A protected back-end system (https://www.runsafe.dk/mtd/admin) is used to logistically handle information on demography, measurements, tests and questionnaires on each participant in the trial (for information on Interval Walking Training using the InterWalk app see '*Interval Walking Training using The InterWalk Application'*. The system was approved in 2014 after an inspection by the Danish Data Protection Agency. Access to personalized data from the InterWalk participants is only possible using a personalized username and password. Only specified researchers are allowed to administrate the back-end system and each researcher and project member with access to the back-end has a unique username and personal password for the back-end system. All activities, including changing data and downloading data, in the back-end system are logged in accordance with the rules and regulations from the Danish Data Protection Agency. A unique subject ID number will be subscribed to all patients in order to anonymize data. The identification key (ID to personal information) will be encrypted and stored securely and separately from the unique ID number on a secure database.

Ethics and Dissemination

The InterWalk trial contributes with important knowledge on different treatment approaches in the rehabilitation of patients with T2D. Physical activity and exercise have beneficial

effect on patients with T2D when the interventions are conducted in well-designed efficacy studies.[2,4,6] However, little is known on whether this effect also is present in effectiveness studies or "real-world setting" studies. These studies are of great importance and relevance regarding evidence-based medicine highlighting the importance of the InterWalk trial.

The InterWalk trial has a pragmatic design that allows for different intervention periods in the participating municipalities. Furthermore, the interventions are conducted directly in the clinical setting giving a more reliable frame of the experienced challenges in a population with T2D. We believe that the implementation of the study results will have a smoother implementation phase, as the health professionals already are familiar with the preceding's.

The trial gives valuable insight into the impact of different motivational and supportive tools as well as knowledge about individual motivation and the impact on sustaining a newly acquired behaviour change regarding physical activity in everyday life.

Interval Walking Training is expected to be a suitable and effective way of providing moderate-vigorous physical activity for at large group of patients with T2D. IWT can be done at any time and anywhere and is thus integrated and tailored to fit individual everyday life. The overall objective is to promote lifelong physical activity for the individual and we believe that experiences from the present trial can help when planning future interventions with IWT to patients with various lifestyle diseases e.g. coronary heart diseases.

It is a major advantage that the trial is designed as a randomised controlled trial in a "real-world setting" with a study population representing patients with T2D referred to rehabilitation. Furthermore, data and results are collected consecutively and directly in the clinical setting in which the interventions are to be used after the trial. Together with the very limited number of inclusion and exclusion criteria and a stratification of patients on gender secures external validity of the trial and thus will add important information to the current body of evidence on T2D treatment.

All data from eHealth solutions as the InterWalk app are electronically monitored. The patient is not dependent on opening hours at the health promotion centre as the InterWalk is either installed on an iPhone or an iPod. This gives a unique possibility for the patient to be physically active whenever it fits in their everyday life.

We acknowledge that physical activity only has effect when adherence is high, which is why we first compare standard care with interval walking for a shorter period (phase one) followed by a re-allocation of patients in the experimental group to either interval walking with or without motivational support (phase two). All groups have a 52-week follow-up. The trial design enables us to investigate if patients are able to maintain a newly acquired behaviour change with physical activity in everyday life with or without motivational support for a longer period.

All personalized data and measures are stored on a central online-based database developed to logistically handle all data collected at baseline and during follow-

up. The backend system (https://www.runsafe.dk/mtd/admin/) secures all information from each patient. The construction of the database with personalized usernames, passwords, and specific permissions to all health professionals and administering permissions to scientific staff in the backend secures all data. Furthermore, all activities are logged.

All outcomes measures are assessed blinded to allocation at baseline and the primary outcome is assessed blinded to intervention in the experimental group after the intervention period. All measures are conducted by the health professionals at the health promotion centres and are blinded for allocation after intervention in the experimental group with IWT until after return of the physical activity monitors by the patient. All statistical analyses are blinded to researchers, reducing the risk of detection and interpretation bias.[51–53] All secondary outcomes, but VO_2-peak and the Sit to Stand Test are self-reported and by nature likely to be biased. The patients answer questionnaires independently of the health professionals at the health promotion centres.

The secondary outcomes of motivation for physical activity and behaviour change are of highly importance as knowledge concerning motivational support and maintenance of effect (new habits with physical activity) to our knowledge is lacking in patients with T2D. This knowledge will help health professionals to better tailor the treatment and herby potentially achieve a higher adherence to the programme following the supervised intervention.

The limitations in this trial are similar to those of other exercise trials where physical testing and time-of-day and day-to-day variation constitute a challenge. We have standardised all testing protocols for all procedures to reduce the variation and run a routine program of on-going calibration and training of the health professionals.

The trial is conducted in accordance with the Helsinki Declaration II.[54] All eligible patients receive written and oral informed consent prior to inclusion before any additional trial procedures. Data on all screened patients are registered in order to report characteristics of in-eligible patients and written informed consent is also obtained from these patients. The patients can withdraw from the trial at all times during the trial period. This has no consequence for any other future treatment. If patients discontinue the trial intervention, standard care is offered for the rest of the intervention period. All results from the trial, negative, positive or inconclusive results, are disseminated in international peer-reviewed scientific papers and at national and international conferences. We follow the guidelines from the International Committee of Medical Journal Editors when authorship is determined. The results will be reported when all long-term data become accessible.

Furthermore, all results are shared with the participating municipalities and participating health professionals and are used to develop future intervention and implementation strategies in the Danish municipalities.

Trial status

The inclusion period started in January 2015 and is scheduled to finish in December 2017 with a 52-week follow-up. To ensure enrolment of patients in the trial we are open for collaborations with new municipalities during the trial period. So far the trial has resulted in collaboration with both rural and urban municipalities in Denmark. The inclusion rate is carefully monitored every week by the research team. In November 2016, 216 patients had been enrolled in the trial.

Contributors LSV, MR-L and HL drafted the manuscript. All authors made substantial contributions to conception and design, and revised the manuscripts critically for important intellectual content. All authors have given their approval for the manuscript to be published.

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Ethics approval

The local regional Research Ethics Committee in Denmark (H-1-2014-074) and the Danish Data Protection Agency (j.nr. 2014-54-0897) has approved the trial.

Acknowledgement

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Competing interests statement

We have read and understood The BMJ policy on declaration of interests and declare no competing interests.

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FIGURE LEGENDS

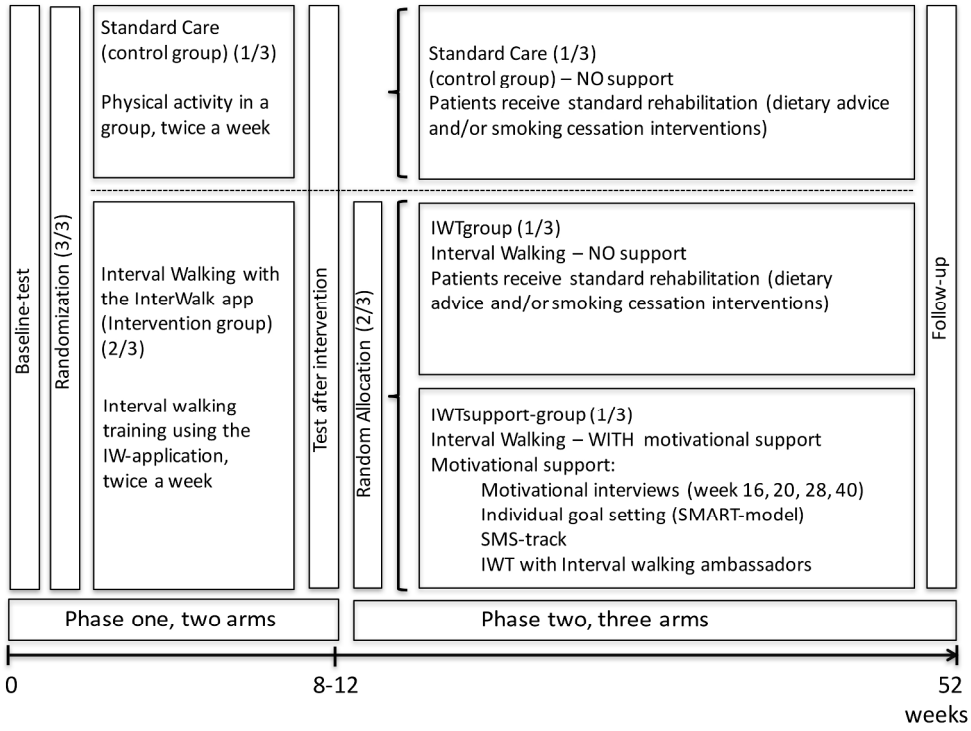
Figure 1. Timeline and overview of interventions in the InterWalk trial
Phase one shows baseline-test, randomization, intervention and test after intervention. Phase two shows the re-allocation of patients in the experimental group who do Interval Walking Training (IWT with the InterWalk app to either IWT with or without motivational support form a health professional. All patients are tested at baseline, after intervention and again at follow-up at 52 weeks

