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**Effects of basic carbohydrate counting versus standard outpatient nutritional education (The BCC Study): study protocol for a randomized, parallel open-label, intervention study focusing on HbA1c and glucose variability in patients with type 2 diabetes**

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Effects of basic carbohydrate counting versus standard outpatient nutritional education (The BCC Study): study protocol for a randomized, parallel open-label, intervention study focusing on HbA1c and glucose variability in patients with type 2 diabetes

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## Abstract

**Introduction:** Recommendations on energy intake are key components for body weight management to improve glycaemic control in patients with type 2 diabetes (T2D). International clinical guidelines recommend a variety of eating patterns to promote calorie restriction as the primary dietetic approach for body weight control in the management of T2D. In addition, individualized guidance on self-monitoring carbohydrate intake to optimize meal timing and food choices (e.g. basic carbohydrate counting (BCC)) is recommended to achieve glycaemic control. However, the evidence for this approach in T2D is limited. The objective of this study is to compare the effect of an educational program in BCC as add-on to the usual dietary care on glycaemic control in patients with T2D.

**Methods and analyses:** The study is designed as a randomized, controlled trial with a parallel-group design. The study duration is 12 months with data collection at baseline, after 6 and 12 months. We plan to include 226 adult patients with T2D. Participants will be randomized to one of two interventions; 1) BCC as add-on to usual dietary care, or 2) usual dietary care. The primary outcome is changes in glycated haemoglobin A1c (HbA1c) or mean amplitude of glycaemic excursions from baseline and after 6-months intervention between and within 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 diet and 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 NCT03623139.

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## Strengths and limitations of this study

1. The study has a long-term follow-up and will provide knowledge on the effects of BCC in patients with T2D
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 T2D 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 T2D
5. The difference in the number of hours and type of dietary education and support between the two groups may also influence the participants’ learning and knowledge

## 1 Introduction

Body weight management is an important aspect of the management of patients with type 2 diabetes (T2D) and even a modest weight loss is recommended to improve glycaemic control and reduce the need for glucose-lowering medication in patients with T2D (1-3). Accordingly, the national and international clinical guidelines for the management of T2D recommend calorie restriction as the primary dietetic approach for body weight control to improve metabolic control with no recommendations concerning the dietary distribution of calories from carbohydrates, fat, and proteins (1, 3, 4). However, carbohydrates are the main energy contributing nutrients in our diet with the highest impact on plasma glucose levels and the total amount of carbohydrates consumed in a meal is a significant predictor for the postprandial glucose response, however, both the quantity and quality (e.g. dietary fibre, added sugar and glycaemic index) of carbohydrates influence plasma glucose levels (5, 6). In contrast, protein, fat, and alcohol have more limited effects on postprandial plasma glucose levels, but obviously have a significant impact on the total energy balance (5, 6). Thus, monitoring the dietary intake of carbohydrates is important to control postprandial glucose fluctuations, which may lead to clinical benefits such as a reduction in plasma glucose variability, the number of hyperglycaemic episodes and thereby improvements in glycated haemoglobin A1c (HbA1c).

Accordingly, the European and American clinical guidelines recommend that patients with T2D receive individualized guidance on self-monitoring carbohydrate intake to optimize meal timing and food choices based on their current dietary intake and glucose-lowering medication (3). This may include carbohydrate counting or similar methods for achieving glycaemic control in patients with T2D (5-8).

Two levels of carbohydrate counting have been defined internationally with different learning objectives and increasing complexity; a basic and an advanced level (9-11). Basic carbohydrate counting (BCC) is a method aiming at increasing carbohydrate awareness. Patients are educated in how to manage a consistent carbohydrate intake with respect to time and amount, which foods are rich in carbohydrates, how to read food labels and estimate carbohydrate portion sizes accurately. All steps in BCC aim at an overall improvement in the control of plasma glucose. Advanced carbohydrate counting (ACC) is targeted the patient who ideally masters BCC and is on intensive insulin therapy and prepared to learn how to match mealtime insulin dosing according to carbohydrate intake using carbohydrate-insulin ratios and sensitivity factor. In other words, the ACC concept does not apply to all patients with T2D because of the complex treatment regimens (e.g. oral antidiabetic agents or other types of insulin than fast-acting meal insulins), potential patient barriers (e.g. difficulties in implementing the method in a real-life context), lack of motivation to learn the method (e.g. too time consuming to match insulin according to the carbohydrate content in each meal, or do pre- and postprandial plasma glucose monitoring), and low levels of education, literacy and/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. In the clinical guidelines and human studies, the term “carbohydrate counting” is often used synonymously with ACC. Systematic reviews and meta-analyses of randomized controlled trials (RCTs) have shown that ACC can improve HbA1c in patients with type 1 diabetes (T1D) (12-14). Only a few RCTs (15, 16) have investigated the effect of ACC in patients with T2D on intensive insulin therapy and found limited effects on HbA1c, while only one recent RCT has investigated the effect of BCC in patients with T2D and found an effect on HbA1c only in a subgroup of the study population (17). These study results need to be confirmed.

