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The Dietary Education Trial in Carbohydrate Counting (DIET-CARB Study): study protocol for a randomized, parallel, open-label, intervention study comparing different approaches to dietary self-management in patients with type 1 diabetes

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Abstract

Introduction: Clinical guidelines recommend that patients with type 1 diabetes (T1D) learn carbohydrate counting or similar methods to improve glycaemic control. Although, systematic educating in carbohydrate counting is still not offered as standard-of-care for all patients on multiple daily injections (MDI) therapy in outpatient diabetes clinics in Denmark. This may be due to the lack of evidence as to which educational methods are the most effective for training patients in carbohydrate counting. The objective of this study is to compare the effect of two different educational programs in carbohydrate counting with the usual dietary care on glycaemic control in patients with T1D.

Methods and analysis: The study is designed as a randomized, controlled trial with a parallel-group design. The total study duration is 12 months with data collection at baseline, 6 and 12 months. We plan to include 231 Danish adult patients with T1D. Participants will be randomized to one of three dietician-led interventions; 1) A program in basic carbohydrate counting, 2) A program in advanced carbohydrate counting including an automated bolus calculator or 3) Usual dietary care. The primary outcome is changes in glycated haemoglobin A1c (HbA1c) or mean amplitude of glycaemic excursions (MAGE) from baseline to end of the intervention period (week 24) between and within each of the three study groups. Other outcome measures include changes in other parameters of plasma glucose variability (e.g. time in range), body weight and composition, lipid profile, blood pressure, mathematical literacy skills, carbohydrate estimation accuracy, dietary intake, diet-related quality of life, perceived competencies in dietary management of diabetes and perceptions of an autonomy supportive dietician-led climate, physical activity and urinary biomarkers.

Ethics and dissemination: The protocol has been approved by the Ethics Committee of the Capital Region, Copenhagen, Denmark.

Registration: The trial protocol is registered on ClinicalTrials.gov NCT03623113.

Strengths and limitations of this study

1. The study has a long-term follow-up and will provide knowledge on the effects of different levels of carbohydrate counting

2. The study applies well-documented measures of glycaemic control as effect-parameters

3. The results obtained have applicability beyond Denmark and has the potential to be included in the recommendations in future guidelines

4. One significant limitation is the lack of a dietary untreated control group

Introduction

Carbohydrate is the nutrient in our diet with by far the highest impact on plasma glucose levels. The total amount of carbohydrates consumed in a meal is the major predictor of the postprandial glucose response. Thus, monitoring dietary intake of carbohydrates is important to control postprandial glucose fluctuations, which may lead to clinical benefits such as a reduction in glucose variability, an improvement of glycated haemoglobin A1c (HbA1c), and a reduction in diabetes-related complications.

Clinical guidelines in medical nutrition therapy recommend that patients with type 1 diabetes (T1D) learn carbohydrate counting or similar experience-based methods to improve glycaemic control (1-4). Two levels of carbohydrate counting have been defined internationally with different learning objectives and increasing complexity; a basic and an advanced level (5, 6). Basic carbohydrate counting (BCC) includes understanding of the relationship between food, physical activity, and plasma glucose levels with special attention on consistency in the timing, type, amount and distribution of carbohydrate-containing foods consumed. Advanced carbohydrate counting (ACC) is targeting the patient who masters BCC, who is on intensive insulin therapy and is prepared to learn how to adjust insulin according to carbohydrate intake. In the clinical guidelines and studies, the term "carbohydrate counting" is often used synonymously with ACC, while the sole effect of BCC on glycaemic control is largely unknown. Systematic reviews and meta-analyses of randomized controlled trials (RCTs) have shown that ACC can reduce HbA1c by up to 7 mmol/mol in adults with poorly controlled T1D (7-9). Despite this, systematic educating and training is still not offered routinely for patients on multiple daily insulin injections (MDI) therapy in outpatient clinics in Denmark. This may be due to the lack of evidence as to which educational methods are the most effective for training patients in carbohydrate counting in terms of supporting patients in implementation and ongoing adherence to the use of carbohydrate counting as a tool for meal planning in their daily life for improving glycaemic control.

Ideally, patients with T1D treated on MDI therapy need to be able to manage the following steps of calculation when using carbohydrate counting: 1) Correct calculation of the total carbohydrate content in each meal according to portion sizes of each carbohydrate containing food item (equal to BCC) and 2) Correct calculation of insulin dose according to the amount of carbohydrates to be consumed using a carbohydrate-to-insulin ratio, an insulin sensitivity factor, and the current and target plasma glucose (equal to ACC). In other words, patients with diabetes need to have sufficient mathematical literacy skills, including numeracy skills, to be able to practice the above-mentioned steps several times each day. Recent studies suggest that lower literacy and numeracy skills are associated with poorer portion size estimation, understanding of food labels, diabetes-related self-management abilities, diabetes control and increased body mass index (BMI) (10-16). Other studies have found that patients with diabetes frequently assess their intake of carbohydrates inaccurately and this has been associated with a poorer HbA1c (17-19). Particularly mixed meals, high-calorie foods, and larger portion sizes resulted in inaccurate carbohydrate estimation. One study also found that underestimation of carbohydrate-rich meals was associated with higher daily plasma glucose variability in adults with T1D (20). Thus, assessment of numeracy skills is highly relevant to ensure that a nutritional education programs address patients with low literacy and numeracy. This may be done by numeracy-focused educational exercises and materials or hands-on learning.

Recent years technological innovations including applications (apps) for smartphones have been introduced to reduce the complexity of carbohydrate counting and possibly compensate for poor numeracy skills. So far, no technological devices can replace the patients' self-estimations of the carbohydrate content in most meals e.g. in mixed meals (addressing step 1). RCTs have demonstrated that ACC supported by the use of automated bolus calculator (ABC) software to assist insulin dose decision making (addressing step 2) compared to

unassisted ACC significantly improves HbA1c and treatment satisfaction in patients with T1D treated with MDI (21-23). However, a recent exploratory study found that lower numeracy skills were associated with smaller reductions in HbA1c after a 12-month education program in ACC with no benefit from the use of an ABC compared to manual calculations (24). These findings support the need for more intensified dietary education in BCC before learning ACC. Additionally, the concept of ACC may not be useful in all patients with T1D on MDI therapy because of potential patient barriers, lack of motivation to learn the method, and low levels of education, literacy or numeracy skills. Other barriers include lack of appropriate learning environments to promote behavioural change and availability of trained dietitians to facilitate the learning process (25). In a study of patients with diabetes perceived competence was predicted by the degree to which the patients experienced the health-care climate to be autonomy supportive, and perceived competence at carrying out the treatment in turn predicted HbA1c (26). Group-based approaches with practised-focused dietary education compared to individual dietary counselling has been practiced in some settings but are under-investigated (27). In line with this we are currently carrying out a RCT based on this protocol.

Aim

The aims are to examine the effectiveness of two different group-based dietitian-led practise-focused educational approaches for dietary self-management compared to the standard nutrition education on glycaemic control in patients with T1D. The BCC concept aims at improving carbohydrate counting accuracy and day-to-day consistency of carbohydrate intake (the BCC intervention) and the concept of ACC aim at improving prandial insulin dose accuracy using an automated bolus calculator (the ABC-ACC intervention).

Methods and analysis

Study design

The study is as a randomized controlled intervention trial with a parallel-group design (see figure 1).

For each participant the study duration is 48 months and includes up to seven visits at the study site (see figure 2). All participants will be instructed to maintain their habitual lifestyle in all other aspects than their diet, e.g. keeping the same level of physical activity during the study period. All participants will be instructed to follow their regular diabetes care in the hospital, which usually includes four yearly visits with a diabetologist (endocrinologist) and one yearly consultation with a diabetes nurse. Participants will be instructed not to receive any further dietary education during the study period. Close relatives can participate in the dietary education in all three study groups if the participant needs support to manage dietary changes.

The study flow is presented in figure 3. The study follows the guidelines of Standard Protocol Items for Randomized Trials (SPIRIT).

Setting

The study will be carried out in the outpatient clinic at Steno Diabetes Center Copenhagen (SDCC) in Gentofte, Denmark.

Recruitment and consent

As a temporary supplementary treatment initiative, SDCC offers courses in BCC and ABC-ACC for all patients with T1D treated in the capital region of Denmark. Participants for the current study will be recruited among patients signing up for these courses or patients directly referred to one of the courses or the study by

a health care professional (diabetologist, diabetes nurse or dietitian) from SDCC or from a Steno Partner hospital in the capital region. A course administrator at SDCC will contact all interested or referred patients by telephone and provide information about the study. In addition, potential study participants will be recruited through information on sdcc.dk and other electronic media or patient-related networks. If the patient is interested in the study, the patient will receive the written patient information by mail or e-mail. If interested in study participation, the study investigator/study personnel will schedule a personal meeting for oral patient information, offering the possibility of bringing a confidant. The patient will be given time to discuss any questions and will be informed that he/she has at least 24 hours to decide on participation in the study. If the patient decides to participate in the study, the patient and the study investigator/study personnel will sign the written informed consent, and the investigator/study personnel will perform a screening. If all inclusion criteria are fulfilled and none of the exclusion criteria are met, the patient will be included in the study and randomised to one of three groups. Patients who decline to participate or do not meet the inclusion criteria will continue their usual care in an outpatient diabetes clinic and will be offered to participate on a BCC or ACC course if they still wish to do so. Participants will be informed that participation is voluntary, and that they may withdraw their consent at any time.

Inclusion criteria

Patients with T1D between 18-75 years of age with a diabetes duration above 12 months and with an initial HbA1c of 53-97 mmol/mol on MDI therapy with a basal-bolus insulin regime are eligible for the study.

Exclusion criteria

Patients are excluded if they have other types of diabetes than T1D, are practicing carbohydrate counting as judged by the investigator, have a low daily intake of carbohydrates (defined as below 25 E% or 100 g/day), have participated in a BCC group program within the last two years, use an insulin pump or plan to have an insulin pump within the study period, use a fixed dose of rapid acting insulin therapy for meals, use split-mixed insulin therapy, use an open CGM or plan to have an open CGM within the study period, use an automated bolus calculator, have gastroparesis, have uncontrolled medical issues affecting the dietary intake as judged by the investigator or a medical expert. Women who are pregnant or breastfeeding or have plans of pregnancy within the study period are also excluded. Furthermore, patients who are either participating in other clinical studies or are unable to understand the informed consent and the study procedures will be excluded.

Randomization

Participants eligible for inclusion in the study will be randomly allocated in a 1:1:1 ratio to one of the three groups (BCC, ABC-ACC or control) using a computer-generated randomization in the software program *REDCap*. The randomization is done by stratifying participants based on sex and HbA1c at baseline. The randomization is done in blocks in to order to ensure an equal number of participants in each group.

Intervention groups

The BCC program consists of two sessions of three hours and a follow-up group session of two hours. The BCC program uses trained dietitians following a planned curriculum which include experience-based learning with problem-solving exercises, hands-on activities, short theoretical presentations, discussions of motivational aspects and coping strategies. The BCC program integrates peer modelling, skills development, goal setting, observational learning and social support into the program content and activities. The training includes identifying carbohydrates in food, reading carbohydrate tables, calculating the carbohydrate content

from food labels, tables and apps and use of a personalized carbohydrate plan with guiding suggestions for daily intake of carbohydrates at meals based on 4-days of personal dietary recording performed before the program including plasma glucose measurements and prandial insulin dosages taken. An app (*Diabetes og Kulhydrattælling*®. The Danish Diabetes Association, Pragma soft A/S, available in Google Play® and AppStore®) will be introduced to support estimation and calculation of carbohydrates and assist in simple insulin dose determination if participants choose to consume more carbohydrates at a meal than suggested in their personal carbohydrate plan.

The ABC-ACC program consists of a 4-hour group session and two individual follow-up sessions (two 45-minutes sessions). The program uses trained dietitians with supervision by a medical doctor and follows a planned curriculum. The ABC-ACC intervention is a group-based educational program based on the well-described BolusCal concept (28). The program includes fast training in BCC, ACC and bolus calculation using an automated bolus calculator (*mySugr Pro*®. Roche, available in Google Play® and AppStore®) taking insulin onboard, insulin sensitivity factor and differentiated carbohydrate-to-insulin ratios during the day into account. The carbohydrate-to-insulin ratios are based on 7-days of personal dietary recording including plasma glucose measurements and prandial insulin dosages taken. The ABC-ACC program contains theoretical and practical training. The teaching is based on theory and examples from everyday life with T1D and the educators help the participants with their specific diabetes-related problems and try to find appropriate practical solutions together with the participant.