Figure 2. Flow-chart, The InterWalk-RCT Trial

Figure 3. The InterWalk front page (A), Protocol for the fitness test in the application (B), The start page for interval walking showing smileys as direct feedback to the user (C) (translated from Danish).[16]

Figure 4. Short Message Service (SMS), send every Sunday to patients in the IWTsupport-group

Figure 5. Short Message Service (SMS), Standardized walking test in the InterWalk application, send every fourth week to patients in the IWTsupport-group



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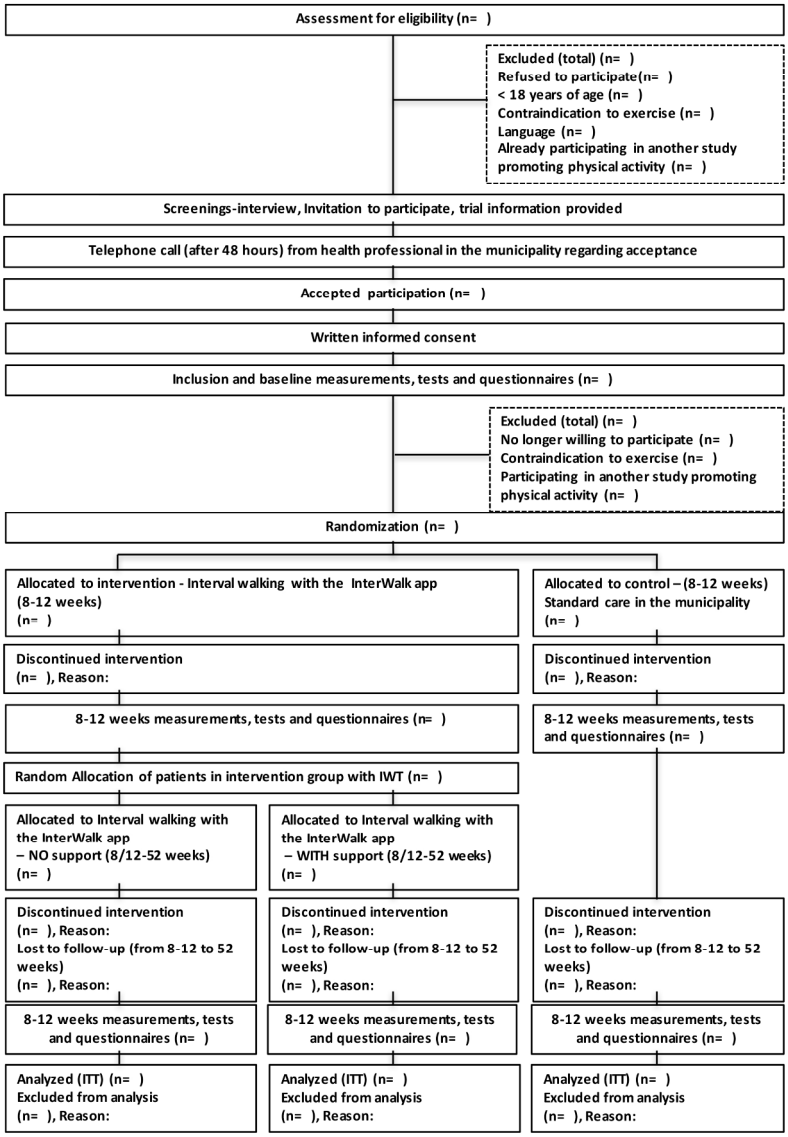
254x190mm (300 x 300 DPI)



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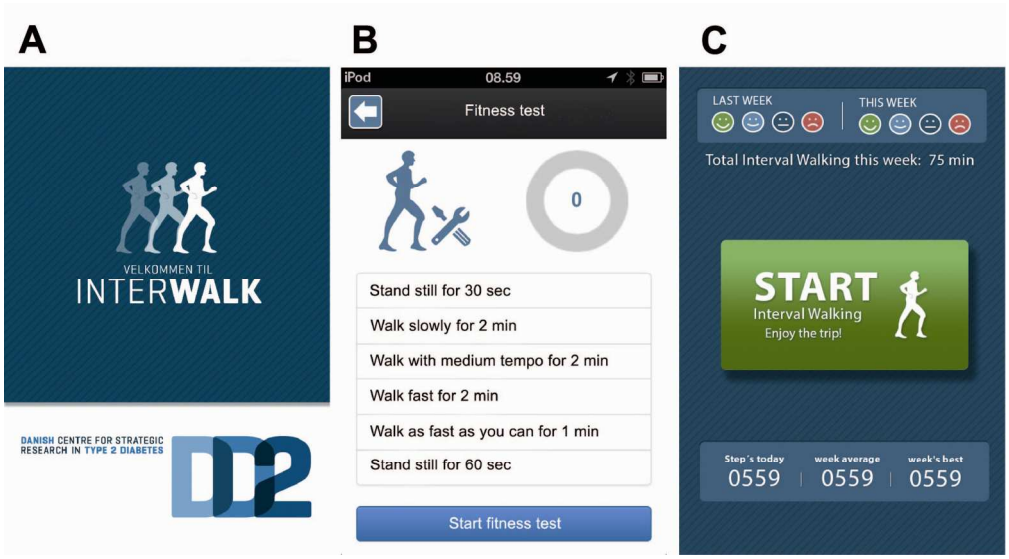

Figure 3. The InterWalk front page (A), Protocol for the fitness test in the application (B), The start page for interval walking showing smileys as direct feedback to the user (C) (translated from Danish).[16]

725x399mm (72 x 72 DPI)

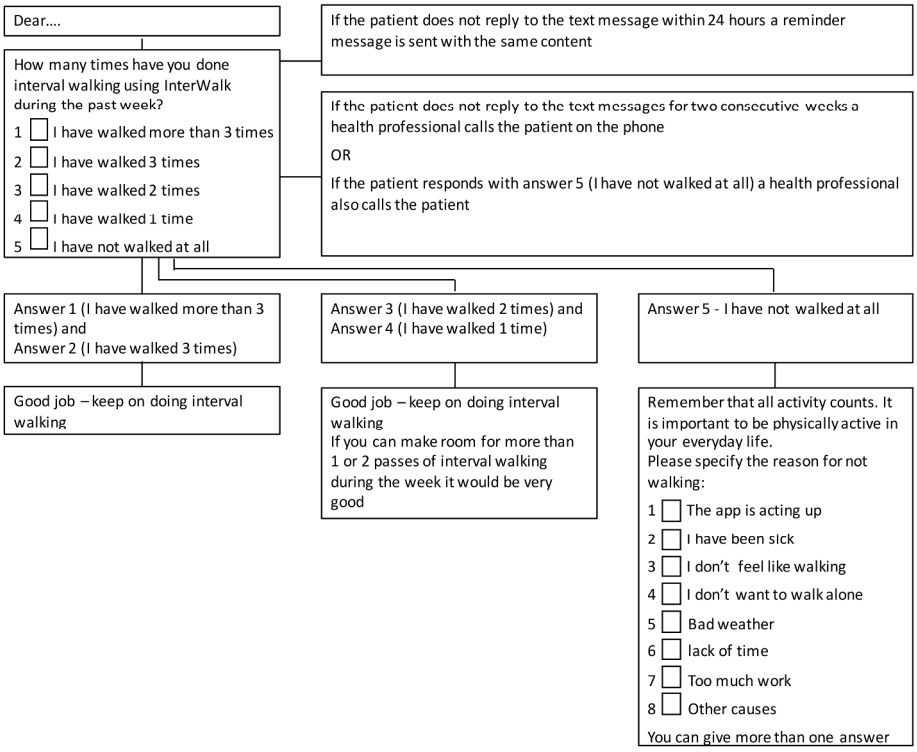

Figure 4. Short Message Service (SMS), send every Sunday to patients in the IWTsupport-group

254x190mm (300 x 300 DPI)

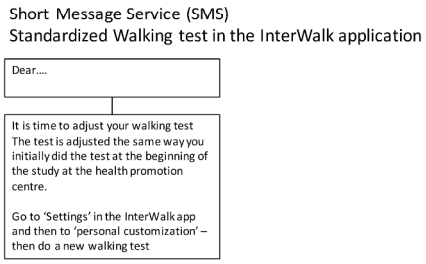

Figure 5. Short Message Service (SMS), Standardized walking test in the InterWalk application, send every fourth week to patients in the IWTsupport-group

338x190mm (300 x 300 DPI)

DANISH CENTRE FOR STRATEGIC RESEARCH IN TYPE 2 DIABETES

To BMJ Open

As the senior author of the published paper "*Implementation of interval walking training in patients with type 2 diabetes in Denmark: rationale, design, and baseline characteristics*" I herby approve the use figure A, B and C in paper "*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*" submitted to BMJ Open by Laura Valentiner.