Accurate portion-size estimation is an important skill in BCC to obtain consistency in the daily carbohydrate intake and is also an important component of body weight management. Recent studies suggest that lower

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4 1 literacy and numeracy skills are associated with poorer portion size estimation skills and understanding of food  
5 2 labels, increased body mass index (BMI), and poorer diabetes-related self-management abilities (18-22).  
6 3 Studies have found that patients with diabetes frequently assess their intake of carbohydrates inaccurately and  
7 4 this has been associated with a poorer HbA1c (23-25). Particularly mixed meals, high-calorie dense foods, and  
8 5 larger portion sizes resulted in inaccurate carbohydrate estimation. Thus, carbohydrate awareness and  
9 6 monitoring including gram counting, experience-based estimation of high-carbohydrate foods and practising  
10 7 numeracy skills seems to be important for obtaining better plasma glucose control. Increased carbohydrate  
11 8 awareness may also lead to a reduced carbohydrate consumption and thus a reduced energy intake which has  
12 9 been shown to be an efficient dietary approach in patients with T2D for body weight loss and improvement in  
13 10 HbA1c at least in the short term (<1 year) (3). The short-term effects of low-carbohydrate diets may be due to  
14 11 a decline in dietary adherence over time indicating that the recommended intake of carbohydrates should be  
15 12 individualised and based on an assessment of the patient's current eating patterns and preferences as practised  
16 13 in the BCC concept. Diabetes management requires many daily self-management activities including  
17 14 managing the diet and long-term dietary adherence remains a key challenge for most dietary interventions.  
18 15 Nutrition therapy is a fundamental part of diabetes self-management education and support to help empower  
19 16 and support patients in managing their diabetes to improve glycaemic control (2). This may be accomplished  
20 17 by including skills training and social support for maintaining dietary changes. Evidence suggest that a hands-  
21 18 on, learning-by-doing approach (problem- and experience-based patient education) can support the  
22 19 development of food skills in general and improve diet quality in particular (26). Adding group-based dietary  
23 20 approaches to individual lifestyle counselling has also been found to improve dietary habits (27). Similarly  
24 21 adding diabetes self-management approaches to the diabetes education has led to lower dropout rates, increased  
25 22 self-efficacy and improved HbA1c in patients with T2D (28). One study also found that perceived competence  
26 23 in managing diabetes as predicted by the degree to which the patients experienced the health-care climate to  
27 24 be autonomy supportive and the perceived competence predicted HbA1c (29).  
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29 26 The sparse scientific knowledge about the effect of group-approaches with practised-focused nutrition  
30 27 education and the BCC concept underlines the need for investigating and evaluating this in a practice-based  
31 28 group educational approach and examining the effect on improved metabolic control in patients with T2D.  
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## 33 30 **Aim**

34 31 The aim is to examine the effectiveness of a group-based dietitian-led practise-focused educational approach  
35 32 for dietary self-management compared to the standard nutrition education on glycaemic control in patients  
36 33 with T2D. The BCC intervention aims at improving carbohydrate counting accuracy and day-to-day  
37 34 consistency of carbohydrate intake.  
38 35

## 39 36 **Methods and analysis**

### 40 37 **Study design**

41 38 The study is as a randomized controlled intervention trial with a parallel-group design (figure 1).  
42 39

43 40 For each participant the study duration is 48 months and includes up to nine visits at the study site (figure 2).  
44 41 All participants will be instructed to maintain their habitual lifestyle in all other aspects than their diet, e.g.  
45 42 keeping the same level of physical activity as habitually during the study period. All participants will be  
46 43 instructed to follow their regular diabetes care in the hospital, which usually includes four yearly visits with a  
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4 1 diabetologist (endocrinologist) and one yearly consultation with a diabetes nurse. Participants will be  
5 2 instructed not to receive any further dietary education during the study period. Close relatives can participate  
6 3 in the dietary education in both study groups if the participant needs support to manage dietary changes.

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9 4 The study flow is presented in figure 3. The study follows the guidelines of Standard Protocol Items for  
10 5 Randomized Trials (SPIRIT).

#### 11 6 12 7 Setting

13 8 The study will be carried out at the outpatient clinic at Steno Diabetes Center Copenhagen (SDCC) in Gentofte,  
14 9 Denmark.