Control group

Participants randomized to the control group receive current standard outpatient nutrition education in T1D. This includes individual guidance by a trained dietitian, with one initial 60 minutes dietary counselling session and two individual 30 minutes follow-up session. The individual guidance is based on the overall treatment goal and the defined personal dietary goals for behavioural change according to patient preferences. Dietary guidance includes topics such as carbohydrate sources (e.g. practicing glycaemic index and dietary fibre intake) and amounts of carbohydrates or more general dietary recommendations according to patient needs.

Data collection

All study data will be collected at the three visits with clinical examination (baseline, after 6 and 12 months). Data will be obtained from a self-reported patient questionnaire, electronic medical records and the physical examinations conducted by the study investigator or study personnel. All questionnaire data will be collected electronically using the software system *REDCap* according to local standards for research projects in the capital region of Denmark. In addition, all sources will be registered in this database. Data generated and stored for specific equipment (e.g. Dual-energy-X-ray absorptiometry (DXA) data stored in the DXA scanner software database), electronic medical data (blood and urine measurements, glucose- and lipid-lowering medicine), data from iPro®2 CGM using software from Medtronic (Northridge, CA, US) to download CGM measurements, dietary data on total energy and nutrients based calculations from the software system *Vitakost* will be added to the database in *REDCap* on an ongoing basis and at the end of study.

The primary outcome is the difference in mean HbA1c or MAGE from baseline to end of the intervention (week 24) between and within each of the three study groups (BCC, ABC-ACC and control).
A schematic overview of outcomes measurements is presented in table 1.

Table 1. Schematic overview of outcomes measured

Week no from start of intervention	**-4 to -1**	**12**	**24**	**48**
HbA1c	X	X	X	X
Plasma lipids	X		X	X
Body weight	X		X	X
Height	X			
Waist and hip circumference	X		X	X
Blood pressure	X		X	X
Blood samples, fasting	X		X	X
Urine samples for 4 days	X		X	
Glucose variability (CGM) including PG diary for 6 days	X		X	
Body composition (DXA)	X		X	
Prescribed lipid- and glucose lowering medication	X		X	X
F: Dietary registration for 4 days	X		X	
Q: Diet-related quality of life	X		X	X
Q: Perceived Competencies in Diabetes	X		X	X
Q: Health-Care Climate	X		X	
Q: Carbohydrate estimation accuracy	X		X	X
Q: Mathematical literacy	X		X	X
Q: Demographic data	X			
Q: Physical activity	X		X	X

Abbreviations CGM=continuous glucose monitoring d=day; DXA=Dual-energy-X-ray absorptiometry; F=forms; PG=plasma glucose; Q=Questionnaire.

Secondary outcomes are listed below:

Clinical parameters: Body weight, body composition (measured by DXA), waist and hip circumference blood pressure, type and dose of prescribed glucose- and lipid lowering medication, other parameters of plasma glucose variability including time in range (3.9-10.0 mmol/l), % time spent in hypoglycaemia (<3.9 mmol/l), % time spent in hyperglycaemia (e.g. >10.0 mmol/l) and standard deviation of mean plasma glucose assessed from CGM measurements.

Blood and urine samples: HbA1c (after 12 and 48 weeks), low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, very low-density lipoprotein cholesterol, total cholesterol, free fatty acids and triglycerides, alanine aminotransferase (ALAT), urine albumin/creatinine ratio and urinary biomarkers based on three daily midstream urine spots collected for four days.

Patient-reported outcomes: Diet-related quality of life, perceived competencies in diabetes, health-care climate, carbohydrate estimation accuracy, mathematical literacy skills, physical activity and demographic questions. The six questionnaires used are:

Diabetes diet-related quality of life questionnaire (DDRQOL): The DDRQOL is a scale which has been validated in patients with diabetes (29). The scale is designed to determine the quantitative and qualitative satisfaction with diet and the degree of restriction of daily life and social life functions due to the dietary changes. A forward translation and cultural adaption of the DDRQOL was done by a Japanese-Danish interpreter with a background as a clinical dietitian and an expert panel of six clinical dietitians working with diabetes. This was followed by a pilot testing by 10 patients.

Perceived Competencies in Diabetes Scale (PCS): The PCS includes four items that reflect participants' feelings of competence about engaging in a healthier behaviour and participating in a nutritional education

program. Forward and backward linguistic translation from English to Danish has been done according to standard procedures in 2001 under the guidance of Professor Vibeke Zoffmann.

Health-Care Climate Questionnaire (HCCQ): The HCCQ chosen in this study is a 5-item short form of the original 15-item measure that assesses patients' perceptions of the degree to which dieticians are autonomy supportive versus controlling in providing dietary treatment.

Carbohydrate photographic questionnaire (CPQ): The CPQ is an electronic questionnaire assessing diabetes patients' abilities to estimate portion sizes of 11 commonly eaten high-carbohydrate foods correctly. The CPQ has been developed and validated against real food in 87 patients with T1D. A manuscript of these study results has been submitted (Ewers et al, unpublished).

Mathematical literacy questionnaire: A 10-item test with modified questions from the nutrition domain of the *Diabetes Numeracy Test* (DNT) (30) was designed and feasibility tested to investigate mathematical literacy including numeracy skills (addition, subtraction, division and multiplication) which are essential for understanding numbers and applying mathematical skills in daily life e.g. for calculating carbohydrates.

International Physical Activity Questionnaire Short Form (IPAQ SF): The Danish version of the IPAQ SF (31) will be used to assess changes in level of physical activity during the study period.

Self-reported demographic questions include level of education, occupation, marital status, household composition and yearly income.

Dietary data: Four days of weighed dietary food records collected at baseline and six months after baseline. Dietary records will be calculated using the software system *Vitakost* (Vitakost Aps, Kolding) where nutrient and energy calculations are based on the Danish national food database. The dietary food records are used to estimate total energy intake (kJ/d), intake of carbohydrates, protein and fat (g/day and g/meal), added sugar (g/d) and total dietary fibre intake (g/d).

Baseline data (from the electronic medical record): type of diabetes, gender, age, smoking status, medical conditions, total number of visits at a diabetologist and diabetes nurse and dietician during the study period.

Data analysis plan

The trial in ongoing. The patient recruitment started in October 2018 and is expected to be completed by October 2021.

Sample size calculation

A power calculation was conducted based on the primary outcome measures HbA1c and MAGE. Allowing for an estimated drop-out rate of 20% and subgroup analyses the sample size was planned to include a total of 231 patients in the study (77 in each arm). This was based on a sample size calculation which suggested that including 64 participants in each of the study groups would give 80% power to detect a clinically meaningful difference in change in HbA1c of 3.5 mmol/mol between the BCC group versus the control group or the ABC-ACC group versus the control group with a 5% significance level using a two-sided test and an estimated standard deviation (SD) of 7 mmol/mol. This SD has previously been used for sample size calculations in ACC trials (21) and was similar to what was found in an evaluation of previous conducted BCC courses at SDCC on mean changes and SD of HbA1c after 6 months among completers with T1D (n=185). MAGE has only been used as an outcome measure of glucose variability in a few randomized controlled dietary intervention

studies of patients with diabetes (32, 33) showing differences in changes in MAGE up to 4.8 mmol/l (SD: 1.0) after a 12-week carbohydrate counting intervention (32), but is regularly used in other clinical studies evaluating glucose variability . By including 77 participants in each study group we will have a power of 80% (alpha level of 0.05) in a two-sided test to detect a clinically meaningful difference in the change in MAGE during the intervention period (week 24) of ≥0.35 mmol/l (SD 0.7 mmol/l) between the study groups.

Statistical methods

Analysis and reporting of the study results will follow the CONSORT (Consolidated Standards of Reporting Trials) guidelines for reporting parallel group randomised trials (34). Results will be presented as means (SD) for normally distributed variables and as medians (inter-quartile range) for non-normally distributed variables. Parametric tests (general linear models) will be used to test differences in outcomes from baseline to follow-up. If model assumptions cannot be met even after logarithmic transformation, non-parametric tests will be used. Plots of residuals versus predicted values will be used to judge normality.

The baseline demographics as well as clinical and diabetes-related characteristics of the intervention and the control groups will be presented and compared. The average changes between baseline and week 24 and 48 in primary and secondary outcomes will be calculated for each of the three groups. Intention-to-treat (ITT) analysis will be performed as the primary analysis on all primary and secondary outcomes after the last participant has ended participation. Missing values will be handled with a last observation carried forward approach for ITT analysis. Per-protocol (PP) analysis will only be performed in case of sensitivity testing. Metabolic patterns will be tested with multivariate statistics. Adjustment for relevant confounders will be performed. Heterogeneity in responsiveness to the interventions will be tested by dividing each intervention group into smaller groups based on data distribution (medians) or clinically meaningful cut-points. Two-sided tests will be used. *P* values of <0.05 are considered significant. The statistical programs SPSS and SAS will be used for data analysis.

Ethics and dissemination

The study will be conducted in accordance with the ethical principles in the Declaration of Helsinki and to the regulations for Good Clinical Practice (GCP) to the extent that this is relevant for non-medical studies. The study has been approved by the Ethics Committee of the Capital Region, Copenhagen (#H-18014897), has been approved for data storage by the Danish Data Protection Agency (journal no VD-2018-124, I-suite no 6367) and has been registered at ClinicalTrials.gov (NCT03623113).

All health-related matters and sensitive personal data will be handled in accordance with the Danish "Act on Processing of Personal Data". All health-related matters and sensitive personal data (blood test results etc.) will be depersonalized. All participants will be given a study number referring to their personal information, which will be stored securely and separately. Data will be stored in coded form for 10 years after last participant has attended the last visit, after which the data will be fully anonymised.

Data is owned by the investigators who are responsible for publishing the results. Positive and negative as well as inconclusive study results will be published by the investigators in international peer-reviewed journals, and all co-authors must comply with the Vancouver rules. BE will be responsible for writing the first draft of the manuscript based on the main study results as a first author under guidance by TV and JMB. The study results will be presented at relevant national and international scientific conferences and meetings and will be published in international peer-reviewed scientific journals.

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Patient and public involvement: Patients were involved in developing the educational content of the program in basic carbohydrate counting. Patients were not involved in setting the research questions or the outcome measures, nor were they involved in developing the study design. Information may be disseminated to the general public via any media coverage of study findings.

Authors' contributions: BE conceived the original idea for this trial, planned the study design, performed the sample size calculations and wrote the first draft of the protocol manuscript. TV and JMB provided valuable input regarding trial design, planning and analytical considerations, and edited the first draft of the protocol manuscript. HUA has contributed intellectually to the protocol. All authors approved the final version of the clinical trial protocol. BE is the principle investigator and is responsible for correspondence with all authorities regarding the study and is responsible for the data collection (recruitment, screening and clinical study examinations), overall monitoring the trial and for conducting the statistical analyses. TV, JMB and HUA are supervisors and coinvestigators of this trial. Should any safety concerns arise during the conduct of the study these will be brought to the attention of HUA, TV and JMB by BE and will carefully reviewed.

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Competing interests: None of the authors have financial relationships with organizations that might have an interest in the submitted work, or other relationships or activities that could appear to have influenced the submitted work.

Figure titles and legends (captions)

Figure 1. Study design

Figure 2. Schematic diagram of the intervention

BCC, basic carbohydrate counting; ABC-ACC, advanced carbohydrate counting with an automated bolus calculator; BP, blood pressure; BW, body weight; CGM, Continuous Glucose Monitoring; DXA, dual-energy-X-ray absorptiometry; V, visit; WHC, waist-hip circumference.

Figure 3. Study flow diagram. The planned flow of participants through the stages of the study

BCC, basic carbohydrate counting; ABC-ACC, advanced carbohydrate counting with an automated bolus calculator.