Original publication of the figures:

"*Implementation of interval walking training in patients with type 2 diabetes in Denmark: rationale, design, and baseline characteristics.* Ried-Larsen M, Thomsen RW, Berencsi K, Brinkløv CF, Brøns C, Valentiner LS, Karstoft K, Langberg H, Vaag AA, Pedersen BK, Nielsen JS. Clin Epidemiol. 2016 Jun 8;8:201-9. doi: 10.2147/CLEP.S97303. eCollection 2016."

Kind regards
PhD Jens Steen Nielsen
2016-08-17

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	
Administrative information			**Page**
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2 & 5
	2b	All items from the World Health Organization Trial Registration Data Set	4, 31, 1, 5, 7-22, 6, 26, 23
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	33
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	33
	5b	Name and contact information for the trial sponsor	N/A
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	7, 16, 17, 31
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3, 7-22
	6b	Explanation for choice of comparators	4, 16, 29
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5, 6

Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-22
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	14, 21
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12, 14
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	14
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	23
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5, 24, 27
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	25
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	4
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	27
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	27
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	27
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	28
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	21
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	24
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	22
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	31
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	28
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	31
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	21, 31
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	5
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	5
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	32
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	31

Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	33
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	31
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	31
	31b	Authorship eligibility guidelines and any intended use of professional writers	31
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	32

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

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

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Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Diabetes and endocrinology, Sports and exercise medicine, Rehabilitation medicine, Evidence based practice
Keywords:	Type 2 diabetes, Rehabilitation, Interval Walking Training, Physical Activity, Behaviour maintenance

TITLE:

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

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RUNNING HEAD

Effect of Interval Walking on Type 2 Diabetics

BRIEF TITLE:

The InterWalk Trial

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ABSTRACT:

Introduction

Physical activity is a cornerstone in Type 2 diabetes (T2D) rehabilitation. Effective long-term and low-cost strategies to keep these patients' physically active are needed. However, maintaining physical activity behaviour is difficult once formalised interventions end. Structured exercise training supported by mobile technology and remote feedback is potentially an effective strategy.

The objective of the trial is to investigate whether mobile health support using the InterWalk application for smartphones is effective in increasing physical activity levels in persons with T2D over time compared to standard care.

We investigate whether Interval Walking Training (IWT) using the InterWalk application is superior to Danish municipality-based rehabilitation in increasing moderate-and-vigorous physical activity levels in patients with T2D across 52 weeks. Secondary, we hypothesize that a motivational programme added from end of intervention to 52-weeks further increases level of physical activity in everyday life in patients with T2D.

Methods and analysis

The trial is a parallel-group, open-labelled, randomised controlled trial with long-term follow-up at 52-week including patients with T2D. The primary outcome is change in moderate-and-vigorous physical activity. The key secondary outcome includes motivation for physical activity behaviour change. Other secondary outcomes are VO_2-peak, strength in

the lower extremities. Exclusion criterion is medical contraindication to exercise. We include up to 246 patients and randomly allocate them into a control (standard group) or an experimental group (8-12 weeks of IWT supported by the smartphone-based InterWalk application) in a 1:2 fashion. After intervention, the experimental group is randomly allocated into two follow-up conditions with unsupervised IWT with or without motivational support until 52-week follow-up. The Intention-To-Treat principle is applied.

Ethics and Dissemination

The local regional Research Ethics Committee in Denmark (H-1-2014-074) and the Danish Data Protection Agency (j.nr. 2014-54-0897) have approved the trial. Positive, negative or inconclusive results will be disseminated in scientific journals and conferences.

Trial registration: NCT02341690

Keywords: Type 2 diabetes, Rehabilitation, Interval Walking Training, Physical activity, Behaviour maintenance

STREGTHS:

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

- 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.

LIMITS:

- The trial has several collaborators in the setup which may cause variation in the testing procedures.
- Lack of clinical endpoints e.g. depression and mental health
- The length of the intervention periods varies between the three collaborating municipalities may influence the results of the trial.
- There may be a risk of contamination in the control group as the InterWalk application can be downloaded in App Store.

INTRODUCTION

Physical activity (PA) is a cornerstone in the clinical care of patients with type 2 diabetes (T2D).[1] PA activity has beneficial effect on glycaemic control and other key metabolic risk factors [2,3], as well as improvements in quality of life.[4,5] Furthermore, supervised long-term PA interventions have proven effective in improving glycaemic control.[2,6] However, experimental evidence does not support the efficiency of advice about physical activity alone.[7] As the number of patients with T2D is estimated to rise to 500 million by 2030 worldwide [8,9] the implementation of structured, long-term and supervised exercise regimes constitutes a large societal challenge and is not feasible. Thus, novel strategies to increase physical activity among patients with T2D are needed.

Smartphones have been used as a tool to register exercise, diet, weight and plasma glucose levels, but the evidence for using a smartphone as an exercise device and a self-management tool in the diabetes care is lacking.[10] However, emerging evidence suggest that eHealth solutions using information and communication technologies [11] can educate and engage patients with T2D in long-term self-management.[12–14] Due to the large ingress and ownership of smartphones, a smartphone-supported approach could prove feasible in increasing physical activity among patients with T2D and accommodate the increasing prevalence of T2D.

Efficiency of Interval Walking Training (IWT) in patients with T2D has been established.[15] In the study by Karstoft and co-workers, IWT was administered and

monitored using a small exercise computer (JD-mate). IWT induced significant improvements in physical fitness level, body composition and glycaemic control and in adherence of more than 85% over a 16 weeks period.[15] The potential benefits of implementing eHealth solutions in T2D management and the apparent health benefits of and adherence to IWT gave rise to the development of the InterWalk application (InterWalk app) to deliver IWT.[16]

There is a lack of knowledge about the integration of PA in the everyday life of the patient following rehabilitation interventions.[17] It is, however, known that successful behavioural change depends on an on-going maintenance of individual motivation regarding the behaviour and behavioural change itself.[18] Furthermore, time since onset of diagnosis, unhealthy behaviour and own beliefs about the cause of the problem, together with the number of previous attempts to change and support from partners, peers and health professionals are of relevance.[18] This underlines the need for new interventions with a direct focus on motivational support and self-control regarding sustaining a newly acquired behavioural change with PA. To better target and structure manageable interventions related to patients with T2D, understanding patients' individual priorities and values are crucial. In this regard, knowledge of individual motivation and self-efficacy to initiate behavioural changes becomes essential to understand.[18]

This paper presents a detailed protocol for the InterWalk Randomised Controlled Trial and is described in accordance with the SPIRIT guidelines (Standard Protocol Items: Recommendations for Interventional Trials).[19] Results from the trial will

follow CONSORT guidelines (CONsolidated Standards Of Reporting Trials) for non-pharmacological interventions.[20]

Trial objective and hypothesis

The objective of the trial is to investigate whether mobile support using the InterWalk application for smartphones is effective in increasing physical activity levels in persons with type 2 diabetes over time compared with a standard care rehabilitation program.

We investigate the effectiveness of the implementation of Interval Walking Training using the InterWalk application in the Danish municipality-based rehabilitation program and study whether the Interval Walking Training is superior to standard care in increasing moderate-vigorous physical activity 52 after weeks. Furthermore, we expect that a motivational support program added from end of the intervention to 52-weeks, will increase the physical activity level in patients with type 2 diabetes and help maintaining a physically active everyday life long-term.

METHODS AND ANALYSIS

Trial design and setting

The trial is a 52-week parallel-arm, open-labelled, randomised controlled trial. The participants are randomly allocated into two groups, 1) standard care or 2) experimental group with moderate-and-vigorous physical activity level, doing interval walking

facilitated by the InterWalk app. After an 8-12-week intervention period, patients in the experimental group are allocated to do interval walking using the InterWalk app with or without motivational support provided by the health professionals (see Figure 1).

[INSERT FIGURE 1 ABOUT HERE]

The intervention is conducted at the health promotion centres in Danish municipalities and hospitals that consecutively are included as cooperation partners. The municipality of Copenhagen is the first collaborator in the trial. Patients are referred to rehabilitation by their general practitioner (GP). Trained health professionals (physical therapists, nurses and staff with a master's degree) working at the health promotion centres recruit the patients, deliver the interventions and conduct all testing. The overall organization of health care in Denmark is fully tax-financed with universal access to health care services. The Danish model is described in detail elsewhere [21,22] and chronic disease care (including T2D) management is in Denmark based in the Chronic Care Model.[23]

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. Patients with a non-complicated course of disease receive rehabilitation consisting of: 1) disease-specific patient education, 2) diet counseling, 3) smoking cessation and 4) exercise. The composition of the individual rehabilitation program depends however on disease progression and on the rehabilitation offered in the municipality-based program or at the hospital. The general focus is patient empowerment, disease-related self-care and prevention of a decay of the functional capacity of patients with T2D.