#### 16 17 10 Recruitment and consent

18 11 As a temporary supplementary treatment initiative, SDCC offers courses in BCC for patients with T2D treated  
19 12 at SDCC. Participants for the current study will be recruited among patients signing up for these courses or  
20 13 patients directly referred to one of the courses or the study by a health care professional (diabetologist, diabetes  
21 14 nurse or dietitian) from SDCC. A course administrator at SDCC will contact all interested or referred patients  
22 15 by telephone and provide information about the study. In addition, potential study participants will be recruited  
23 16 through information on sdcc.dk and other electronic media or patient-related networks. If the patient is  
24 17 interested in the study, the patient will receive the written patient information by mail or e-mail. If interested  
25 18 in study participation, the study investigator/study personnel will schedule a personal meeting for oral patient  
26 19 information, offering the possibility of bringing a confidant. The patient will be given time to discuss any  
27 20 questions and will be informed that he/she has at least 24 hours to decide on participation in the study. If the  
28 21 patient decides to participate in the study, the patient and the study investigator/study personnel will sign the  
29 22 written informed consent, and the investigator/study personnel will perform a screening. If all inclusion criteria  
30 23 are fulfilled and none of the exclusion criteria are met, the patient will be included in the study and randomised  
31 24 to one of the groups. Patients who decline to participate or do not meet the inclusion criteria will continue their  
32 25 usual care in an outpatient diabetes clinic and will be offered to participate on a BCC course if they still wish  
33 26 to do so. Participants will be informed that participation is voluntary, and that they may withdraw their consent  
34 27 at any time.

#### 39 28 40 29 Inclusion criteria

41 30 Patients with T2D between 18-75 years with a diabetes duration of at least 12 months and baseline HbA1c of  
42 31 53-97 mmol/mol treated with diet or any glucose-lowering medication are eligible for the study.

#### 45 32 46 33 Exclusion criteria

47 34 Patients are excluded if they have other types of diabetes than T2D, are practicing carbohydrate counting as  
48 35 judged by the investigator, have a low daily intake of carbohydrates (defined as below 25 E% or 100 g/day),  
49 36 have participated in a BCC group program within the last two years, use of an automated bolus calculator,  
50 37 have gastroparesis, have uncontrolled medical issues affecting the dietary intake as judged by the investigator  
51 38 or a medical expert. Women who are pregnant or breastfeeding or have plans of pregnancy within the study  
52 39 period are also excluded. Furthermore, patients who are either participating in other clinical studies or are  
53 40 unable to understand the informed consent and the study procedures will be excluded.

#### 55 41 56 57 42 58 43 Randomization

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Participants eligible for inclusion in the study will be randomly allocated in a 1:1 ratio to one of the two groups (BCC or control) using a computer-generated randomization in the software program *REDCap*. The randomization is done by stratifying participants based on sex (male or female), BMI ( $<30$  kg/m<sup>2</sup> or  $\geq 30$  kg/m<sup>2</sup>) and HbA1c ( $<70$  mmol/mol or  $\geq 70$  mmol/mol) at baseline. The randomization is done in blocks in to order to ensure an equal number of participants in each group.

### Intervention group

Participants receive education in BCC in addition to the standard outpatient nutrition education as described for the control group. 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 applications (app) for smartphones and use of a personalized carbohydrate plan with guiding suggestions for daily intake of carbohydrates at meals based on personal dietary recordings including plasma glucose measurements. An app from the Danish Diabetes Association (*Diabetes og Kulhydrattælling*<sup>®</sup>. The Danish Diabetes Association's app, Pragma soft A/S, available in Google Play<sup>®</sup> and App Store<sup>®</sup> 12/2014, Free) will be introduced to support estimation and calculation of carbohydrates.

### Control group

Participants randomized to the control group receive current standard outpatient nutrition education in T2D. 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 healthy dietary habits and weight loss approaches for replacement of high calorie foods with low calorie foods or special attention to carbohydrate quality (e.g. glycaemic index and dietary fibre intake), fat quality and other dietary recommendations according to patient needs.

### Data collection

All study data will be collected at 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<sup>®</sup>2 a continuous glucose monitor (CMG) 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 two study groups (BCC and control).

A schematic overview of outcomes measurements is presented in table 1.

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4 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.

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4 Secondary outcomes are listed below:

5 *Clinical parameters:* Body weight, body composition (measured by DXA), waist and hip circumference blood  
6 pressure, type and dose of prescribed glucose- and lipid lowering medication, other parameters of plasma  
7 glucose variability including time in range (3.9-10.0 mmol/l), % time spent in hypoglycaemia (<3.9 mmol/l),  
8 % time spent in hyperglycaemia (>10.0 mmol/l) and standard deviation of mean plasma glucose assessed from  
9 CGM measurements.