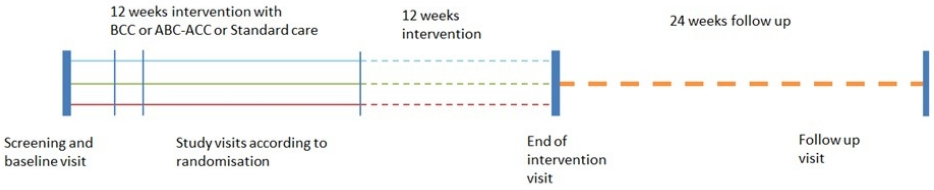

Figure 1. Study design

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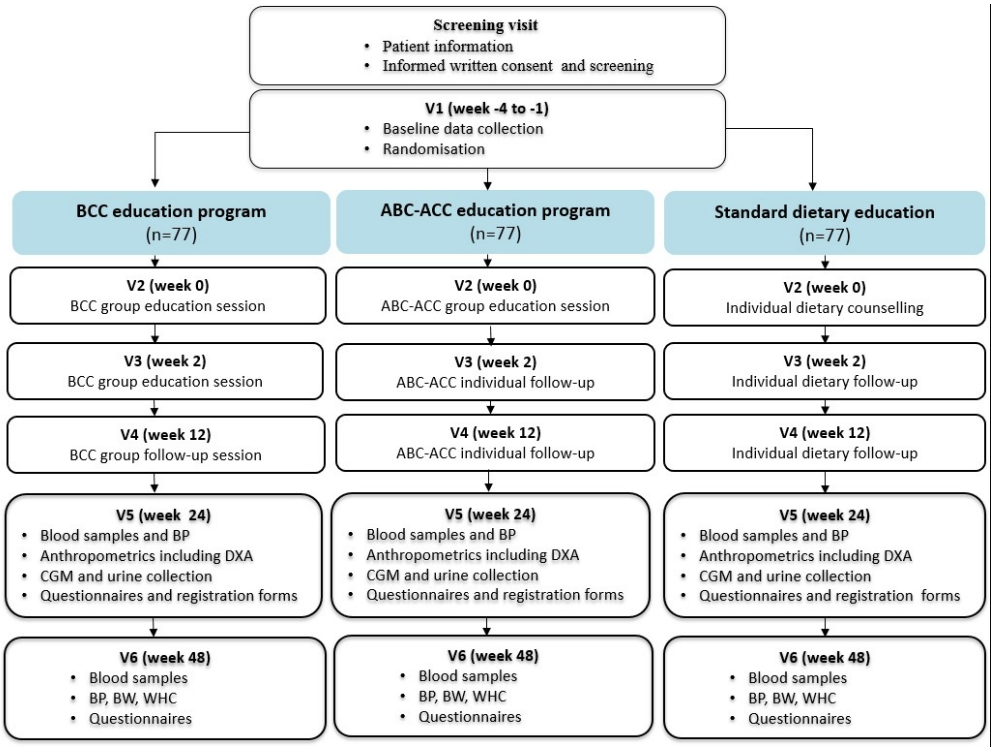

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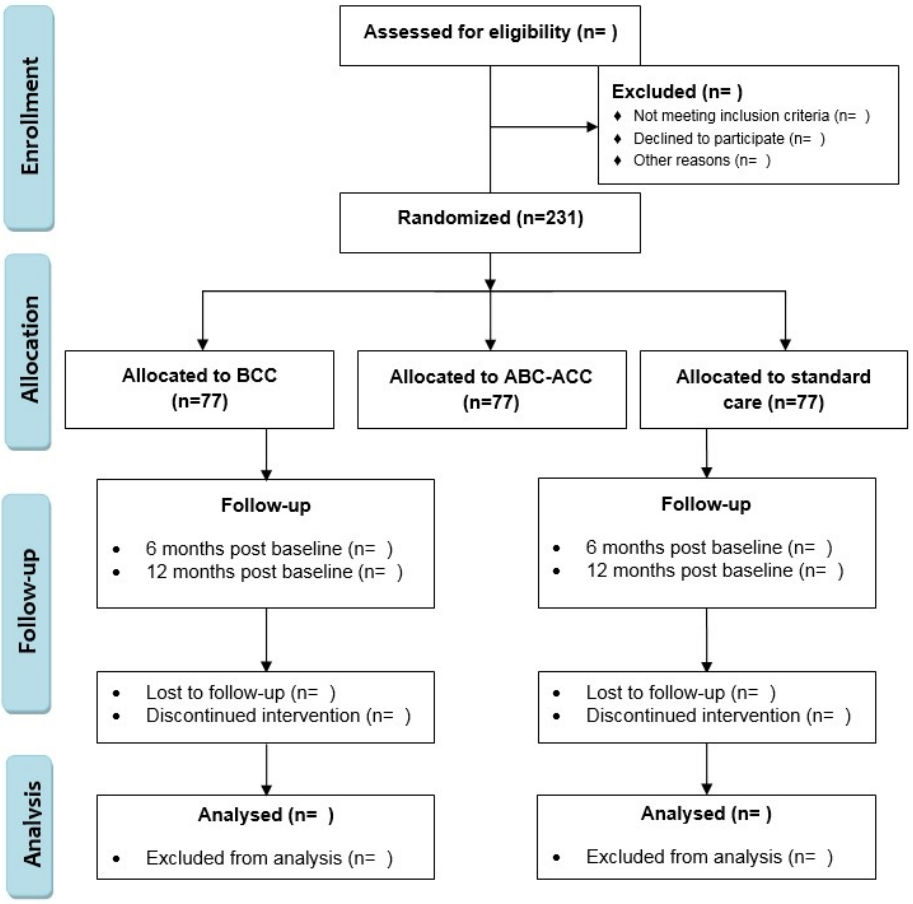

Figure 3. Study flow diagram. The planned flow of participants through the stages of the study

BCC, basic carbohydrate counting; ABC-ACC, advanced carbohydrate counting with an automated bolus calculator.

166x165mm (120 x 120 DPI)

BMJ Open

The Dietary Education Trial in Carbohydrate Counting (DIET-CARB Study): study protocol for a randomized, parallel, open-label, intervention study comparing different approaches to dietary self-management in patients with type 1 diabetes

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Keywords:	Randomized controlled trial, Type 1 diabetes, Carbohydrate counting, Basic carbohydrate counting, Advanced carbohydrate counting, Nutritional education

The Dietary Education Trial in Carbohydrate Counting (DIET-CARB Study): study protocol for a randomized, parallel, open-label, intervention study comparing different approaches to dietary self-management in patients with type 1 diabetes

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Abstract

Introduction: Clinical guidelines recommend that patients with type 1 diabetes (T1D) learn carbohydrate counting or similar methods to improve glycaemic control. Although, systematic educating in carbohydrate counting is still not offered as standard-of-care for all patients on multiple daily injections (MDI) therapy in outpatient diabetes clinics in Denmark. This may be due to the lack of evidence as to which educational methods are the most effective for training patients in carbohydrate counting. The objective of this study is to compare the effect of two different educational programs in carbohydrate counting with the usual dietary care on glycaemic control in patients with T1D.

Methods and analysis: The study is designed as a randomized, controlled trial with a parallel-group design. The total study duration is 12 months with data collection at baseline, 6 and 12 months. We plan to include 231 Danish adult patients with T1D. Participants will be randomized to one of three dietician-led interventions; 1) A program in basic carbohydrate counting, 2) A program in advanced carbohydrate counting including an automated bolus calculator or 3) Usual dietary care. The primary outcome is changes in glycated haemoglobin A1c (HbA1c) or mean amplitude of glycaemic excursions (MAGE) from baseline to end of the intervention period (week 24) between and within each of the three study groups. Other outcome measures include changes in other parameters of plasma glucose variability (e.g. time in range), body weight and composition, lipid profile, blood pressure, mathematical literacy skills, carbohydrate estimation accuracy, dietary intake, diet-related quality of life, perceived competencies in dietary management of diabetes and perceptions of an autonomy supportive dietician-led climate, physical activity and urinary biomarkers.

Ethics and dissemination: The protocol has been approved by the Ethics Committee of the Capital Region, Copenhagen, Denmark. Study findings will be disseminated widely through peer-reviewed publications and conference presentations.

Registration: The trial protocol is registered on ClinicalTrials.gov NCT03623113.

Strengths and limitations of this study

1. The study has a long-term follow-up and will provide knowledge on the effects of different levels of carbohydrate counting

2. The study applies well-documented measures of glycaemic control as effect-parameters

3. The results obtained have applicability beyond Denmark and has the potential to be included in the recommendations in future guidelines

4. A limitation is the lack of a dietary "untreated" control group, however; it would be unethical not to offer standard dietary care for patients with type 1 diabetes

5. The difference in the number of hours and type of dietary education and support between the groups may also influence the participants' learning

Introduction

Carbohydrate is the nutrient in our diet with by far the highest impact on plasma glucose levels. The total amount of carbohydrates consumed in a meal is the major predictor of the postprandial glucose response. Thus, monitoring dietary intake of carbohydrates is important to control postprandial glucose fluctuations, which may lead to clinical benefits such as a reduction in glucose variability, an improvement of glycated haemoglobin A1c (HbA1c), and a reduction in diabetes-related complications.

Clinical guidelines in medical nutrition therapy recommend that patients with type 1 diabetes (T1D) learn carbohydrate counting or similar experience-based methods to improve glycaemic control (1-4). Two levels of carbohydrate counting have been defined internationally with different learning objectives and increasing complexity; a basic and an advanced level (5, 6). Basic carbohydrate counting (BCC) includes understanding of the relationship between food, physical activity, and plasma glucose levels with special attention on consistency in the timing, type, amount and distribution of carbohydrate-containing foods consumed. Advanced carbohydrate counting (ACC) is targeting the patient who masters BCC, who is on intensive insulin therapy and is prepared to learn how to adjust insulin according to carbohydrate intake. In the clinical guidelines and studies, the term "carbohydrate counting" is often used synonymously with ACC, while the sole effect of BCC on glycaemic control is largely unknown. Systematic reviews and meta-analyses of randomized controlled trials (RCTs) have shown that ACC can reduce HbA1c by up to 7 mmol/mol in adults with poorly controlled T1D (7-9). Despite this, systematic educating and training is still not offered routinely for patients on multiple daily insulin injections (MDI) therapy in outpatient clinics in Denmark. This may be due to the lack of evidence as to which educational methods are the most effective for training patients in carbohydrate counting in terms of supporting patients in implementation and ongoing adherence to the use of carbohydrate counting as a tool for meal planning in their daily life for improving glycaemic control.

Ideally, patients with T1D treated on MDI therapy need to be able to manage the following steps of calculation when using carbohydrate counting: 1) Correct calculation of the total carbohydrate content in each meal according to portion sizes of each carbohydrate containing food item (equal to BCC) and 2) Correct calculation of insulin dose according to the amount of carbohydrates to be consumed using a carbohydrate-to-insulin ratio, an insulin sensitivity factor, and the current and target plasma glucose (equal to ACC). In other words, patients with diabetes need to have sufficient mathematical literacy skills, including numeracy skills, to be able to practice the above-mentioned steps several times each day. Recent studies suggest that lower literacy and numeracy skills are associated with poorer portion size estimation, understanding of food labels, diabetes-related self-management abilities, diabetes control and increased body mass index (BMI) (10-16). Other studies have found that patients with diabetes frequently assess their intake of carbohydrates inaccurately and this has been associated with a poorer HbA1c (17-19). Particularly mixed meals, high-calorie foods, and larger portion sizes resulted in inaccurate carbohydrate estimation. One study also found that underestimation of carbohydrate-rich meals was associated with higher daily plasma glucose variability in adults with T1D (20). Thus, assessment of numeracy skills is highly relevant to ensure that a nutritional education programs address patients with low literacy and numeracy. This may be done by numeracy-focused educational exercises and materials or hands-on learning.

Recent years technological innovations including applications (apps) for smartphones have been introduced to reduce the complexity of carbohydrate counting and possibly compensate for poor numeracy skills. So far, no technological devices can replace the patients' self-estimations of the carbohydrate content in most meals e.g. in mixed meals (addressing step 1). RCTs have demonstrated that ACC supported by the use of automated bolus calculator (ABC) software to assist insulin dose decision making (addressing step 2) compared to

unassisted ACC significantly improves HbA1c and treatment satisfaction in patients with T1D treated with MDI (21-23). However, a recent exploratory study found that lower numeracy skills were associated with smaller reductions in HbA1c after a 12-month education program in ACC with no benefit from the use of an ABC compared to manual calculations (24). These findings support the need for more intensified dietary education in BCC before learning ACC. Additionally, the concept of ACC may not be useful in all patients with T1D on MDI therapy because of potential patient barriers, lack of motivation to learn the method, and low levels of education, literacy or numeracy skills. Other barriers include lack of appropriate learning environments to promote behavioural change and availability of trained dietitians to facilitate the learning process (25). In a study of patients with diabetes perceived competence was predicted by the degree to which the patients experienced the health-care climate to be autonomy supportive, and perceived competence at carrying out the treatment in turn predicted HbA1c (26). Group-based approaches with practised-focused dietary education compared to individual dietary counselling have been practiced in some settings but are under-investigated (27). In line with this we are currently carrying out a RCT based on this protocol.

Aim

The aims are to examine the effectiveness of two different group-based dietitian-led practise-focused educational approaches for dietary self-management compared to the standard nutrition education on glycaemic control in patients with T1D. The BCC concept aims at improving carbohydrate counting accuracy and day-to-day consistency of carbohydrate intake (the BCC intervention) and the concept of ACC aim at improving prandial insulin dose accuracy using an automated bolus calculator (the ABC-ACC intervention).

Methods and analysis

Study design

The study is as a randomized controlled intervention trial with a parallel-group design (see figure 1).