The Scientific Ethical Committee at the Capital Region of Denmark (H-1-2014-074), and the Danish Data Protection Agency (j.nr. 2014-54-0897) have approved the trial. The InterWalk application is approved by the Danish Data Protection Agency (2008-58-0035). The trial has been registered at http://www.clinicaltrials.org (NCT02341690) on January 9th, 2015. Amendments to the protocol will be approved by the Scientific Ethical Committee at the Capital Region of Denmark. Amendments will be reported to http://www.clinicaltrials.org. The trial is conducted in accordance with the Helsinki Declaration.

Participants

Eligibility

All non-complicated patients diagnosed with T2D (out-patients), referred to a health promotion centre or hospital in the participating municipalities by their GP, are eligible if more than 18 years of age. A flow chart of participants is presented in Figure 2.

[INSERT FIGURE 2 ABOUT HERE]

The exclusion criteria are medical contraindications to exercise e.g. chronic complications in the locomotive apparatus, painful osteoarthritis or heart conditions.[24] Information is collected through medical records and at a screening interview with a health professional at the health promotion centre. Furthermore, patients are excluded if they do not want to be physically active in the rehabilitation setting or are already participating in other intervention studies at a health promotion centre. The patients have to be able to talk, read and understand the Danish language (for overview over in- and exclusion criterion, see Table 1).

Table 1. ELIGIBILITY CRITERIA

Inclusion criteria
• Diagnosed with type 2 diabetes
• Referred by General practitioner to a health promoting centre in participating municipality or hospital
Exclusion criteria
• < 18 years of age
• Medical contraindications to exercise
• Already participating in other exercise trials
• Does not talk and read Danish

If eligible, health professionals give oral and formalized written information with two days to consider participation in the trial. Written informed consent is obtained before any additional trial procedures. Enrolment was initiated in January 2015 and recruitment is terminated on December 15th 2016. Last-patient-last-visit is expected in December 2017.

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. The investigators (LSV, CB and HL) led four workshops (16 hours in total) with the health professionals during year 2014, in which the interventions of the study and work routines were discussed in detail. Furthermore, all participating health professionals underwent a thorough education program (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. The applicability of the trial results is hereby

increased, as the interventions are already part of the rehabilitation programme offered to patients with T2D in the municipalities.

The interventions in the trial consist of two phases (Figure 1). In phase one (8-12 weeks), patients are randomised to either a standard care group (control intervention) or an experimental group doing IWT using the InterWalk app. The present trial uses the standard care programme as control intervention and is conducted directly in the clinical setting. All patients receive supervision across phase one. In phase two (40-44 weeks), patients in the standard care group have no follow-up until 52 weeks post baseline. Patients in the experimental intervention group are in phase two randomly allocated to either IWT with or without motivational support (see section Experimental intervention – Interval Walking with the InterWalk application). Additional rehabilitation care (co-interventions) with disease-specific patient education, diet counseling and smoking cessation is offered to all patients across the intervention groups. The interventions are summarized in Table 2.

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
	3. Interval Walking Ambassadors	• Educated patients with T2D do interval walking in local community near the health promotion centres • One session per week
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 counsellors The course lasts 10-12 hours and can be either individually or group based

Experimental intervention – Interval Walking Training with the InterWalk application

Patients allocated to the experimental intervention do interval walking after baseline test provided by health professionals (phase one). IWT is provided by health professionals to smaller groups of 3-12 patients. After the intervention period in phase two patients are allocated to either receive IWT without motivational support during follow-up (IWTgroup) or IWT with motivational support during follow-up (IWTsupport-group) (Figure 1). Trained health professionals conduct the IWT sessions (see below) and the motivational support in phase two. Table 2 gives an example of a typical week with interval walking in the experimental intervention group.

Interval Walking Training using The InterWalk Application

Interval Walking Training is performed using the InterWalk app, which works as a personal trainer as well as a monitoring unit allowing researchers to continuously and automatically monitor and store the physical activity level in a central database (Figure 3).[16]

Interval Walking Training is personalized through a standardised eight-minute walking test, performed with the app before engaging in IWT.[25] The InterWalk app guides the user in IWT with repeated cycles of 3 minutes fast and 3 minutes slow walking. During Interval Walking Training (IWT) the InterWalk app provides the patient with continuous feedback on the walking speed. The patients are able to track exercise history and receive historic feedback on the quality of the IWT session using the app. The feedback system

employs the on-board accelerometer of the phone and GPS system to assess intensity and geographical location. Information on training intensity, total number of steps per day, IWT-data and data from the standardised walking test is stored in the smartphone or iPod and automatically transmitted to the central database at the Danish Strategic Research Centre for Type 2 Diabetes (DD2) when connected to Wi-Fi or mobile data network.[16]

[INSERT FIGURE/IMAGE 3 ABOUT HERE]

Experimental intervention, phase one

The patient receives a thorough introduction to the InterWalk app with follow-up instructions. The introduction consists of information and test of the app and the patient can ask clarifying questions if needed. A detailed manual regarding the InterWalk app is extradited to each patient. The health professional provides technical guidance and helps the patient to structure an everyday life with IWT during phase one. Patients are encouraged to perform IWT using the InterWalk app (see section: InterWalk Walking Training using the InterWalk Application) as a minimum three times per week, 30 to 60 minutes per session, with two of the sessions taking place at the health promotion centre and the third is conducted in the patient's everyday life environment. The aim is that all patients are capable of continuing IWT using the InterWalk app at the end of phase one (Table 3).

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		

	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.

Experimental intervention, phase two

In phase two patients in the experimental intervention group are randomly allocated into two follow-up conditions: with unsupervised Interval Walking Training without support (IWTgroup) or with motivational support (IWTsupport-group) following the intervention period until 52-week follow-up (see Figure 1).

Interval Walking Group without support (IWTgroup)

All patients in the Interval Walking Group (IWTgroup) are encouraged to continue to perform IWT with the InterWalk app three times a week, 30 to 60 minutes per session. The patients are not provided with any follow-up or support from health professionals from the end of the intervention period until follow-up at 52-weeks. However, patients are allowed to contact the health professionals at the health promotion centre at any time if necessary.

Interval Walking Group with support (IWTsupport-group)

Patients in the Interval Walking Group with support (IWTsupport-group) are also encouraged to do IWT with the InterWalk app three times per week. All patients in the IWTsupport-group receive additional motivational support by the health professionals at the promotion centre (see below for information regarding the motivational support).

Motivational support (phase two)

The motivational support is summarised in Table 4. The motivational intervention consists of four motivational interviews with individual goal setting and weekly Short Message

Service via the mobile phone (a SMS-track), (see Figure 5 and 6). Furthermore, patients have the opportunity to participate in IWT at predefined timeslots with an Interval Walking Ambassador in the local community near the health promotion centre (see Figure 1).

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. The Motivational interview is a semi-structured interview used to structure the communication between the patient and the health professional. The interview works as a partnership were focused and detailed questions reveal and visualize the patients motivation and barriers towards behaviour change and acknowledgement of patient autonomy.[26] Four motivational interviews are scheduled for each patient in the IWT support-group. See Table 4 for more detail. 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 that 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 goal setting is based on the S.M.A.R.T.-principle derived from the Goal Setting Theory developed by Edwin Locke.[28] S stands for Specific

(e.g. what do I want to accomplish?), M for Measurable (e.g. specific and measurable), A for achievable (realistic), R for relevant (individual goals) and T for timely (not too big to achieve in a short period).[29]

Table 4. MOTIVATIONAL INTERVIEWS WITH INDIVIDUAL GOAL SETTING PHASE TWO, IWTsupport-group

Four semi-structured motivational interviews with individual goal setting,	○ The interviews aim at helping the patient to reflect on why and how physical activity can be incorporated in everyday life ○ Make informed choices regarding behavioral changes regarding physical activity ○ Relate to own everyday life ○ Clarify barriers and facilitators of importance for the individual ○ Two to three individual goals are set at all interviews ○ The goals is based on need in the individual everyday life
A short resume with the individual goal setting is written after all interviews in the database. The written text is prospectively incorporated in the following interviews with the patient at the health promotion centre	

The interviews are placed in Week 16, 20, 28, 40 post baseline-test. Goal setting in the interviews are based on the *the S.M.A.R.T.- principle derived from the Goal Setting Theory developed by Edwin Locke.*[28]

Short Message Service (henceforth referred to as text message) enables inexpensive and possibly effective interaction between patients and health professionals at any time or place.[30,31] Communication as well as feedback is believed to enhance motivation through feelings of competence and relatedness [32], which may positively affect adherence to treatment. Text messages have shown positive effect on various health outcomes including diabetes self-management when used in behavior change interventions. Further, a higher effectiveness and lower attrition rate has been observed when customized and tailored messages is used.[30] In the present study, the patient receives two types of text messages during phase two (see Figure 4 and 5). The first type is a weekly and interactive

text message consisting of questions regarding the amount of IWT performed during the past week (see Figure 4). The patients are required to give feedback by returning a text message with one of the three response options provided. If the patient does not reply for two consecutive weeks, or if the patient answers that she/he has not been walking, a personal phone call to the patient is conducted from a health professional from the local health promotion centre. The aim of the call is to encourage and help the patient to plan IWT to fit the individual life of the patient. The second type of text message is sent every fourth week, encouraging the patients to perform the walking test using the InterWalk app without a requirement of feedback (see Figure 5).