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

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

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19 *Diabetes diet-related quality of life questionnaire (DDRQOL):* The DDRQOL is a 31-item scale which has  
20 been validated in patients with diabetes (30). The scale is designed to determine the quantitative and qualitative  
21 satisfaction with diet and the degree of restriction of daily life and social life functions due to the dietary  
22 changes. A forward translation and cultural adaption of the DDRQOL was done by a Japanese-Danish  
23 interpreter with a background as a clinical dietitian and an expert panel of six clinical dietitians working with  
24 diabetes. This was followed by a pilot testing by 10 patients.

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

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

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

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

10 *Mathematical literacy questionnaire*: A 10-item test with modified questions from the nutrition domain of the  
11 *Diabetes Numeracy Test (DNT)* (31) was designed and feasibility tested to investigate mathematical literacy  
12 including numeracy skills (addition, subtraction, division and multiplication) which are essential for  
13 understanding numbers and applying mathematical skills in daily life e.g. for calculating carbohydrates.

14 *International Physical Activity Questionnaire Short Form (IPAQ SF)*: The Danish version of the IPAQ SF (32)  
15 will be used to assess changes in level of physical activity during the study period.

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

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

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

#### 25 Data analysis plan

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

#### 28 Sample size calculation

29 A power calculation was conducted based on the primary outcome measures HbA1c and MAGE. Allowing  
30 for an estimated drop-out rate of 30% and subgroup analyses the sample size was planned to include a total of  
31 226 patients in the study (113 in each arm). This was based on a sample size calculation which suggested that  
32 including 87 participants in each of the study groups would give 80% power to detect a clinically meaningful  
33 difference in change in HbA1c of 3.0 mmol/mol between the BCC group versus the control group with a 5%  
34 significance level using a two-sided test and an estimated standard deviation (SD) of 7 mmol/mol. This SD  
35 and dropout rate have previously been used for sample size calculations and were similar to what we found  
36 when evaluating previous BCC courses at SDCC on dropout rate, mean changes and SD of HbA1c after 6  
37 months in completers with T2D. MAGE has only been used as an outcome measure of glucose variability in a  
38 few randomized controlled dietary intervention studies of patients with diabetes (33, 34) showing differences

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4 1 in changes in MAGE up to 4.8 mmol/l (SD: 1.0) after a 12-week carbohydrate counting intervention (33), but  
5 2 is regularly used in other clinical studies evaluating glucose variability . By including 113 participants in each  
6 3 study group we will have a power of 80% (alpha level of 0.05) in a two-sided test to detect a clinically  
7 4 meaningful difference in the change in MAGE during the intervention period (week 24) of  $\geq 0.30$  mmol/l (SD  
8 5 0.7 mmol/l) between the two study groups.  
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## 12 7 Statistical methods

13 8 Analysis and reporting of the study results will follow the CONSORT (Consolidated Standards of Reporting  
14 9 Trials) guidelines for reporting parallel group randomised trials (35). Results will be presented as means (SD)  
15 10 for normally distributed variables and as medians (inter-quartile range) for non-normally distributed variables.  
16 11 Paired samples t-test will be used to compare baseline data between and within the two study groups for normal  
17 12 data and Wilcoxon signed rank test for non-normal data. Mixed-effect models will be used to test differences  
18 13 in outcomes from baseline to follow-up to take repeated measurements into account. If model assumptions  
19 14 cannot be met even after logarithmic transformation, non-parametric tests will be used. Examinations of the  
20 15 relevant diagnostic plots, including QQ-plots, will be used to evaluate normality of the residuals.  
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24 17 The baseline demographics as well as clinical and diabetes-related characteristics of the intervention and the  
25 18 control groups will be presented and compared. The average changes between baseline and week 24 and 48 in  
26 19 primary and secondary outcomes will be calculated for each of the three groups. Intention-to-treat (ITT)  
27 20 analysis will be performed as the primary analysis on all primary and secondary outcomes after the last  
28 21 participant has ended participation. Missing values will be handled with a last observation carried forward  
29 22 approach for ITT analysis with the use of the multiple imputation approach in a sensitivity analysis. Per-  
30 23 protocol (PP) analysis will only be performed in case of sensitivity testing. Metabolic patterns will be tested  
31 24 with multivariate statistics. Adjustment for relevant confounders will be performed including adjustment for  
32 25 the stratified variables. Heterogeneity in responsiveness to the interventions will be tested by dividing each  
33 26 intervention group into smaller groups based on data distribution (medians) or clinically meaningful cut-points.  
34 27 Two-sided tests will be used. *P* values of  $< 0.05$  are considered significant. The statistical programs SPSS and  
35 28 SAS will be used for data analysis.  
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40 30 **Patient and public involvement:** Patients were involved in developing the educational content of the  
41 31 program in basic carbohydrate counting. Patients were not involved in setting the research questions or the  
42 32 outcome measures, nor were they involved in developing the study design. Information may be disseminated  
43 33 to the public via any media coverage of study findings.  
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## 46 35 Ethics and dissemination