For each participant the study duration is 48 months and includes up to seven visits at the study site (see figure 2). All participants will be instructed to maintain their habitual lifestyle in all other aspects than their diet, e.g. keeping the same level of physical activity during the study period. All participants will be instructed to follow their regular diabetes care in the hospital, which usually includes four yearly visits with a diabetologist (endocrinologist) and one yearly consultation with a diabetes nurse. Participants will be instructed not to receive any further dietary education during the study period. Close relatives can participate in the dietary education in all three study groups if the participant needs support to manage dietary changes.

The study flow is presented in figure 3. The study follows the guidelines of Standard Protocol Items for Randomized Trials (SPIRIT).

Setting

The study will be carried out in the outpatient clinic at Steno Diabetes Center Copenhagen (SDCC) in Gentofte, Denmark.

Recruitment and consent

As a temporary supplementary treatment initiative, SDCC offers courses in BCC and ABC-ACC for all patients with T1D treated in the capital region of Denmark. Participants for the current study will be recruited among patients signing up for these courses or patients directly referred to one of the courses or the study by

a health care professional (diabetologist, diabetes nurse or dietitian) from SDCC or from a Steno Partner hospital in the capital region. A course administrator at SDCC will contact all interested or referred patients by telephone and provide information about the study. In addition, potential study participants will be recruited through information on sdcc.dk and other electronic media or patient-related networks. If the patient is interested in the study, the patient will receive the written patient information by mail or e-mail. If interested in study participation, the study investigator/study personnel will schedule a personal meeting for oral patient information, offering the possibility of bringing a confidant. The patient will be given time to discuss any questions and will be informed that he/she has at least 24 hours to decide on participation in the study. If the patient decides to participate in the study, the patient and the study investigator/study personnel will sign the written informed consent, and the investigator/study personnel will perform a screening. If all inclusion criteria are fulfilled and none of the exclusion criteria are met, the patient will be included in the study and randomised to one of three groups. Patients who decline to participate or do not meet the inclusion criteria will continue their usual care in an outpatient diabetes clinic and will be offered to participate on a BCC or ACC course if they still wish to do so. Participants will be informed that participation is voluntary, and that they may withdraw their consent at any time.

Inclusion criteria

Patients with T1D between 18-75 years of age with a diabetes duration above 12 months and with an initial HbA1c of 53-97 mmol/mol on MDI therapy with a basal-bolus insulin regime are eligible for the study.

Exclusion criteria

Patients are excluded if they have other types of diabetes than T1D, are practicing carbohydrate counting as judged by the investigator, have a low daily intake of carbohydrates (defined as below 25 E% or 100 g/day), have participated in a BCC group program within the last two years, use an insulin pump or plan to have an insulin pump within the study period, use split-mixed insulin therapy, use an open CGM or plan to have an open CGM within the study period, use an automated bolus calculator, have gastroparesis, have uncontrolled medical issues affecting the dietary intake as judged by the investigator or a medical expert. Women who are pregnant or breastfeeding or have plans of pregnancy within the study period are also excluded. Furthermore, patients who are either participating in other clinical studies or are unable to understand the informed consent and the study procedures will be excluded.

Randomization

Participants eligible for inclusion in the study will be randomly allocated in a 1:1:1 ratio to one of the three groups (BCC, ABC-ACC or control) using a computer-generated randomization in the software program *REDCap*. The randomization is done by stratifying participants based on sex and HbA1c at baseline. The randomization is done in blocks in to order to ensure an equal number of participants in each group.

Intervention groups

The BCC program consists of two sessions of three hours and a follow-up group session of two hours. The BCC program uses trained dietitians following a planned curriculum which include experience-based learning with problem-solving exercises, hands-on activities, short theoretical presentations, discussions of motivational aspects and coping strategies. The BCC program integrates peer modelling, skills development, goal setting, observational learning and social support into the program content and activities. The training includes identifying carbohydrates in food, reading carbohydrate tables, calculating the carbohydrate content

from food labels, tables and apps and use of a personalized carbohydrate plan with guiding suggestions for daily intake of carbohydrates at meals based on 4-days of personal dietary recording performed before the program including plasma glucose measurements and prandial insulin dosages taken. An app (*Diabetes og Kulhydrattælling*®. The Danish Diabetes Association, Pragma soft A/S, available in Google Play® and AppStore®) will be introduced to support estimation and calculation of carbohydrates and assist in simple insulin dose determination if participants choose to consume more carbohydrates at a meal than suggested in their personal carbohydrate plan.

The ABC-ACC program consists of a 4-hour group session and two individual follow-up sessions (two 45-minutes sessions). The program uses trained dietitians with supervision by a medical doctor and follows a planned curriculum. The ABC-ACC intervention is a group-based educational program based on the well-described BolusCal concept (28). The program includes fast training in BCC, ACC and bolus calculation using an automated bolus calculator (*mySugr Pro*®. Roche, available in Google Play® and AppStore®) taking insulin onboard, insulin sensitivity factor and differentiated carbohydrate-to-insulin ratios during the day into account. The carbohydrate-to-insulin ratios are based on 7-days of personal dietary recording including plasma glucose measurements and prandial insulin dosages taken. The ABC-ACC program contains theoretical and practical training. The teaching is based on theory and examples from everyday life with T1D and the educators help the participants with their specific diabetes-related problems and try to find appropriate practical solutions together with the participant.

Control group

Participants randomized to the control group receive current standard outpatient nutrition education in T1D. This includes individual guidance by a trained dietitian, with one initial 60 minutes dietary counselling session and two individual 30 minutes follow-up session. The individual guidance is based on the overall treatment goal and the defined personal dietary goals for behavioural change according to patient preferences. Dietary guidance includes topics such as carbohydrate sources (e.g. practicing glycaemic index and dietary fibre intake) and amounts of carbohydrates or more general dietary recommendations according to patient needs.

Data collection

All study data will be collected at the three visits with clinical examination (baseline, after 6 and 12 months). Data will be obtained from a self-reported patient questionnaire, electronic medical records and the physical examinations conducted by the study investigator or study personnel. All questionnaire data will be collected electronically using the software system *REDCap* according to local standards for research projects in the capital region of Denmark. In addition, all sources will be registered in this database. Data generated and stored for specific equipment (e.g. Dual-energy-X-ray absorptiometry (DXA) data stored in the DXA scanner software database), electronic medical data (blood and urine measurements, glucose- and lipid-lowering medicine), data from iPro®2 CGM using software from Medtronic (Northridge, CA, US) to download CGM measurements, dietary data on total energy and nutrients based calculations from the software system *Vitakost* will be added to the database in *REDCap* on an ongoing basis and at the end of study.

The primary outcome is the difference in mean HbA1c or MAGE from baseline to end of the intervention (week 24) between and within each of the three study groups (BCC, ABC-ACC and control).
A schematic overview of outcomes measurements is presented in table 1.

Table 1. Schematic overview of outcomes measured

Week no from start of intervention	-4 to -1	12	24	48
HbA1c	X	X	X	X
Plasma lipids	X		X	X
Body weight	X		X	X
Height	X			
Waist and hip circumference	X		X	X
Blood pressure	X		X	X
Blood samples, fasting	X		X	X
Urine samples for 4 days*	X		X	
Glucose variability (CGM) including PG diary for 6 days*	X		X	
Body composition (DXA)	X		X	
Prescribed lipid- and glucose lowering medication	X		X	X
F: Dietary registration for 4 days*	X		X	
Q: Diet-related quality of life	X		X	X
Q: Perceived Competencies in Diabetes	X		X	X
Q: Health-Care Climate	X		X	
Q: Carbohydrate estimation accuracy	X		X	X
Q: Mathematical literacy	X		X	X
Q: Demographic data	X			
Q: Physical activity	X		X	X

Abbreviations CGM=continuous glucose monitoring d=day; DXA=Dual-energy-X-ray absorptiometry; F=forms; PG=plasma glucose; Q=Questionnaire.

*Measured in the days following the study visits.

Secondary outcomes are listed below:

Clinical parameters: Body weight, body composition (measured by DXA), waist and hip circumference blood pressure, type and dose of prescribed glucose- and lipid lowering medication, other parameters of plasma glucose variability including time in range (3.9-10.0 mmol/l), % time spent in hypoglycaemia (<3.9 mmol/l), % time spent in hyperglycaemia (e.g. >10.0 mmol/l) and standard deviation of mean plasma glucose assessed from CGM measurements.

Blood and urine samples: HbA1c (after 12 and 48 weeks), low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, very low-density lipoprotein cholesterol, total cholesterol, free fatty acids and triglycerides, alanine aminotransferase (ALAT), urine albumin/creatinine ratio and urinary biomarkers based on three daily midstream urine spots collected for four days.

Patient-reported outcomes: Diet-related quality of life, perceived competencies in diabetes, health-care climate, carbohydrate estimation accuracy, mathematical literacy skills, physical activity and demographic questions. The six questionnaires used are:

Diabetes diet-related quality of life questionnaire (DDRQOL): The DDRQOL is a 31-item scale which has been validated in patients with diabetes (29). The scale is designed to determine the quantitative and qualitative satisfaction with diet and the degree of restriction of daily life and social life functions due to the dietary changes. A forward translation and cultural adaption of the DDRQOL was done by a Japanese-Danish interpreter with a background as a clinical dietitian and an expert panel of six clinical dietitians working with diabetes. This was followed by a pilot testing by 10 patients.

Perceived Competencies in Diabetes Scale (PCS): The PCS includes four items that reflect participants' feelings of competence about engaging in a healthier behaviour and participating in a nutritional education

program. Forward and backward linguistic translation from English to Danish has been done according to standard procedures in 2001 under the guidance of Professor Vibeke Zoffmann.

Health-Care Climate Questionnaire (HCCQ): The HCCQ chosen in this study is a 5-item short form of the originally validated 15-item measure that assesses patients' perceptions of the degree to which dieticians are autonomy supportive versus controlling in providing dietary treatment.

Carbohydrate photographic questionnaire (CPQ): The CPQ is an electronic questionnaire assessing diabetes patients' abilities to estimate portion sizes of 11 commonly eaten high-carbohydrate foods correctly. The CPQ has been developed and validated against real food in 87 patients with T1D. A manuscript of these study results has been submitted (Ewers et al, unpublished).

Mathematical literacy questionnaire: A 10-item test with modified questions from the nutrition domain of the *Diabetes Numeracy Test* (DNT) (30) was designed and feasibility tested to investigate mathematical literacy including numeracy skills (addition, subtraction, division and multiplication) which are essential for understanding numbers and applying mathematical skills in daily life e.g. for calculating carbohydrates.

International Physical Activity Questionnaire Short Form (IPAQ SF): The Danish version of the IPAQ SF (31) will be used to assess changes in level of physical activity during the study period.

Self-reported demographic questions include level of education, occupation, marital status, household composition and yearly income.

Dietary data: Four days of weighed dietary food records collected at baseline and six months after baseline. Dietary records will be calculated using the software system *Vitakost* (Vitakost Aps, Kolding) where nutrient and energy calculations are based on the Danish national food database. The dietary food records are used to estimate total energy intake (kJ/d), intake of carbohydrates, protein and fat (g/day and g/meal), added sugar (g/d) and total dietary fibre intake (g/d).

Baseline data (from the electronic medical record): type of diabetes, gender, age, smoking status, medical conditions, total number of visits at a diabetologist and diabetes nurse and dietician during the study period.

Data analysis plan

The trial in ongoing. The patient recruitment started in October 2018 and is expected to be completed by October 2021.

Sample size calculation

A power calculation was conducted based on the primary outcome measures HbA1c and MAGE. Allowing for an estimated drop-out rate of 20% and subgroup analyses the sample size was planned to include a total of 231 patients in the study (77 in each arm). This was based on a sample size calculation which suggested that including 64 participants in each of the study groups would give 80% power to detect a clinically meaningful difference in change in HbA1c of 3.5 mmol/mol between the BCC group versus the control group or the ABC-ACC group versus the control group with a 5% significance level using a two-sided test and an estimated standard deviation (SD) of 7 mmol/mol. This SD has previously been used for sample size calculations in ACC trials (21) and was similar to what was found in an evaluation of previous conducted BCC courses at SDCC on mean changes and SD of HbA1c after 6 months among completers with T1D (n=185). MAGE has only been used as an outcome measure of glucose variability in a few randomized controlled dietary intervention

studies of patients with diabetes (32, 33) showing differences in changes in MAGE up to 4.8 mmol/l (SD: 1.0) after a 12-week carbohydrate counting intervention (32), but is regularly used in other clinical studies evaluating glucose variability . By including 77 participants in each study group we will have a power of 80% (alpha level of 0.05) in a two-sided test to detect a clinically meaningful difference in the change in MAGE during the intervention period (week 24) of ≥0.35 mmol/l (SD 0.7 mmol/l) between the study groups.