[INSERT FIGURE 4 AND 5 ABOUT HERE]

Interval Walking Ambassadors: Using peers to educate other patients with T2D has shown effective in providing ongoing support over a longer period.[33,34] In this study, volunteer patients with T2D are recruited through the Danish Diabetes Association, where a consultant contacts possible patients via e-mail. The Interval Walking Ambassadors do IWT locally in phase two with patients from the IWTsupport group. The Interval Walking Ambassadors receives a two-day training programme in the participating municipality by researchers from the InterWalk research group. At any time during phase

two, patients can attend IWT at predefined timeslots with an Interval Walking Ambassador (see Table 2).

Adherence to interventions

To prevent patients from dropping out during phase one of the trial, patients are contacted by phone by a trained health professional if they fail to appear at the planned training sessions. Up to five attempts are made to contact the patient. In phase two only patients allocated to the IWTsupport-group are monitored by SMS-track and supervised during the phase until week 52. Patients in IWTgroup have no contact with the health professionals until 52-weeks follow-up (see Figure 1).

Control intervention – Standard care

Patients in the control group receive the standard rehabilitation treatment offered to patients with T2D in Denmark in a multimodal setting including physical activity (phase one, Figure 1). The duration of rehabilitation treatment differs between participating municipalities, but may not be shorter than eight weeks during phase one. At the end of the standard care rehabilitation program in the municipalities there is no follow-up on the exercise intervention, which is the normal procedure in Danish municipalities (phase two, Figure 1).[35]

The participating municipalities offer group exercise twice a week at the health promotion centres with 6-15 patients participating depending on the population size in the participating municipality. The content of the group exercise period is based on clinical guidelines in Denmark. A typical session is structured with first a short warm-up session followed by a strength and cardio part and finished with a cool-down period with strengthening (See Table 2). Furthermore, it is recommended that the patients have regularly consultation at the general practitioner every third month.

Additional rehabilitation care (Co-interventions)

All patients receiving rehabilitation at either a health promotion centre or at the hospital receives an offer of specific disease related patient education, diet counselling and smoking cessation.[35] It is optional whether the patient participate in one or all additional offers.

Disease specific patient education includes a section focused on behaviour modification and self-management and a specific part on diseases were the patients get knowledge regarding sequelae. *Diet counselling* regarding nutritional advice when living with T2D is handled by a dietitian. *Smoking cessation* is either group based or in individual process and is handled by smoking cessation counsellors.

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.

Data on the primary and secondary outcomes are obtained at baseline, post intervention (after 8-12 weeks) and 52 weeks after enrolment (Table 5). To standardize all measurements between health professionals and participating centres, all health professionals uses standardised protocols crafted for the trial regarding procedures and measurements. All data are entered directly in an online database (see section: Data management and quality control).

Effect of Interval walking on type 2 diabetics

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Table 5, SUMMARY OF DATA COLLECTION AND MEASURES

Measurements		Description	Baseline	8-12 weeks	52 weeks
Demographic†‡*					
	Age (median)	Obtained using self report	x	-	-
	Women		x	-	-
	Marital status		x	-	-
	Diabetes duration		x	-	-
	Education level		x	-	-
	Height, weight, body mass index	Obtained using standard procedures	x	x	x
Medical history†‡*		Obtained using medical records			
	History of Heart disease		x	x	x
	Hypertension		x	x	x
	Kidney disease		x	x	x
	Chronic Obstructive Pulmonary Disease (COPD)	Defined by FEV1<70%	x	x	x
Medicine†*					
	Self-reported use of medication		x	x	x
	Register-data use of medicine		x	x	x
*Physical fitness**					
	Moderate-to-Vigorous-intensity	Accelerometer (Axivity AX3, Newcastle, UK), worn for seven consecutive days, 3 times	x	x	x
	Total physical activity (VO_2-peak)	InterWalk - Walking test performed using an iPod touch or IPhone	x	x	x
*Strength**	Lower extremities	Sit-To-Stand	x	x	x
*Patient Reported Outcomes (PROs)**					
	Behavioural Regulation in Exercise	*Obtained using BREQ-2,* Behavioural Regulation in Exercise Questionnaire	x	x	x

Physical Activity	*Obtained using R-PAQ*, Resent Physical Activity Questionnaire	x	x	x
Health related quality of life	*Obtained using SF-12*, Short Form - Health Related Quality of life Questionnaire	x	x	x
Automaticity of behaviour	The Self-Report Habit Index		x	x
Personality traits†	*Obtained using NEO-FFI,* Neuroticism, Extroversion and Openness – Five Factor Inventory (Personality traits)	x	-	-
Risk behaviour†	*Obtained using SES,* Sensation Seeking Scale (risk behaviour)	x	x	x
*Adherence to interventions**				
Attendance registration	From baseline to 8-12 weeks	x	x	x
Log in the InterWalk app	Measured by the electronic log in the InterWalk-app	x	x	x
Registry data assessment‡*				
Mortality, cause of death	Obtained using medical records	-	x	x
Hospitalization		-	x	x
Contract with general practitioner		-	x	x

* Article 1: The effectiveness of smartphone delivered Interval Walking Training on moderate-and-vigorous physical activity versus standard care in patients with type 2 diabetes: a parallel group single-blinded randomized controlled trial.
†Article 2: Baseline characteristics and personality traits in patients with type 2 diabetes: descriptive study of all participants
‡Article 3: Nay Sayers – Characteristics of patients who does not want to be part of a physical activity study related to everyday life; all patients referred to the health promotion centre in the municipalities participating in the randomized controlled trial.
§Article 4: Effectiveness of smartphone delivered Interval Walking Training versus standard care in patients with type 2 diabetes on HbA1c and HDL, high-density lipoprotein; LDL, low-density lipoprotein: A sub-study to the randomized controlled trial (The InterWalk Trial, article 1), measured in a sub-sample (n=40).

Primary outcome

The primary outcome is change in moderate-to-vigorous-intensity physical activity from baseline to 52-week follow-up.

Secondary outcomes

The key secondary outcome changes in motivation for sustaining a behavioural change with physical activity in everyday life at 52-week follow-up.

Other secondary outcomes of interest are changes in patients' fitness level measured as VO_2-peak by the standardised walking test (part of the InterWalk application) and health-related quality of life. Strength in the lower extremities, adherence to intervention and impact of personality traits on physical activity in everyday life are also considered exploratory secondary outcomes. All outcomes are measured at baseline, after intervention and at 52-week follow-up (see Figure 2).

Data collection

Level of daily moderate-to-vigorous-intensity physical activity

It is important to gain knowledge into physical activity in everyday life. To determine level of daily moderate-to-vigorous-intensity physical activity a hip-mounted physical activity monitor (Axivity AX3, Newcastle, UK) is worn for seven consecutive days, at three time periods during the trial period; after baseline-test, after the intervention period and again at

52-weeks follow-up. The monitor is fixed using adhesive tape (Leukomed T, BSN medical, Germany) on right side the lumbar spine. Additionally, a monitor is fixed on on the lateral side of the right thigh (Leukomed T, BSN medical, Germany) for supporting information about posture.[25] The patients are instructed not to remove the physical activity monitor at any time during the three time periods. If de-attached, the participants are trained in fixing the monitors correctly and are instructed to note the incident. If the patients need help in fixing the monitors correctly the health professionals at the health promotion centre are educated to help.

Physical activity diary

In order to validate the physical activity level during the seven days with physical activity monitors we ask the patient to complete a seven-day diary to report number of work- and sleep hours, bicycling and strength training sessions at the three time periods on a daily basis. The physical activity monitor and the diary are returned free-of-charge via mail. The patient is contacted by phone after within one week if the physical activity monitors are not returned as expected.