47 36 The study will be conducted in accordance with the ethical principles in the Declaration of Helsinki and to the  
48 37 regulations for Good Clinical Practice (GCP) to the extent that this is relevant for non-medical studies. The  
49 38 study has been approved by the Ethics Committee of the Capital Region, Copenhagen (#H-18014918), has  
50 39 been approved for data storage by the Danish Data Protection Agency (journal no VD-2018-233, I-suite no  
51 40 6474) and has been registered at ClinicalTrials.gov (NCT03623139).  
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55 42 All health-related matters and sensitive personal data will be handled in accordance with the Danish “Act on  
56 43 Processing of Personal Data”. All health-related matters and sensitive personal data (blood test results etc.)  
57 44 will be depersonalized. All participants will be given a study number referring to their personal information,  
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1 which will be stored securely and separately. Data will be stored in coded form for 10 years after last participant  
2 has attended the last visit, after which the data will be fully anonymised.

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

10 Data sharing: Requests regarding dataset must be send to the corresponding author [bettina.ewers@regionh.dk](mailto:bettina.ewers@regionh.dk)

11  
For peer review only



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4 1 **Authors' contributions:** BE conceived the original idea for this trial, planned the study design, performed  
5 2 the sample size calculations and wrote the first draft of the protocol manuscript. TV and JMB provided valuable  
6 3 input regarding trial design, planning and analytical considerations, and edited the first draft of the protocol  
7 4 manuscript. All authors approved the final version of the clinical trial protocol. BE is the principle investigator  
8 5 and is responsible for correspondence with all authorities regarding the study and is responsible for the data  
9 6 collection (recruitment, screening and clinical study examinations), overall monitoring the trial and for  
10 7 conducting the statistical analyses. TV and JMB are supervisors and coinvestigators of this trial. Should any  
11 8 safety concerns arise during the conduct of the study these will be brought to the attention of TV and JMB by  
12 9 BE and will be carefully reviewed.  
13 10

14 11 **Funding statement:** This work was supported by The Beckett Foundation (grant number 17-2-0957), the  
15 12 Axel Muusfeldts Foundation (grant no 2017-856) and the Novo Nordisk Foundation (No assigned grant  
16 13 number) as part of a supplementary treatment initiative at SDCC in 2018-2020.  
17 14

18 15 **Competing interests:** None of the authors have financial relationships with organizations that might have  
19 16 an interest in the submitted work, or other relationships or activities that could appear to have influenced the  
20 17 submitted work.  
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1 **Figure titles and legends (captions)**

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3 **Figure 1.** Study design

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5 **Figure 2.** Schematic diagram of the intervention

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7 BCC, basic carbohydrate counting; BP, blood pressure; BW, body weight; CGM, Continuous Glucose  
8 Monitoring; DXA, dual-energy-X-ray absorptiometry; V, visit; WHC, waist-hip circumference.

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

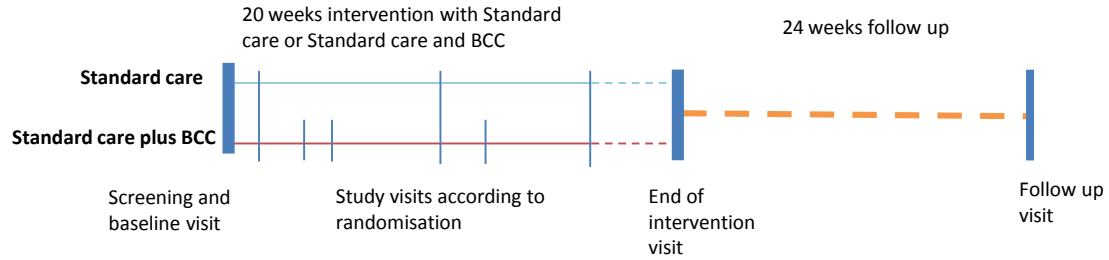
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12 BCC, basic carbohydrate counting.