Statistical methods

Analysis and reporting of the study results will follow the CONSORT (Consolidated Standards of Reporting Trials) guidelines for reporting parallel group randomised trials (34). Results will be presented as means (SD) for normally distributed variables and as medians (inter-quartile range) for non-normally distributed variables. One-way ANOVA will be used to compare baseline data between the three study groups for normal data and Kruskal-Wallis H test for non-normal data. Paired samples t-test will be used for within group comparison for normal data and Wilcoxon signed rank test for non-normal data. Mixed-effect models will be used to test differences in outcomes from baseline to follow-up to take repeated measurements into account. If model assumptions cannot be met even after logarithmic transformation, non-parametric tests will be used. Examinations of the relevant diagnostic plots, including QQ-plots, will be used to evaluate normality of the residuals.

The baseline demographics as well as clinical and diabetes-related characteristics of the intervention and the control groups will be presented and compared. The average changes between baseline and week 24 and 48 in primary and secondary outcomes will be calculated for each of the three groups. Intention-to-treat (ITT) analysis will be performed as the primary analysis on all primary and secondary outcomes after the last participant has ended participation. Missing values will be handled with a last observation carried forward approach for ITT analysis with the use of the multiple imputation approach in a sensitivity analysis. Per-protocol (PP) analysis will only be performed in case of sensitivity testing. Metabolic patterns will be tested with multivariate statistics. Adjustment for relevant confounders will be performed including adjustment for the stratified variables. Heterogeneity in responsiveness to the interventions will be tested by dividing each intervention group into smaller groups based on data distribution (medians) or clinically meaningful cut-points. Two-sided tests will be used. *P* values of <0.05 are considered significant. The statistical programs SPSS and SAS will be used for data analysis.

Patient and public involvement

Patients were involved in developing the educational content of the program in basic carbohydrate counting. Patients were not involved in setting the research questions or the outcome measures, nor were they involved in developing the study design. Information may be disseminated to the general public via any media coverage of study findings.

Ethics and dissemination

The study will be conducted in accordance with the ethical principles in the Declaration of Helsinki and to the regulations for Good Clinical Practice (GCP) to the extent that this is relevant for non-medical studies. The study has been approved by the Ethics Committee of the Capital Region, Copenhagen (#H-18014897), has been approved for data storage by the Danish Data Protection Agency (journal no VD-2018-124, I-suite no 6367) and has been registered at ClinicalTrials.gov (NCT03623113).

All health-related matters and sensitive personal data will be handled in accordance with the Danish "Act on Processing of Personal Data". All health-related matters and sensitive personal data (blood test results etc.) will be depersonalized. All participants will be given a study number referring to their personal information, which will be stored securely and separately. Data will be stored in coded form for 10 years after last participant has attended the last visit, after which the data will be fully anonymised.

Data is owned by the investigators who are responsible for publishing the results. Positive and negative as well as inconclusive study results will be published by the investigators in international peer-reviewed journals, and all co-authors must comply with the Vancouver rules. BE will be responsible for writing the first draft of the manuscript based on the main study results as a first author under guidance by TV and JMB. The study results will be presented at relevant national and international scientific conferences and meetings and will be published in international peer-reviewed scientific journals.

Data sharing: Requests regarding dataset must be send to the corresponding author bettina.ewers@regionh.dk

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Authors' contributions: BE conceived the original idea for this trial, planned the study design, performed the sample size calculations and wrote the first draft of the protocol manuscript. TV and JMB provided valuable input regarding trial design, planning and analytical considerations, and edited the first draft of the protocol manuscript. HUA has contributed intellectually to the protocol. All authors approved the final version of the clinical trial protocol. BE is the principle investigator and is responsible for correspondence with all authorities regarding the study and is responsible for the data collection (recruitment, screening and clinical study examinations), overall monitoring the trial and for conducting the statistical analyses. TV, JMB and HUA are supervisors and coinvestigators of this trial. Should any safety concerns arise during the conduct of the study these will be brought to the attention of HUA, TV and JMB by BE and will carefully reviewed.

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Competing interests: None of the authors have financial relationships with organizations that might have an interest in the submitted work, or other relationships or activities that could appear to have influenced the submitted work.

Figure titles and legends (captions)

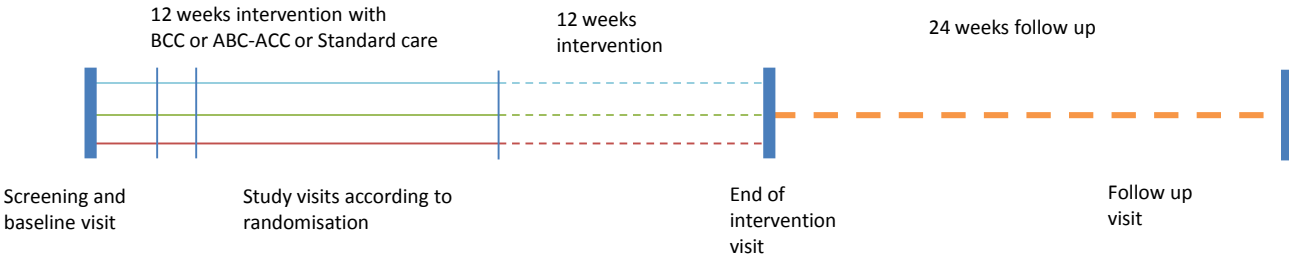
Figure 1. Study design

Figure 2. Schematic diagram of the intervention

BCC, basic carbohydrate counting; ABC-ACC, advanced carbohydrate counting with an automated bolus calculator; BP, blood pressure; BW, body weight; CGM, Continuous Glucose Monitoring; DXA, dual-energy-X-ray absorptiometry; V, visit; WHC, waist-hip circumference.

Figure 3. Study flow diagram. The planned flow of participants through the stages of the study

BCC, basic carbohydrate counting; ABC-ACC, advanced carbohydrate counting with an automated bolus calculator.


12 weeks intervention with
BCC or ABC-ACC or Standard care
12 weeks
intervention
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Screening and
baseline visit
Study visits according to
randomisation
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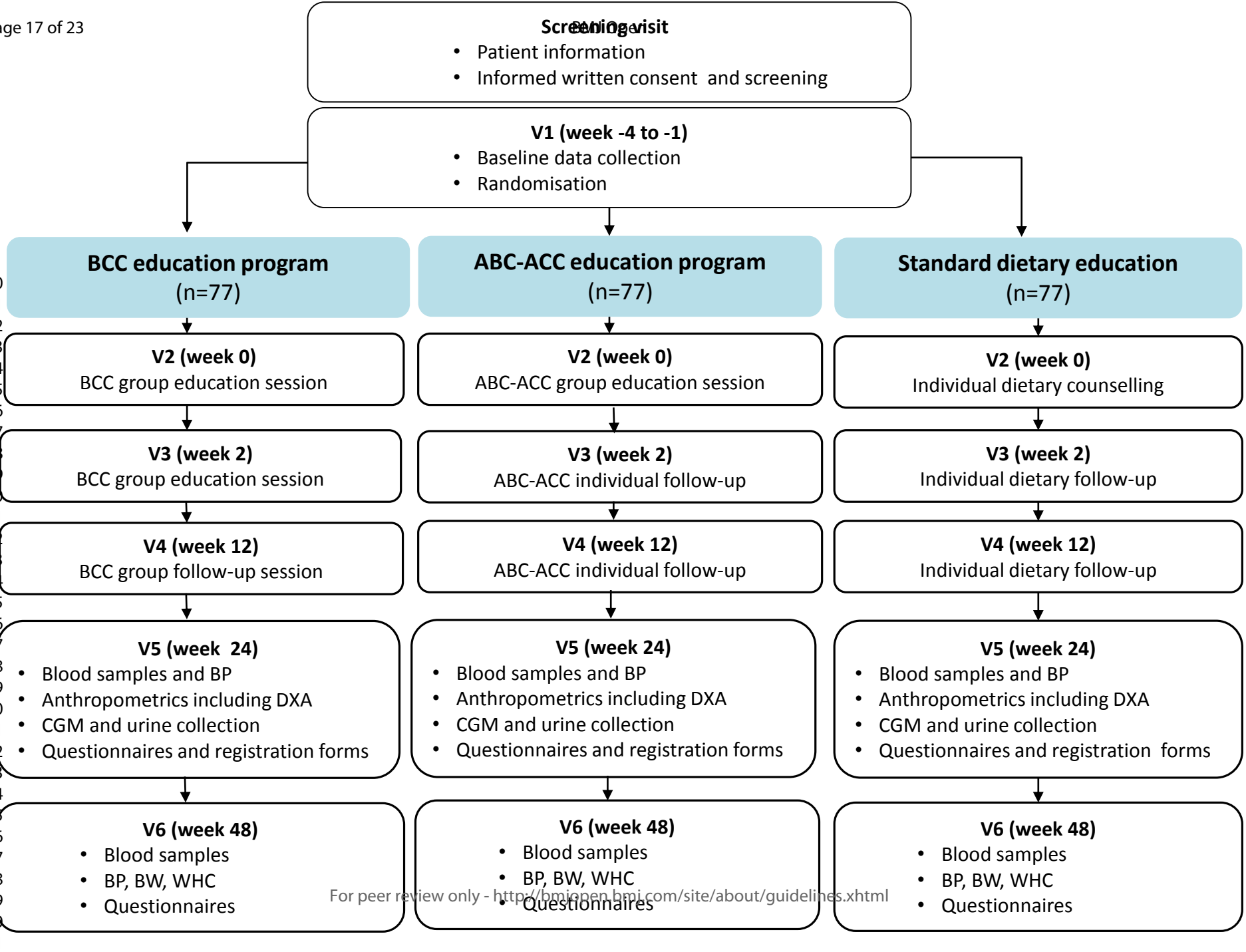

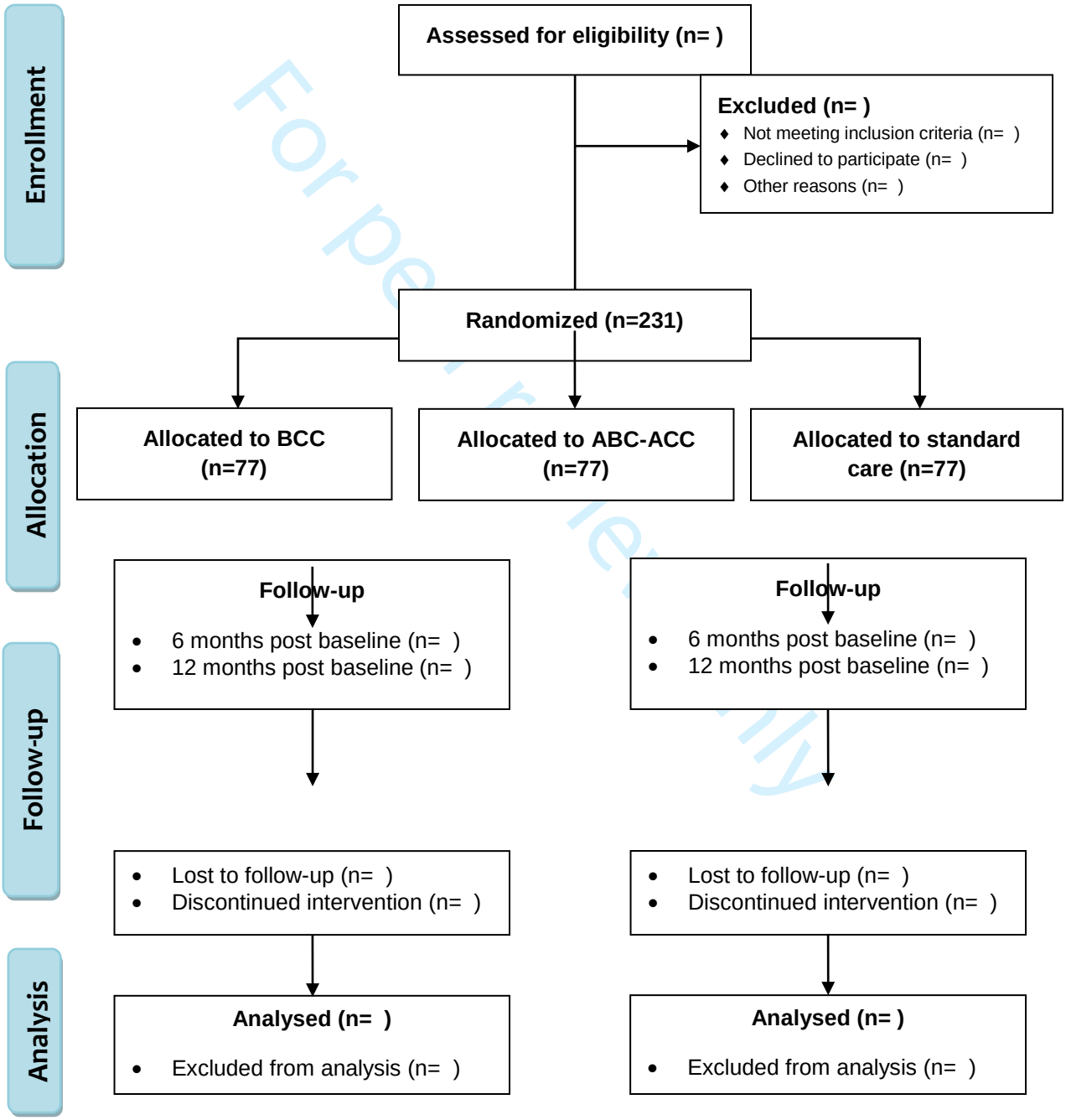

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description for the DIET-CARB study	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____p 1___
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____p 1 ___
	2b	All items from the World Health Organization Trial Registration Data Set	_____n/a___
Protocol version	3	Date and version identifier	_____p 1___
Funding	4	Sources and types of financial, material, and other support	_____p 40__
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	____p 2, 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)	_____n/a____