Motivation for behaviour change with physical activity

Changes in motivation for sustaining a behavioural change with physical activity in everyday life is measured with the Behavioural Regulation of Exercise Questionnaire

(BREQ-2) which measures individual motivation for physical activity. The questionnaire consists of 19 questions in a 0-4 Likert format.[40] In addition to the questionnaire, patients are asked to answer four questions in a 0-4 Likert format, regarding motivation for physical activity after being diagnosed with T2D.

Health Related Quality of Life

The patients Health Related Quality of Life is very important to maintain after being diagnosed with T2D.[41] To gain knowledge into the individual perception of quality of life on a physical and mental level we use the Short-Form Health Survey (SF-12). The questionnaire consists of 12 questions and uses a Likert scale of 1-3 for the physical function items; 1-5 for the bodily pain, social function, and general health perceptions items; 1-6 for the vitality and mental health; and a dichotomous scale of yes/no for the presence of role function limitations. The higher score, the higher level of health or functioning.[42]

Maintenance of behaviour change with physical activity

Automaticity of behaviour is essential when new habits become present in the everyday life.[43] To measure if the patient has adopted new habits as a result of the intervention we ask the patient to answer four questions from The Self-Report Habit Index. The Index uses a 0-4 Likert format and the four questions to be answered measures automatic activation, frequency of behaviour and relevance to self-identity related to physical activity.[44]

VO_2-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] The test is performed with an iPod placed in the pocket at the hip and the instructions are delivered from the app through earphones. To ensure the right walking intensity in the intervention period, the patients are asked to perform the test every 4th week.[16]

Strength in the lower extremities

The sit-to-stand test (30 seconds) measures the lower body strength and will be administered using a chair without arms. The patient is encouraged to complete as many full stands as possible within a 30-sec time limit.[45]

Adherence to the intervention

Adherence is determined by an evaluation and quantification of the electronic log of data from the InterWalk app to the central database of all uploaded data.

S*elf-rated physical activity*

The "Recent Physical Activity Questionnaire" (RPAQ) has 9 main questions, which covers 4 domains of physical activity: domestic life, work, recreation and transport. Physical Activity is estimated in MET's (Metabolic Equivalent). In answering the questions in the questionnaire, the patient will answer in regards to the last four weeks with physical activity in the everyday life.[46]

Personality traits

The NEO-Five Factor Inventory (NEO-FFI) [47] consists of 60 questions in a 0-4 Likert format constructed by selecting 2 items from each of the six facets characterizing each of the five personality traits (Neuroticism, Extraversion, Openness, Agreeableness, Conscientiousness) assessed by NEO-PI-R. The Sensation Seeking Scale (SES) [48] is a 40 items self-administered questionnaire consisting of 40 questions designed to test the tendency towards varied, novel and intense sensations.

Demographic, social economic and anthropometry measures

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. 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.

Height measurement is conducted using a portable altimeter (Tanita Stadiometer). The measurement is done without shoes and is repeated two times with each measure to nearest 0,1 cm. If the two measures are dissimilar with more than 0,5 cm, then the measurement is repeated. *Weigh* is measured in kilograms (kg) using an electronic weight. The measure is repeated two times with each measure to nearest 0,1 cm. If the two measures are dissimilar with more than 0,5 kg, then the measurement is repeated a third time. The patient is weighed fully dressed and one kilo is subtracted from each measure. *Hip circumference* is measured on the skin on the crest of the hipbone. The patient is asked to place a finger in the belly bottom and the measure is done with a tape measure (2 meters) placed on the upper side of the patients' finger. If the two measures are dissimilar with more than 0,5 cm, then the measurement is repeated a third time.

Safety criteria and adverse events

Patients are informed that performing the InterWalk walking test may cause some degree of breathlessness as patients are expected to reach 80-85% of VO_2-peak during the walking test. All other measurements are not associated with any known risk or discomfort. Injuries linked to the intervention are registered, if informed to the health professionals at the health

promotion centres, during the trial period. In case of severe adverse events, the Scientific Ethical Committee of the Capital Region of Demark is informed.

Sample size considerations

The minimum difference of interest (MDI) is 10 minutes per day. Based on existing experimental evidence, we expect the standard deviation (SD) of the change in moderate-and-vigorous physical activity from baseline to 12 month follow up to be between 1.2 – 2.3 times the effect size.[49,50] Therefore, SD twice the MDI (20 min of moderate-and-vigorous physical activity) per day was applied in the sample size calculations. After applying Bonferroni adjustment due to multiple comparisons in the three group trial a total of 190 participants are needed to obtain a statistical power (1-β) of 80% with an α of 0.017 (two-tailed). Allowing for an attrition rate of 30%, 272 patients (91 in the control group and 181 in experimental group) are recruited. The setting enables recruitment until December 15st 2016. The sample size is truncated at 272 participants or the N reached at the end of recruitment period - whatever is reached first (see section 'Participants').

Randomisation, sequence generation and allocation concealment

After returning the physical activity monitors patients are randomised to either standard care or experimental group after baseline test (phase one). Allocation to either IWTgroup or IWTsupport-group on patients allocated to the experimental group is concealed until after

the post intervention test (phase two). A health professional associated with the trial, telephones the patient and inform about random allocation after returning the PA monitors to either IWT-group or IWTsupport-group. The patients are stratified by gender to ensure an equal number across all groups. The allocation sequence is generated through a standardised computer program by an independent researcher (RC). The allocation sequence is concealed until the trial arms are assigned. A Flow of patients is depicted in Figure 2.

Blinding

The scientific staff is blinded to patient allocation from baseline to the 52-week follow-up is completed for all patients. The health professionals at the promotion centre are not blinded to allocation to either standard care or experimental groups.

Statistical methods

All analyses will be conducted according to the Intention-To-Treat principle. Continuous endpoints will be analysed using repeated measures analysis of covariance in a mixed linear model. Categorical and dichotomous end points will be analysed with the use of logistic regression. The model will include with group, and sex as fixed effects, with the baseline value as a covariate.

All patients randomised to one treatment, will be analysed according to the treatment to which the patient was allocated, irrespective of whether they received this or some other treatment, or no treatment at all. The ITT population will be handled all patients randomised

to the three treatment arms, and the dataset is equal to the "all patients randomized set" (APRS). Missing values due to patients' absence from follow-ups or withdrawal from the study are to be expected in clinical trials. Several approaches are described for handling missing data in the ITT analysis, and among them "baseline observation carried forward" (BOCF: i.e., a null-responder imputation, where the level at baseline is also considered the last). 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 (i.e. an extra pre-specified sensitivity analysis). Exploratory analyses of the treatment effects will be performed on some the secondary outcomes.

Data management and quality control

All data are entered in an SSL-secured, online-based database developed by the Danish Stakeholder Help2Run (CVR: 34801088). The online-based database logistically handles the data gathered at baseline, after intervention in phase one, and during follow-up (phase two) and after 52 weeks. Data on demography, measurements, tests and questionnaires are

entered directly in the database available via a project-specific homepage (http://www.runsafe.dk/mtd/login/admin-signihttps://www.runsafe.dk/mtd/login/admin-signin). A protected back-end system (https://www.runsafe.dk/mtd/admin) is used to logistically handle information on demography, measurements, tests and questionnaires on each participant in the trial (for information on Interval Walking Training using the InterWalk app see '*Interval Walking Training using The InterWalk Application'*. The system was approved in 2014 after an inspection by the Danish Data Protection Agency. Access to personalized data from the InterWalk participants is only possible using a personalized username and password. Only specified researchers are allowed to administrate the back-end system and each researcher and project member with access to the back-end has a unique username and personal password for the back-end system. All activities, including changing data and downloading data, in the back-end system are logged in accordance with the rules and regulations from the Danish Data Protection Agency. A unique subject ID number will be subscribed to all patients in order to anonymize data. The identification key (ID to personal information) will be encrypted and stored securely and separately from the unique ID number on a secure database.

Ethics and Dissemination

The InterWalk trial contributes with important knowledge on different treatment approaches in the rehabilitation of patients with T2D. Physical activity and exercise have beneficial

effect on patients with T2D when the interventions are conducted in well-designed efficacy studies.[2,4,6] However, little is known on whether this effect also is present in effectiveness studies or "real-world setting" studies. These studies are of great importance and relevance regarding evidence-based medicine highlighting the importance of the InterWalk trial.

The InterWalk trial has a pragmatic design that allows for different intervention periods in the participating municipalities. Furthermore, the interventions are conducted directly in the clinical setting giving a more reliable frame of the experienced challenges in a population with T2D. We believe that the implementation of the study results will have a smoother implementation phase, as the health professionals already are familiar with the preceding's.