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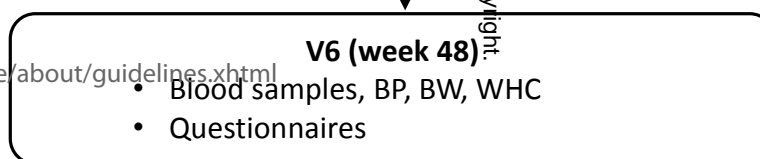
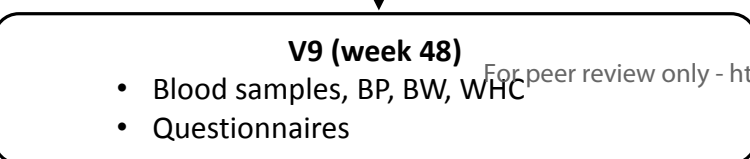
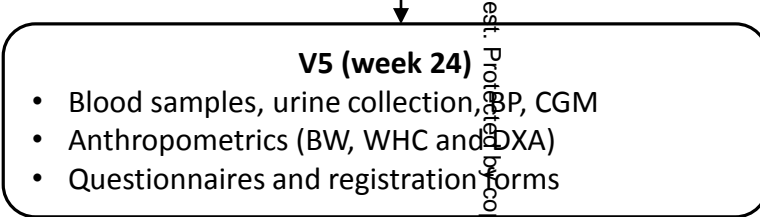
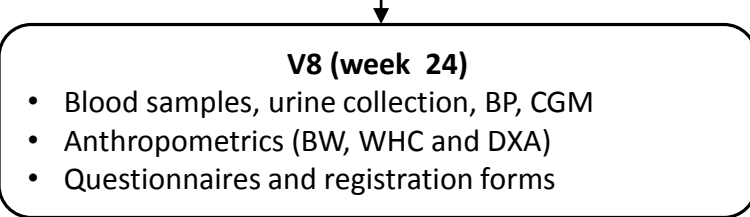
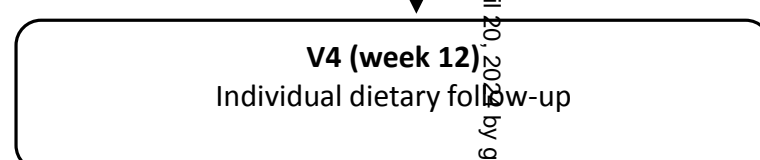
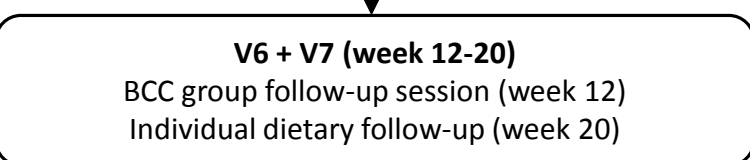
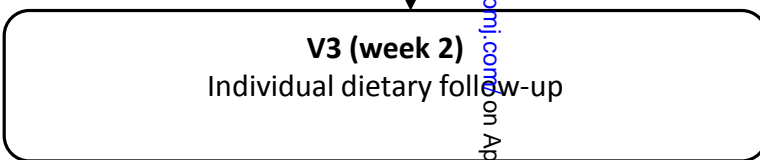
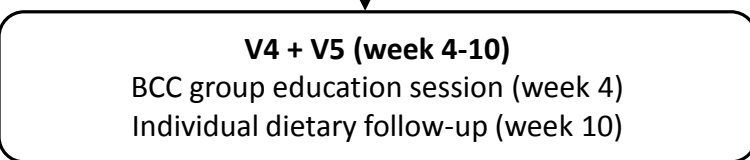