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	__p 9-11____
	6b	Explanation for choice of comparators	_____
Objectives	7	Specific objectives or hypotheses	__p 12-13___
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)	___p 15_____
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	__p 17, 21__
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)	___p 18____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	____p 15-16_
	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)	____p 19____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	____p 14____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	____p 17____
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	____p 14____
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)	Table 1 page 22, Fig 2 page 26

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	___p 32____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	___p 17-18__
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	____p 20____
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	_____n/a___
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	____p 37____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____n/a____
	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	___p 23-25__
	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	____ p 19___

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	p 33
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	p 32
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	p 32
	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)	p 32
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	p 35
	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	p 35-36
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	p 35
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	p 35
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)	p 36

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	____p 20____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	___p 30-31___
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	___p 33-34___
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	____p 40_____
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	____p 37_____
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	_____p 38____
	31b	Authorship eligibility guidelines and any intended use of professional writers	____p 33_____
	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	Appendix 1, 2, 4, 5
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	____p 29-30__

*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. n/a, not relevant.

BMJ Open

The Dietary Education Trial in Carbohydrate Counting (DIET-CARB Study): study protocol for a randomized, parallel, open-label, intervention study comparing different approaches to dietary self-management in patients with type 1 diabetes

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Primary Subject Heading:	Nutrition and metabolism
Secondary Subject Heading:	Diabetes and endocrinology, Nutrition and metabolism
Keywords:	Randomized controlled trial, Type 1 diabetes, Carbohydrate counting, Basic carbohydrate counting, Advanced carbohydrate counting, Nutritional education

The Dietary Education Trial in Carbohydrate Counting (DIET-CARB Study): study protocol for a randomized, parallel, open-label, intervention study comparing different approaches to dietary self-management in patients with type 1 diabetes

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Abstract

Introduction: Clinical guidelines recommend that patients with type 1 diabetes (T1D) learn carbohydrate counting or similar methods to improve glycaemic control. Although, systematic educating in carbohydrate counting is still not offered as standard-of-care for all patients on multiple daily injections (MDI) therapy in outpatient diabetes clinics in Denmark. This may be due to the lack of evidence as to which educational methods are the most effective for training patients in carbohydrate counting. The objective of this study is to compare the effect of two different educational programs in carbohydrate counting with the usual dietary care on glycaemic control in patients with T1D.

Methods and analysis: The study is designed as a randomized, controlled trial with a parallel-group design. The total study duration is 12 months with data collection at baseline, 6 and 12 months. We plan to include 231 Danish adult patients with T1D. Participants will be randomized to one of three dietician-led interventions; 1) A program in basic carbohydrate counting, 2) A program in advanced carbohydrate counting including an automated bolus calculator or 3) Usual dietary care. The primary outcome is changes in glycated haemoglobin A1c (HbA1c) or mean amplitude of glycaemic excursions (MAGE) from baseline to end of the intervention period (week 24) between and within each of the three study groups. Other outcome measures include changes in other parameters of plasma glucose variability (e.g. time in range), body weight and composition, lipid profile, blood pressure, mathematical literacy skills, carbohydrate estimation accuracy, dietary intake, diet-related quality of life, perceived competencies in dietary management of diabetes and perceptions of an autonomy supportive dietician-led climate, physical activity and urinary biomarkers.

Ethics and dissemination: The protocol has been approved by the Ethics Committee of the Capital Region, Copenhagen, Denmark. Study findings will be disseminated widely through peer-reviewed publications and conference presentations.

Registration: The trial protocol is registered on ClinicalTrials.gov NCT03623113.

Strengths and limitations of this study

1. The study has a long-term follow-up and will provide knowledge on the effects of different levels of carbohydrate counting

2. The study applies well-documented measures of glycaemic control as effect-parameters

3. The results obtained have applicability beyond Denmark and has the potential to be included in the recommendations in future guidelines

4. A limitation is the lack of a dietary "untreated" control group, however; it would be unethical not to offer standard dietary care for patients with T1D

5. The difference in the number of hours and type of dietary education and support between the groups may also influence the participants' learning

Introduction

Carbohydrate is the nutrient in our diet with by far the highest impact on plasma glucose levels. The total amount of carbohydrates consumed in a meal is the major predictor of the postprandial glucose response. Thus, monitoring dietary intake of carbohydrates is important to control postprandial glucose fluctuations, which may lead to clinical benefits such as a reduction in glucose variability, an improvement of glycated haemoglobin A1c (HbA1c), and a reduction in diabetes-related complications.

Clinical guidelines in medical nutrition therapy recommend that patients with type 1 diabetes (T1D) learn carbohydrate counting or similar experience-based methods to improve glycaemic control (1-4). Two levels of carbohydrate counting have been defined internationally with different learning objectives and increasing complexity; a basic and an advanced level (5, 6). Basic carbohydrate counting (BCC) includes understanding of the relationship between food, physical activity, and plasma glucose levels with special attention on consistency in the timing, type, amount and distribution of carbohydrate-containing foods consumed. Advanced carbohydrate counting (ACC) is targeting the patient who masters BCC, who is on intensive insulin therapy and is prepared to learn how to adjust insulin according to carbohydrate intake. In the clinical guidelines and studies, the term "carbohydrate counting" is often used synonymously with ACC, while the sole effect of BCC on glycaemic control is largely unknown. Systematic reviews and meta-analyses of randomized controlled trials (RCTs) have shown that ACC can reduce HbA1c by up to 7 mmol/mol in adults with poorly controlled T1D (7-9). Despite this, systematic educating and training is still not offered routinely for patients on multiple daily insulin injections (MDI) therapy in outpatient clinics in Denmark. This may be due to the lack of evidence as to which educational methods are the most effective for training patients in carbohydrate counting in terms of supporting patients in implementation and ongoing adherence to the use of carbohydrate counting as a tool for meal planning in their daily life.

Ideally, patients with T1D treated on MDI therapy need to be able to manage the following steps of calculation when using carbohydrate counting: 1) Correct calculation of the total carbohydrate content in each meal according to portion sizes of each carbohydrate containing food item (equal to BCC) and 2) Correct calculation of insulin dose according to the amount of carbohydrates to be consumed using a carbohydrate-to-insulin ratio, an insulin sensitivity factor, and the current and target plasma glucose (equal to ACC). In other words, patients with diabetes need good mathematical literacy skills, including numeracy skills, to be able to practice the above-mentioned steps several times each day. Recent studies suggest that lower literacy and numeracy skills are associated with poorer portion size estimation, understanding of food labels, diabetes-related self-management abilities, diabetes control and increased body mass index (BMI) (10-16). Other studies have found that patients with diabetes frequently assess their intake of carbohydrates inaccurately and this has been associated with a poorer HbA1c (17-19). Particularly mixed meals, high-calorie foods, and larger portion sizes resulted in inaccurate carbohydrate estimation. One study also found that underestimation of carbohydrate-rich meals was associated with higher daily plasma glucose variability in adults with T1D (20). Thus, assessment of numeracy skills is highly relevant to ensure that a nutritional education programs address patients with low literacy and numeracy. This may be done by numeracy-focused educational exercises and materials or hands-on learning.

In recent years technological innovations including applications (apps) for smartphones have been introduced to reduce the complexity of carbohydrate counting and possibly compensate for poor numeracy skills. So far, no technological devices can replace the patients' self-estimations of the carbohydrate content in most meals e.g. in mixed meals (addressing step 1). RCTs have demonstrated that ACC supported by the use of automated bolus calculator (ABC) software to assist insulin dose decision making (addressing step 2) compared to

unassisted ACC significantly improves HbA1c and treatment satisfaction in patients with T1D treated with MDI (21-23). However, a recent exploratory study found that lower numeracy skills were associated with smaller reductions in HbA1c after a 12-month education program in ACC with no benefit from the use of an ABC compared to manual calculations (24). These findings support the need for more intensified dietary education in BCC before learning ACC. Additionally, the concept of ACC may not be useful in all patients with T1D on MDI therapy because of potential patient barriers, lack of motivation to learn the method, and low levels of education, literacy or numeracy skills. Other barriers include lack of appropriate learning environments to promote behavioural change and availability of trained dietitians to facilitate the learning process (25). In a study of patients with diabetes, perceived competence was predicted by the degree to which the patients experienced the health-care climate to be autonomy supportive, and perceived competence at carrying out the treatment in turn predicted HbA1c (26). Group-based approaches with practised-focused dietary education compared to individual dietary counselling have been practiced in some settings but are under-investigated (27). In line with this we are currently carrying out a RCT based on this protocol.

Aim

The aims are to examine the effectiveness of two different group-based dietitian-led practise-focused educational approaches for dietary self-management compared to the standard nutrition education on glycaemic control in patients with T1D. The BCC concept aims at improving carbohydrate counting accuracy and day-to-day consistency of carbohydrate intake (the BCC intervention) and the concept of ACC aim at improving prandial insulin dose accuracy using an automated bolus calculator (the ABC-ACC intervention).

Methods and analysis

Study design

The study is as a randomized controlled intervention trial with a parallel-group design (see figure 1). The study duration is 48 months for each participant and includes up to seven visits at the study site (see figure 2). All participants will be instructed to maintain their habitual lifestyle in all other aspects than their diet, e.g. keeping the same level of physical activity during the study period. All participants will be instructed to follow their regular diabetes care in the hospital, which usually includes four yearly visits with a diabetologist (endocrinologist) and one yearly consultation with a diabetes nurse. Participants will be instructed not to receive any further dietary education during the study period. Close relatives can participate in the dietary education in all three study groups if the participant needs support to manage dietary changes.

The study flow is presented in figure 3. The study follows the guidelines of Standard Protocol Items for Randomized Trials (SPIRIT).

Setting

The study will be carried out in the outpatient diabetes clinic at Steno Diabetes Center Copenhagen (SDCC) in Gentofte, Denmark.

Recruitment and consent

As a temporary supplementary treatment initiative, SDCC offers courses in BCC and ABC-ACC for all patients with T1D treated in the capital region of Denmark. Participants for the current study will be recruited among patients signing up for these courses or patients directly referred to one of the courses or the study by a health care professional (diabetologist, diabetes nurse or dietitian) from SDCC or from a Steno Partner

hospital in the capital region. A course administrator at SDCC will contact all interested or referred patients by telephone and provide information about the study. In addition, potential study participants will be recruited through information on sdcc.dk and other electronic media or patient-related networks. If the patient is interested in the study, the patient will receive the written patient information by mail or e-mail. If interested in study participation, the study investigator/study personnel will schedule a personal meeting for oral patient information, offering the possibility of bringing a confidant. The patient will be given time to discuss any questions and will be informed that he/she has at least 24 hours to decide on participation in the study. If the patient decides to participate in the study, the patient and the study investigator/study personnel will sign the written informed consent, and the investigator/study personnel will perform a screening. If all inclusion criteria are fulfilled and none of the exclusion criteria are met, the patient will be included in the study and randomized to one of three groups. Patients who decline to participate or do not meet the inclusion criteria will continue their usual care in an outpatient diabetes clinic and will be offered to participate on a BCC or ACC course if they still wish to do so. Participants will be informed that participation is voluntary, and that they may withdraw their consent at any time.

Inclusion criteria

Patients with T1D between 18-75 years of age with a diabetes duration above 12 months and with an initial HbA1c of 53-97 mmol/mol on MDI therapy with a basal-bolus insulin regime are eligible for the study.

Exclusion criteria

Patients are excluded if they have other types of diabetes than T1D, are practicing carbohydrate counting as judged by the investigator, have a low daily intake of carbohydrates (defined as below 25 E% or 100 g/day), have participated in a BCC group program within the last two years, use an insulin pump or plan to have an insulin pump within the study period, use split-mixed insulin therapy, use an automated bolus calculator, have gastroparesis, have uncontrolled medical issues affecting the dietary intake as judged by the investigator or a medical expert. Women who are pregnant or breastfeeding or have plans of pregnancy within the study period are also excluded. Furthermore, patients who are either participating in other clinical studies or are unable to understand the informed consent and the study procedures will be excluded.