The trial gives valuable insight into the impact of different motivational and supportive tools as well as knowledge about individual motivation and the impact on sustaining a newly acquired behaviour change regarding physical activity in everyday life.

Interval Walking Training is expected to be a suitable and effective way of providing moderate-vigorous physical activity for at large group of patients with T2D. IWT can be done at any time and anywhere and is thus integrated and tailored to fit individual everyday life. The overall objective is to promote lifelong physical activity for the individual and we believe that experiences from the present trial can help when planning future interventions with IWT to patients with various lifestyle diseases e.g. coronary heart diseases.

It is a major advantage that the trial is designed as a randomised controlled trial in a "real-world setting" with a study population representing patients with T2D referred to rehabilitation. Furthermore, data and results are collected consecutively and directly in the clinical setting in which the interventions are to be used after the trial. Together with the very limited number of inclusion and exclusion criteria and a stratification of patients on gender secures external validity of the trial and thus will add important information to the current body of evidence on T2D treatment.

All data from eHealth solutions as the InterWalk app are electronically monitored. The patient is not dependent on opening hours at the health promotion centre as the InterWalk is either installed on an iPhone or an iPod. This gives a unique possibility for the patient to be physically active whenever it fits in their everyday life.

We acknowledge that physical activity only has effect when adherence is high, which is why we first compare standard care with interval walking for a shorter period (phase one) followed by a re-allocation of patients in the experimental group to either interval walking with or without motivational support (phase two). All groups have a 52-week follow-up. The trial design enables us to investigate if patients are able to maintain a newly acquired behaviour change with physical activity in everyday life with or without motivational support for a longer period.

All personalized data and measures are stored on a central online-based database developed to logistically handle all data collected at baseline and during follow-

up. The backend system (https://www.runsafe.dk/mtd/admin/) secures all information from each patient. The construction of the database with personalized usernames, passwords, and specific permissions to all health professionals and administering permissions to scientific staff in the backend secures all data. Furthermore, all activities are logged.

All outcomes measures are assessed blinded to allocation at baseline and the primary outcome is assessed blinded to intervention in the experimental group after the intervention period. All measures are conducted by the health professionals at the health promotion centres and are blinded for allocation after intervention in the experimental group with IWT until after return of the physical activity monitors by the patient. All statistical analyses are blinded to researchers, reducing the risk of detection and interpretation bias.[51–53] All secondary outcomes, but VO_2-peak and the Sit to Stand Test are self-reported and by nature likely to be biased. The patients answer questionnaires independently of the health professionals at the health promotion centres.

The secondary outcomes of motivation for physical activity and behaviour change are of highly importance as knowledge concerning motivational support and maintenance of effect (new habits with physical activity) to our knowledge is lacking in patients with T2D. This knowledge will help health professionals to better tailor the treatment and herby potentially achieve a higher adherence to the programme following the supervised intervention.

The limitations in this trial are similar to those of other exercise trials where physical testing and time-of-day and day-to-day variation constitute a challenge. We have standardised all testing protocols for all procedures to reduce the variation and run a routine program of on-going calibration and training of the health professionals.

The trial is conducted in accordance with the Helsinki Declaration II.[54] All eligible patients receive written and oral informed consent prior to inclusion before any additional trial procedures. Data on all screened patients are registered in order to report characteristics of in-eligible patients and written informed consent is also obtained from these patients. The patients can withdraw from the trial at all times during the trial period. This has no consequence for any other future treatment. If patients discontinue the trial intervention, standard care is offered for the rest of the intervention period. All results from the trial, negative, positive or inconclusive results, are disseminated in international peer-reviewed scientific papers and at national and international conferences. We follow the guidelines from the International Committee of Medical Journal Editors when authorship is determined. The results will be reported when all long-term data become accessible.

Furthermore, all results are shared with the participating municipalities and participating health professionals and are used to develop future intervention and implementation strategies in the Danish municipalities.

Trial status

The inclusion period started in January 2015 and is scheduled to finish in December 2017 with a 52-week follow-up. To ensure enrolment of patients in the trial we are open for collaborations with new municipalities during the trial period. So far the trial has resulted in collaboration with both rural and urban municipalities in Denmark. The inclusion rate is carefully monitored every week by the research team. In November 2016, 216 patients had been enrolled in the trial.

Contributors LSV, MR-L and HL drafted the manuscript. All authors made substantial contributions to conception and design, and revised the manuscripts critically for important intellectual content. All authors have given their approval for the manuscript to be published.

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Ethics approval

The local regional Research Ethics Committee in Denmark (H-1-2014-074) and the Danish Data Protection Agency (j.nr. 2014-54-0897) has approved the trial.

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Competing interests statement

We have read and understood The BMJ policy on declaration of interests and declare no competing interests.

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FIGURE LEGENDS

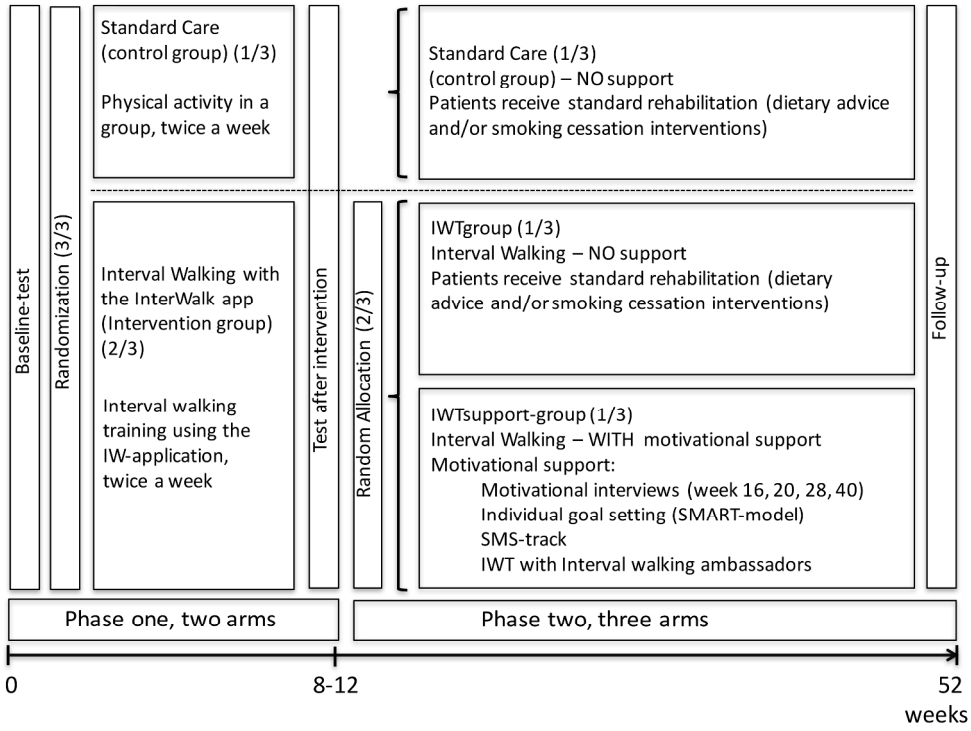
Figure 1. Timeline and overview of interventions in the InterWalk trial
Phase one shows baseline-test, randomization, intervention and test after intervention. Phase two shows the re-allocation of patients in the experimental group who do Interval Walking Training (IWT with the InterWalk app to either IWT with or without motivational support form a health professional. All patients are tested at baseline, after intervention and again at follow-up at 52 weeks

Figure 2. Flowchart, The InterWalk-RCT Trial

Figure 3. The InterWalk front page (A), Protocol for the fitness test in the application (B), The start page for interval walking showing smileys as direct feedback to the user (C) (translated from Danish).[16]

Figure 4. Short Message Service (SMS), send every Sunday to patients in the IWTsupport-group

Figure 5. Short Message Service (SMS), Standardized walking test in the InterWalk application, send every fourth week to patients in the IWTsupport-group