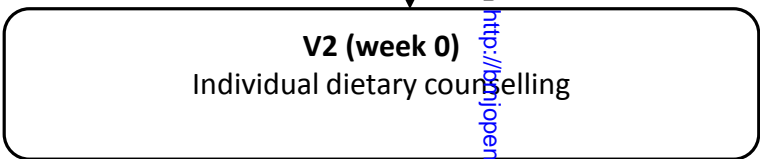
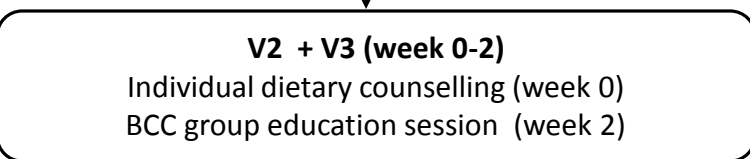
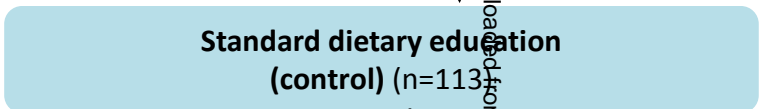
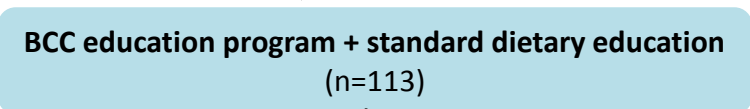
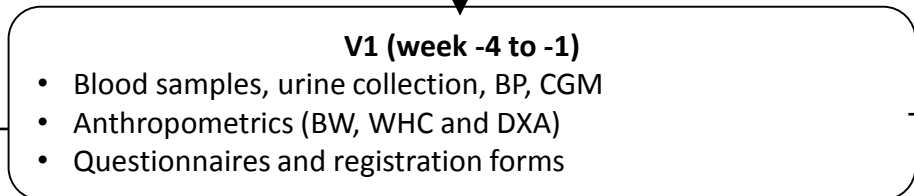
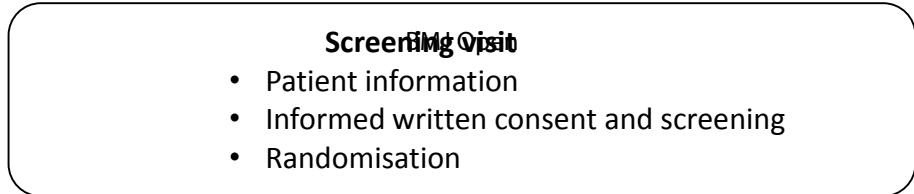
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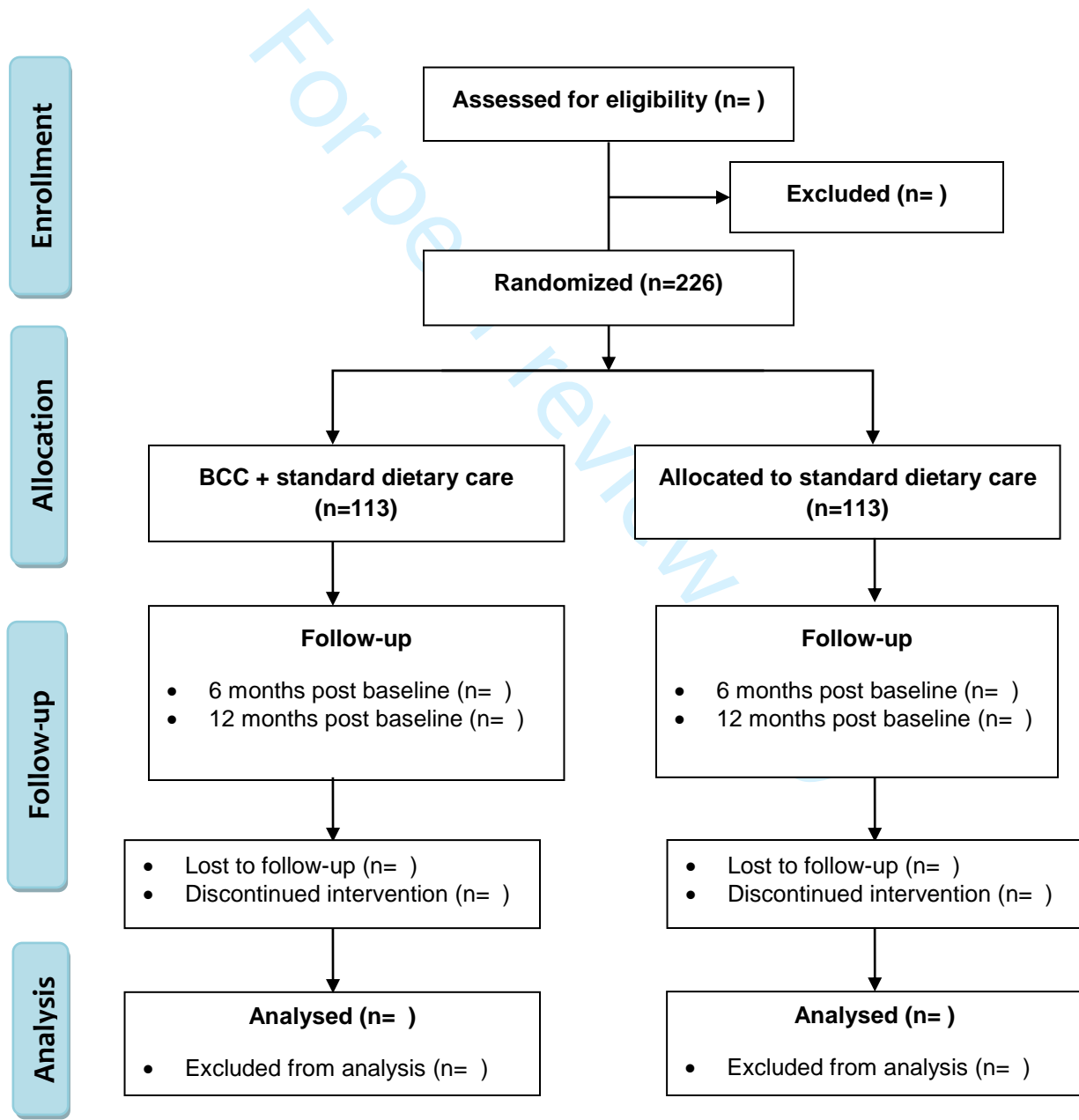
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Enrollment