Randomization

Participants eligible for inclusion in the study will be randomly allocated in a 1:1:1 ratio to one of the three groups (BCC, ABC-ACC or control) using a computer-generated randomization in the software program *REDCap*. The randomization is done by stratifying participants based on sex and HbA1c at baseline. The randomization is done in blocks in to order to ensure an equal number of participants in each group.

Intervention groups

The BCC program consists of two sessions of three hours and a follow-up group session of two hours. The BCC program uses trained dietitians following a planned curriculum which include experience-based learning with problem-solving exercises, hands-on activities, short theoretical presentations, discussions of motivational aspects and coping strategies. The BCC program integrates peer modelling, skills development, goal setting, observational learning and social support into the program content and activities. The training includes identifying carbohydrates in food, reading carbohydrate tables, calculating the carbohydrate content from food labels, tables and apps and use of a personalized carbohydrate plan with guiding suggestions for daily intake of carbohydrates at meals based on 4-days of personal dietary recording performed before the

program including plasma glucose measurements and prandial insulin dosages taken. An app (*Diabetes og Kulhydrattælling*®. The Danish Diabetes Association, Pragma soft A/S, available in Google Play® and AppStore®) will be introduced to support estimation and calculation of carbohydrates and assist in simple insulin dose determination if participants choose to consume more carbohydrates at a meal than suggested in their personal carbohydrate plan.

The ABC-ACC program consists of a 4-hour group session and two individual follow-up sessions (two 45-minutes sessions). The program uses trained dietitians with supervision by a medical doctor and follows a planned curriculum. The ABC-ACC intervention is a group-based educational program based on the well-described BolusCal concept (28). The program includes fast training in BCC, ACC and bolus calculation using an automated bolus calculator (*mySugr Pro*®. Roche, available in Google Play® and AppStore®) taking insulin onboard, insulin sensitivity factor and differentiated carbohydrate-to-insulin ratios during the day into account. The carbohydrate-to-insulin ratios are based on 7-days of personal dietary recording including plasma glucose measurements and prandial insulin dosages taken. The ABC-ACC program contains theoretical and practical training. The teaching is based on theory and examples from everyday life with T1D and the educators help the participants with their specific diabetes-related problems and try to find appropriate practical solutions together with the participant.

Control group

Participants randomized to the control group receive current standard outpatient nutrition education in T1D. This includes individual guidance by a trained dietitian, with one initial 60 minutes dietary counselling session and two individual 30 minutes follow-up session. The individual guidance is based on the overall treatment goal and the defined personal dietary goals for behavioural change according to patient preferences. Dietary guidance includes topics such as carbohydrate sources (e.g. practicing glycaemic index and dietary fibre intake) and amounts of carbohydrates or more general dietary recommendations according to patient needs.

Delivery of dietary education

The educational program in both the standard treatment group and the intervention groups will be delivered by the same study dietitians. The dietitians have been trained by the PI (Bettina Ewers) in what to deliver in each study-arm according to the study protocol and in case of doubt, they will discuss each case with the PI to make sure that they provide the correct guidance to all participants. Data on which of the dietitians each participant has been exposed to during the trial is registered for later data analysis. Additionally, all study dietitians have an interest in providing the best possible dietary guidance irrespective of it being the standard treatment or the two intervention concepts being tested.

Data collection

All study data will be collected at the three visits with clinical examinations (baseline, after 6 and 12 months). Data will be obtained from a self-reported patient questionnaire, electronic medical records and the physical examinations conducted by the study investigator or study personnel. All questionnaire data will be collected electronically using the software system *REDCap* according to local standards for research projects in the capital region of Denmark. In addition, all sources will be registered in this database. Data generated and stored for specific equipment (e.g. Dual-energy-X-ray absorptiometry (DXA) data stored in the DXA scanner software database), electronic medical data (blood and urine measurements, glucose- and lipid-lowering medicine), data from iPro®2 CGM using software from Medtronic (Northridge, CA, US) to download CGM measurements, dietary data on total energy and nutrients based on calculations from the software system *Vitakost* will be added to the database in *REDCap* on an ongoing basis and at the end of study.

The primary outcome is the difference in mean HbA1c or MAGE from baseline to end of the intervention (week 24) between and within each of the three study groups (BCC, ABC-ACC and control).
A schematic overview of outcomes measurements is presented in table 1.

Table 1. Schematic overview of outcomes measured

Week no from start of intervention	**-4 to -1**	**12**	**24**	**48**
HbA1c	X	X	X	X
Plasma lipids	X		X	X
Body weight	X		X	X
Height	X			
Waist and hip circumference	X		X	X
Blood pressure	X		X	X
Blood samples, fasting	X		X	X
Urine samples for 4 days*	X		X	
Glucose variability (CGM) including PG diary for 6 days*	X		X	
Body composition (DXA)	X		X	
Prescribed lipid- and glucose lowering medication	X		X	X
F: Dietary registration for 4 days*	X		X	
Q: Diet-related quality of life	X		X	X
Q: Perceived Competencies in Diabetes	X		X	X
Q: Health-Care Climate	X		X	
Q: Carbohydrate estimation accuracy	X		X	X
Q: Mathematical literacy	X		X	X
Q: Demographic data	X			
Q: Physical activity	X		X	X

Abbreviations CGM=continuous glucose monitoring d=day; DXA=Dual-energy-X-ray absorptiometry; F=forms; PG=plasma glucose; Q=Questionnaire.

*Measured in the days following the study visits.

Secondary outcomes are listed below:
Clinical parameters: Body weight, body composition (measured by DXA), waist and hip circumference, blood pressure, type and dose of prescribed glucose- and lipid lowering medication, other parameters of plasma glucose variability including time in range (3.9-10.0 mmol/l), % time spent in hypoglycaemia (<3.9 mmol/l), % time spent in hyperglycaemia (e.g. >10.0 mmol/l) and standard deviation of mean plasma glucose assessed from CGM measurements.

Blood and urine samples: HbA1c (after 12 and 48 weeks), plasma lipids (low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, very low-density lipoprotein cholesterol, total cholesterol, free fatty acids and triglycerides), alanine aminotransferase (ALAT), urine albumin/creatinine ratio and urinary biomarkers based on three daily midstream urine spots collected for four days.

Patient-reported outcomes: Diet-related quality of life, perceived competencies in diabetes, health-care climate, carbohydrate estimation accuracy, mathematical literacy skills, physical activity and demographic questions. The six questionnaires used are:

Diabetes diet-related quality of life questionnaire (DDRQOL): The DDRQOL is a 31-item scale which has been validated in patients with diabetes (29). The scale is designed to determine the quantitative and qualitative satisfaction with diet and the degree of restriction of daily life and social life functions due to the dietary

changes. A forward translation and cultural adaption of the DDRQOL was done by a Japanese-Danish interpreter with a background as a clinical dietitian and an expert panel of six clinical dietitians working with diabetes. This was followed by a pilot testing by 10 patients with diabetes.

Perceived Competencies in Diabetes Scale (PCS): The PCS includes four items that reflect participants' feelings of competence about engaging in a healthier behaviour and participating in a nutritional education program. Forward and backward linguistic translation from English to Danish has been done according to standard procedures in 2001 under the guidance of Professor Vibeke Zoffmann.

Health-Care Climate Questionnaire (HCCQ): The HCCQ chosen in this study is a 5-item short form of the originally validated 15-item measure that assesses patients' perceptions of the degree to which dieticians are autonomy supportive versus controlling in providing dietary treatment.

Carbohydrate photographic questionnaire (CPQ): The CPQ is an electronic questionnaire assessing diabetes patients' abilities to estimate portion sizes of 11 commonly eaten high-carbohydrate foods correctly. The CPQ has been developed and validated against real food in 87 patients with T1D. A manuscript of these study results has been submitted (Ewers et al, unpublished).

Mathematical literacy questionnaire: A 10-item test with modified questions from the nutrition domain of the *Diabetes Numeracy Test* (DNT) (30) was designed and feasibility tested to investigate mathematical literacy including numeracy skills (addition, subtraction, division and multiplication) which are essential for understanding numbers and applying mathematical skills in daily life e.g. for calculating carbohydrates.

International Physical Activity Questionnaire Short Form (IPAQ SF): The Danish version of the IPAQ SF (31) will be used to assess changes in level of physical activity during the study period.

Self-reported demographic questions include level of education, occupation, marital status, household composition and yearly income.

Dietary data: Four days of weighed dietary food records collected at baseline and six months after baseline. Dietary records will be calculated using the software system *Vitakost* (Vitakost Aps, Kolding) where nutrient and energy calculations are based on the Danish national food database. The dietary food records are used to estimate total energy intake (kJ/d), intake of carbohydrates, protein and fat (g/day and g/meal), added sugar (g/d) and total dietary fibre intake (g/d). The dietitian performing the analysis of the food records only have access to the study ID number and participant initials.

Baseline data (from the electronic medical record): type of diabetes, diabetes duration, use of an open CGM, use of Freestyle Libre, gender, age, smoking status, medical conditions, total number of visits at a diabetologist and diabetes nurse and dietician during the study period.

Data analysis plan

The trial is ongoing. The patient recruitment started in October 2018 and is expected to be completed by October 2021.

Sample size calculation

A power calculation was conducted based on the primary outcome measures HbA1c and MAGE. Allowing for an estimated drop-out rate of 20% and subgroup analyses the sample size was planned to include a total of

231 patients in the study (77 in each arm). This was based on a sample size calculation which suggested that including 64 participants in each of the study groups would give 80% power to detect a clinically meaningful difference in change in HbA1c of 3.5 mmol/mol between the BCC group versus the control group or the ABC-ACC group versus the control group with a 5% significance level using a two-sided test and an estimated standard deviation (SD) of 7 mmol/mol. This SD has previously been used for sample size calculations in ACC trials (21) and was similar to what was found in an evaluation of previous conducted BCC courses at SDCC on mean changes and SD of HbA1c after 6 months among completers with T1D (n=185). MAGE has only been used as an outcome measure of glucose variability in a few randomized controlled dietary intervention studies of patients with diabetes (32, 33) showing differences in changes in MAGE up to 4.8 mmol/l (SD: 1.0) after a 12-week carbohydrate counting intervention (32), but is regularly used in other clinical studies evaluating glucose variability . By including 77 participants in each study group we will have a power of 80% (alpha level of 0.05) in a two-sided test to detect a clinically meaningful difference in the change in MAGE during the intervention period (week 24) of ≥0.35 mmol/l (SD 0.7 mmol/l) between the study groups.

Statistical methods

Analysis and reporting of the study results will follow the CONSORT (Consolidated Standards of Reporting Trials) guidelines for reporting parallel group randomized trials (34). Results will be presented as means (SD) for normally distributed variables and as medians (inter-quartile range) for non-normally distributed variables. One-way ANOVA will be used to compare baseline data between the three study groups for normal data and Kruskal-Wallis H test for non-normal data. Paired samples t-test will be used for within group comparison for normal data and Wilcoxon signed rank test for non-normal data. Mixed-effect models will be used to test differences in outcomes from baseline to follow-up to take repeated measurements into account. If model assumptions cannot be met even after logarithmic transformation, non-parametric tests will be used. Examinations of the relevant diagnostic plots, including QQ-plots, will be used to evaluate normality of the residuals.

The baseline demographics as well as clinical and diabetes-related characteristics of the intervention and the control groups will be presented and compared. The average changes between baseline and week 24 and 48 in primary and secondary outcomes will be calculated for each of the three groups. Intention-to-treat (ITT) analysis will be performed as the primary analysis on all primary and secondary outcomes after the last participant has ended participation. Missing values will be handled with a last observation carried forward approach for ITT analysis with the use of the multiple imputation approach in a sensitivity analysis. Per-protocol (PP) analysis will only be performed in case of sensitivity testing. Metabolic patterns will be tested with multivariate statistics. Adjustment for relevant confounders will be performed including adjustment for the stratified variables. Heterogeneity in responsiveness to the interventions will be tested by dividing each intervention group into smaller groups based on data distribution (medians) or clinically meaningful cut-points. Two-sided tests will be used. *P* values of <0.05 are considered significant. The statistical programs SPSS and SAS will be used for data analysis.

Patient and public involvement

Patients were involved in developing the educational content of the BCC program. Patients were not involved in setting the research questions or the outcome measures, nor were they involved in developing the study design. Information may be disseminated to the public via any media coverage of study findings.

Ethics and dissemination

The study will be conducted in accordance with the ethical principles in the Declaration of Helsinki and to the regulations for Good Clinical Practice (GCP) to the extent that this is relevant for non-medical studies. The study has been approved by the Ethics Committee of the Capital Region, Copenhagen (#H-18014897), has been approved for data storage by the Danish Data Protection Agency (journal no VD-2018-124, I-suite no 6367) and has been registered at ClinicalTrials.gov (NCT03623113).