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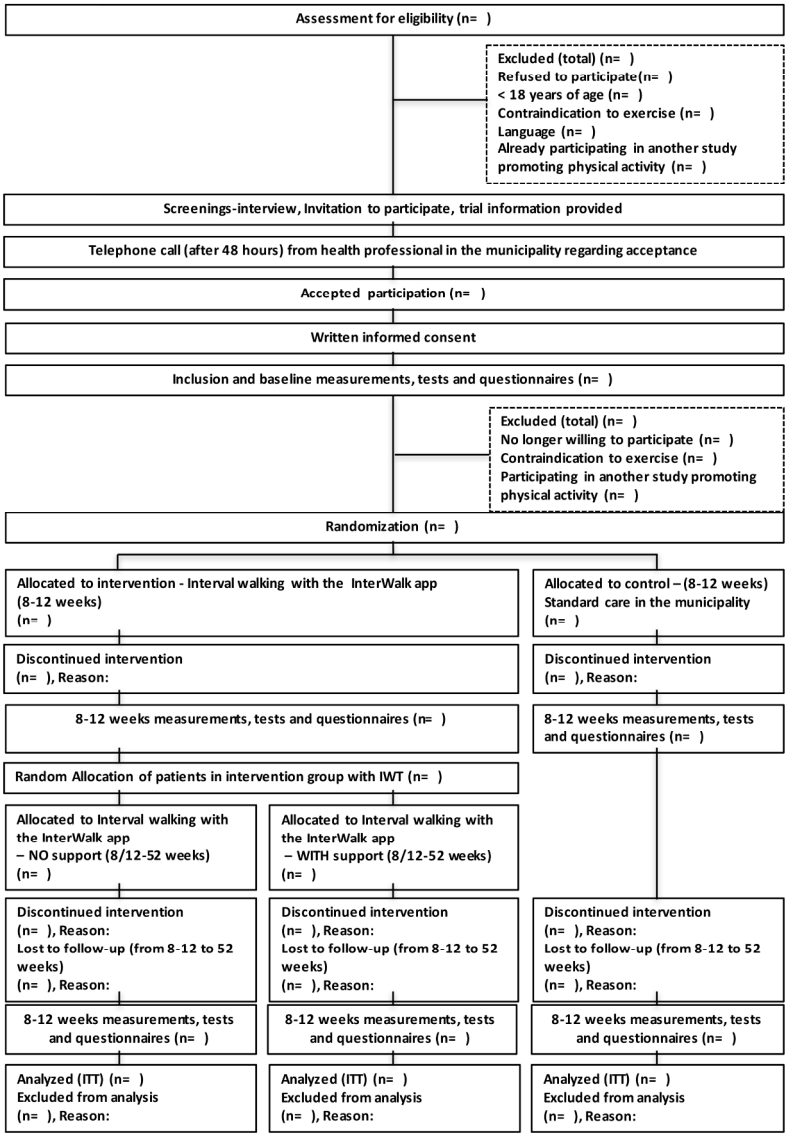
254x190mm (300 x 300 DPI)



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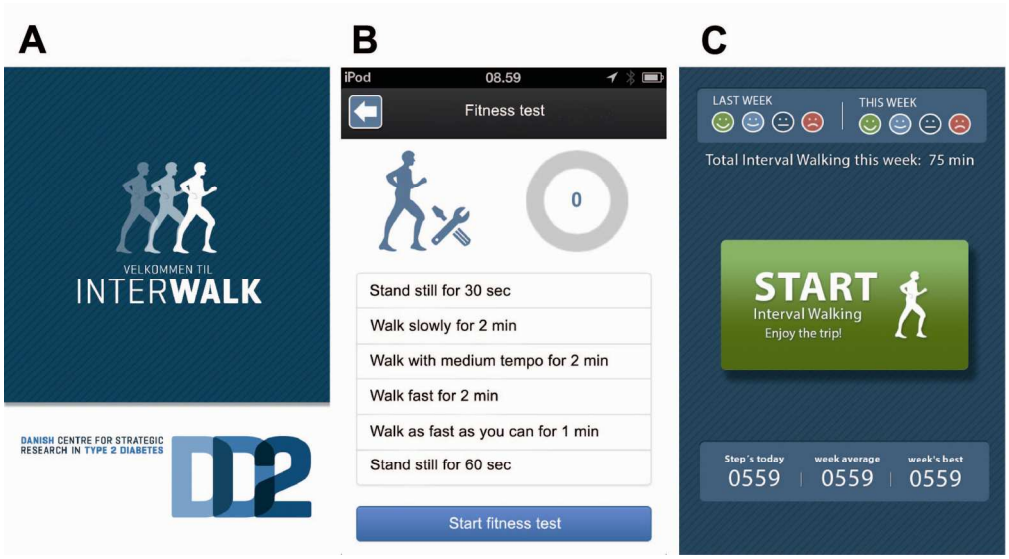
190x254mm (300 x 300 DPI)



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725x399mm (72 x 72 DPI)

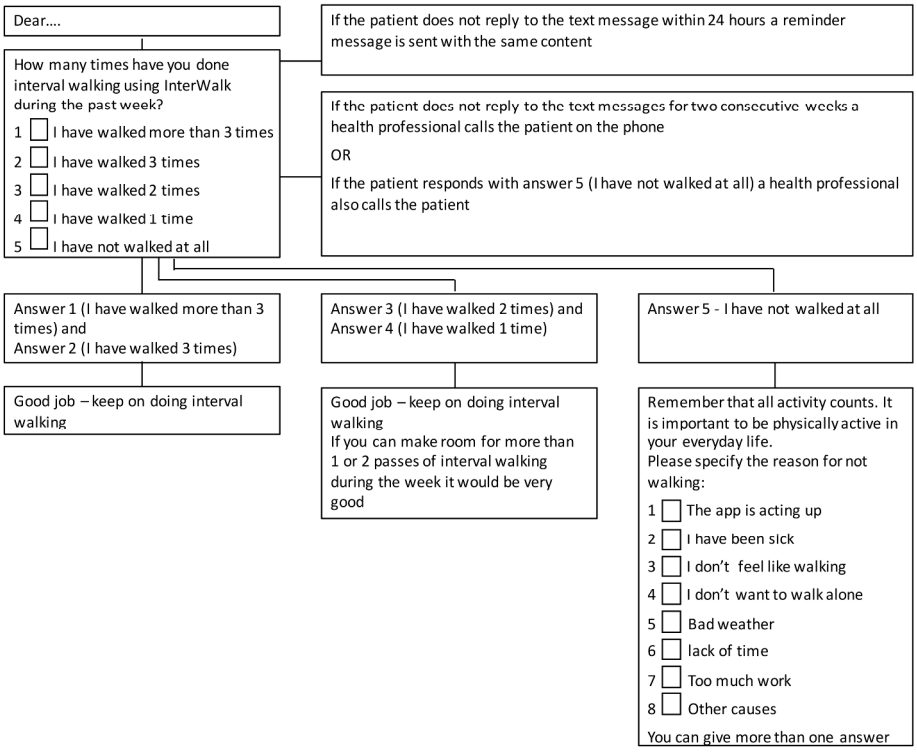

Figure 4. Short Message Service (SMS), send every Sunday to patients in the IWTsupport-group

254x190mm (300 x 300 DPI)

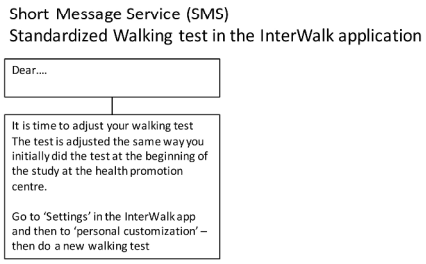

Figure 5. Short Message Service (SMS), Standardized walking test in the InterWalk application, send every fourth week to patients in the IWTsupport-group

338x190mm (300 x 300 DPI)

DANISH CENTRE FOR STRATEGIC RESEARCH IN TYPE 2 DIABETES

To BMJ Open

As the senior author of the published paper "*Implementation of interval walking training in patients with type 2 diabetes in Denmark: rationale, design, and baseline characteristics*" I herby approve the use figure A, B and C in paper "*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*" submitted to BMJ Open by Laura Valentiner.

Original publication of the figures:

"*Implementation of interval walking training in patients with type 2 diabetes in Denmark: rationale, design, and baseline characteristics.* Ried-Larsen M, Thomsen RW, Berencsi K, Brinkløv CF, Brøns C, Valentiner LS, Karstoft K, Langberg H, Vaag AA, Pedersen BK, Nielsen JS. Clin Epidemiol. 2016 Jun 8;8:201-9. doi: 10.2147/CLEP.S97303. eCollection 2016."

Kind regards
PhD Jens Steen Nielsen
2016-08-17

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	
Administrative information			**Page**
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	5 & 11
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	44-45
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-3 & 44
	5b	Name and contact information for the trial sponsor	N/A
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	10-11, 13-14, 17-20, 22, 24-27, 35-38
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4, 7-9
	6b	Explanation for choice of comparators	7-9, 13-14, 17-18, 21-26
Objectives	7	Specific objectives or hypotheses	9
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	9-11
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	10-11

Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	11-13
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	13-26
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	13-26
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	26
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	30-35
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	4, 9-10, 14, 26-30
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	5, 36
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	10-12
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	27-28
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	36-37
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	36-38
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	37
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13-14, 26-35
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13-26
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	38-39
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	37-38
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	37-38
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	38
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	5, 11
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11-13
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	38-39

Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	45
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	44-45
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	43
	31b	Authorship eligibility guidelines and any intended use of professional writers	44
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.