All health-related matters and sensitive personal data will be handled in accordance with the Danish "Act on Processing of Personal Data". All health-related matters and sensitive personal data (blood test results etc.) will be depersonalized. All participants will be given a study number referring to their personal information, which will be stored securely and separately. Data will be stored in coded form for 10 years after last participant has attended the last visit, after which the data will be fully anonymised.

Data is owned by the investigators who are responsible for publishing the results. Positive and negative as well as inconclusive study results will be published by the investigators in international peer-reviewed journals, and all co-authors must comply with the Vancouver rules. BE will be responsible for writing the first draft of the manuscript based on the main study results as a first author under guidance by TV and JMB. The study results will be presented at relevant national and international scientific conferences and meetings and will be published in international peer-reviewed scientific journals.

Data sharing: Requests regarding dataset must be send to the corresponding author bettina.ewers@regionh.dk

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Authors' contributions: BE conceived the original idea for this trial, planned the study design, performed the sample size calculations and wrote the first draft of the protocol manuscript. TV and JMB provided valuable input regarding trial design, planning and analytical considerations, and edited the first draft of the protocol manuscript. HUA has contributed intellectually to the protocol. All authors approved the final version of the clinical trial protocol. BE is the principle investigator and is responsible for correspondence with all authorities regarding the study and is responsible for the data collection (recruitment, screening and clinical study examinations), overall monitoring the trial and for conducting the statistical analyses. TV, JMB and HUA are supervisors and coinvestigators of this trial. Should any safety concerns arise during the conduct of the study these will be brought to the attention of HUA, TV and JMB by BE and will carefully reviewed.

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Competing interests: None of the authors have financial relationships with organizations that might have an interest in the submitted work, or other relationships or activities that could appear to have influenced the submitted work.

Figure titles and legends (captions)

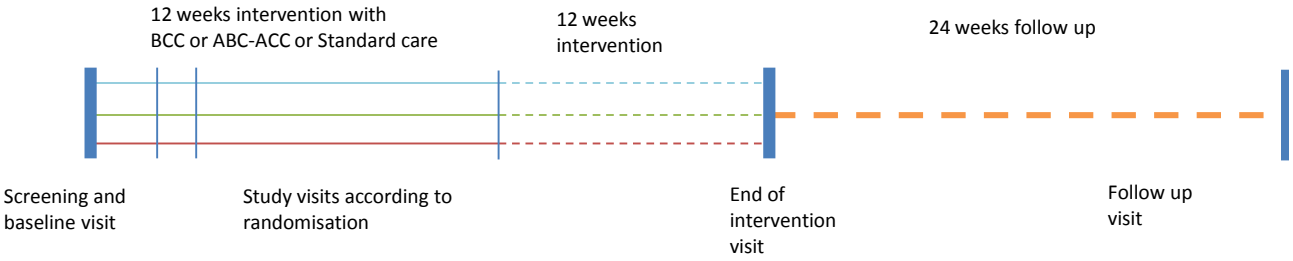
Figure 1. Study design

Figure 2. Schematic diagram of the intervention

BCC, basic carbohydrate counting; ABC-ACC, advanced carbohydrate counting with an automated bolus calculator; BP, blood pressure; BW, body weight; CGM, Continuous Glucose Monitoring; DXA, dual-energy-X-ray absorptiometry; V, visit; WHC, waist-hip circumference.

Figure 3. Study flow diagram. The planned flow of participants through the stages of the study

BCC, basic carbohydrate counting; ABC-ACC, advanced carbohydrate counting with an automated bolus calculator.


12 weeks intervention with
BCC or ABC-ACC or Standard care
12 weeks
intervention
24 weeks follow up
Screening and
baseline visit
Study visits according to
randomisation
End of
intervention
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Follow up
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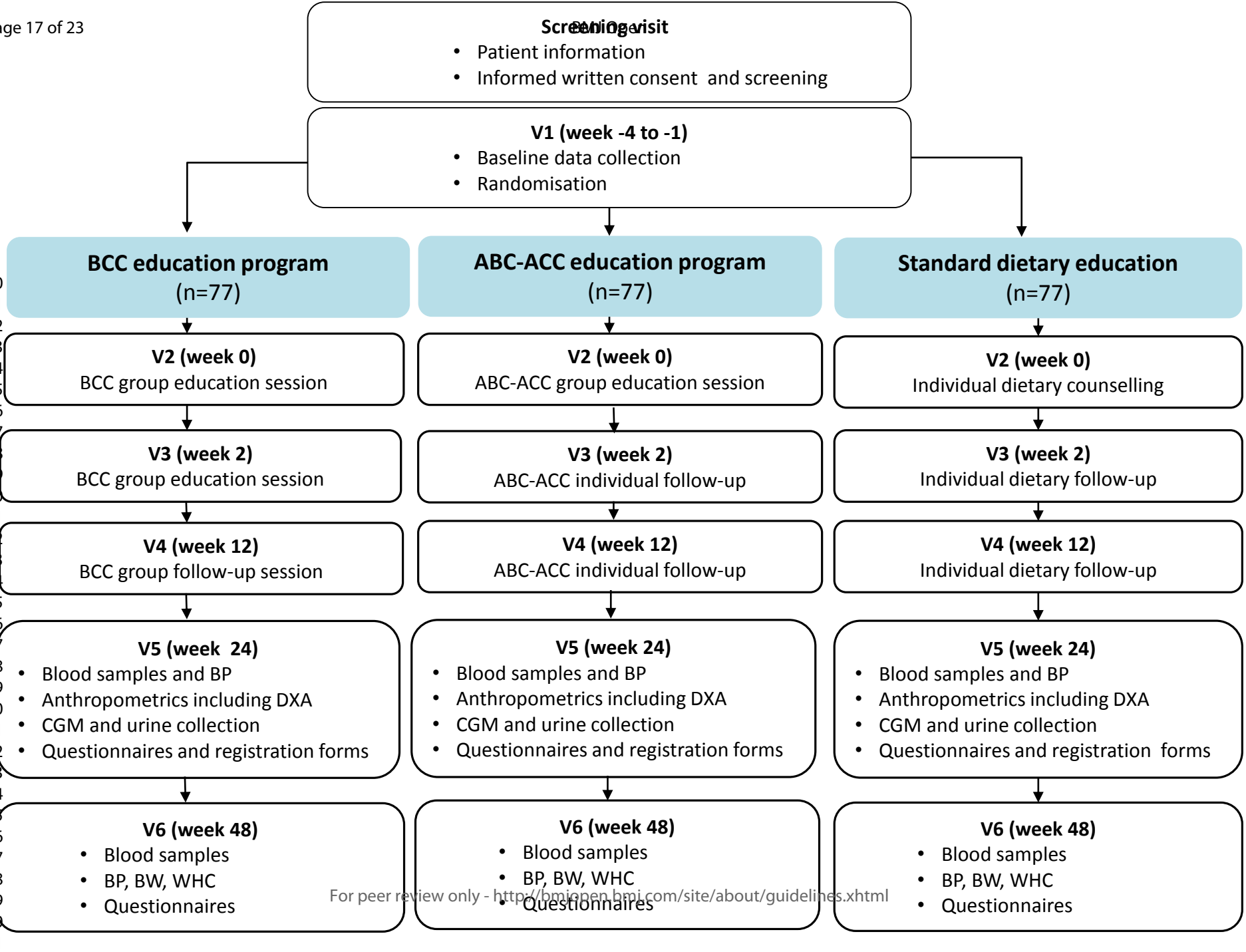

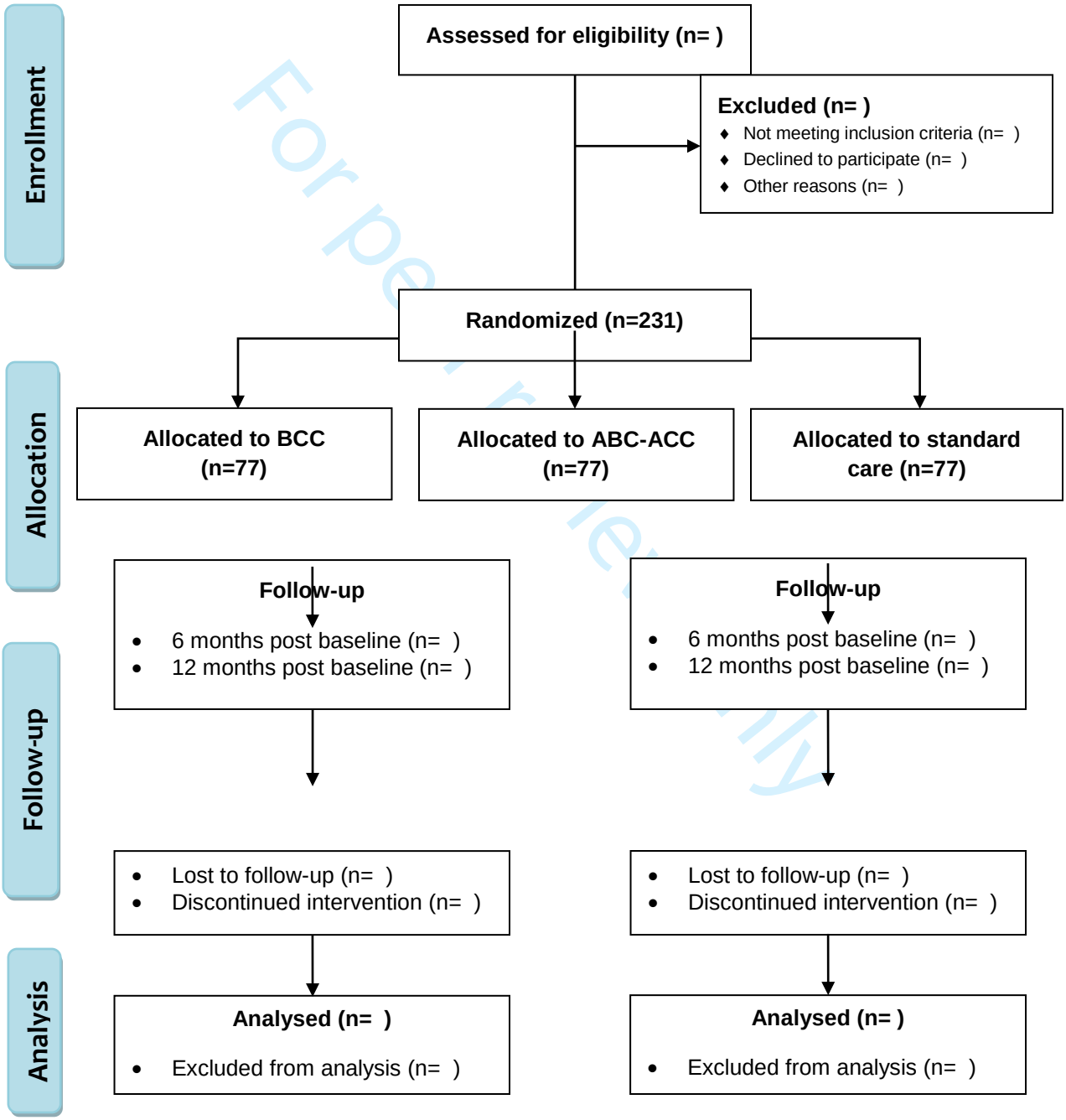

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description for the DIET-CARB study	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____p 1___
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____p 1 ___
	2b	All items from the World Health Organization Trial Registration Data Set	_____n/a___
Protocol version	3	Date and version identifier	_____p 1___
Funding	4	Sources and types of financial, material, and other support	_____p 40__
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	____p 2, 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)	_____n/a____

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	__p 9-11____
	6b	Explanation for choice of comparators	_____
Objectives	7	Specific objectives or hypotheses	__p 12-13___
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)	___p 15_____
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	__p 17, 21__
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)	___p 18____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	____p 15-16_
	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)	____p 19____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	____p 14____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	____p 17____
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	____p 14____
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)	Table 1 page 22, Fig 2 page 26

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	___p 32____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	___p 17-18__
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	____p 20____
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	_____n/a___
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	____p 37____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____n/a____
	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	___p 23-25__
	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	____ p 19___

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	p 33
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	p 32
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	p 32
	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)	p 32
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	p 35
	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	p 35-36
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	p 35
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	p 35
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)	p 36

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	____p 20____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	___p 30-31___
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	___p 33-34___
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	____p 40_____
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	____p 37_____
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	_____p 38____
	31b	Authorship eligibility guidelines and any intended use of professional writers	____p 33_____
	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	Appendix 1, 2, 4, 5
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	____p 29-30__

*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. n/a, not relevant.