Allocation

Follow-up

Analysis



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 BCC study	Addressed on page number
<b>Administrative information</b>			
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 39___
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	___p 2___
	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___

## 1 Introduction

2			
3	Background and	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
4	rationale		__p 9-10__
5			
6		6b	Explanation for choice of comparators
7			_____
8	Objectives	7	Specific objectives or hypotheses
9			__p 11__
10	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial or single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
11			__p 13__
12			
13			

## 14 Methods: Participants, interventions, and outcomes

15			
16	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
17			__p 18-19__
18			
19	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)
20			__p 16__
21			
22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
23			__p 13-14__
24			
25		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)
26			__p 16__
27			
28		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
29			__p 15__
30			
31		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
32			__p 14__
33			
34	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
35			__p 12__
36			
37	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)
38			Table 1 page 20, Fig 2 page 25
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1	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 31___
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4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	___p 15___
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6	<b>Methods: Assignment of interventions (for controlled trials)</b>			
7	<b>Allocation:</b>			
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10	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 18___
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16	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___
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20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	___p 36___
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24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	___n/a___
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27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	___n/a___
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31	<b>Methods: Data collection, management, and analysis</b>			
32				
33	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 23-24___
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39		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 16-17___
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1	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 32___
2				
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5	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 31___
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8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	___p 31___
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10		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 31___
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14	<b>Methods: Monitoring</b>			
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16	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 32-33___
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22		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 36___
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25	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 33___
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28	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___
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32	<b>Ethics and dissemination</b>			
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34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	___p 32___
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37	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 34___
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	___p 17___
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3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	___p 29-30___
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7	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 32-33___
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10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	___p 39___
11				
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13	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 32___
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15				
16	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___
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20	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	___p 37___
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24		31b	Authorship eligibility guidelines and any intended use of professional writers	___p 32___
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26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	___n/a___
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29	<b>Appendices</b>			
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31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix 1, 2, 3, 4, 5
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34	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 28-30___
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37 \*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.  
 38 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons  
 39 "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by/4.0/)" license. n/a, not relevant.  
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# BMJ Open

**Effects of basic carbohydrate counting vs. standard outpatient nutritional education (The BCC Study): study protocol for a randomized, parallel open-label, intervention study focusing on HbA1c and glucose variability in patients with type 2 diabetes**

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4 Effects of basic carbohydrate counting vs. standard outpatient nutritional education (The BCC Study): study  
5 protocol for a randomised, parallel open-label, intervention study focusing on HbA1c and glucose variability  
6 in patients with type 2 diabetes  
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## Abstract

**Introduction:** Recommendations on energy intake are key in body weight management to improve glycaemic control in people with type 2 diabetes (T2D). International clinical guidelines recommend a variety of eating patterns to promote energy restriction as the primary dietetic approach to body weight control in managing T2D. In addition, individualized guidance on self-monitoring carbohydrate intake to optimize meal timing and food choices (e.g. basic carbohydrate counting (BCC)) is recommended to achieve glycaemic control. However, the evidence for this approach in T2D is limited. The objective of this study is to compare the effect of an educational program in BCC as add-on to the usual dietary care on glycaemic control in people with T2D.

**Methods and analyses:** The study is designed as a randomised, controlled trial with a parallel-group design. The study duration is 12 months with data collection at baseline, and after 6 and 12 months. We plan to include 226 adults with T2D. Participants will be randomised to one of two interventions: 1) BCC as add-on to usual dietary care, or 2) usual dietary care. The primary outcome is changes in glycated haemoglobin A1c (HbA1c) or mean amplitude of glycaemic excursions (MAGE) from baseline and after 6 months intervention between and within study groups. Further outcome measures include changes in 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 diet and 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 NCT03623139.

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### Strengths and limitations of this study

1. The study has a long-term follow-up and will provide knowledge on the effects of BCC in people with T2D
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 T2D 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 participants in the control group for 1 year
5. The difference in the number of hours and type of dietary education and support between the two groups may also influence the participants’ learning and knowledge.

## 1 Introduction

Body weight management is central in managing people with type 2 diabetes (T2D) and even a modest weight loss is recommended to improve glycaemic control and reduce the need for glucose-lowering medication in people with T2D (1-3). Accordingly, the national and international clinical guidelines for managing T2D recommend energy restriction as the primary dietetic approach for body weight control to improve metabolic control with no recommendations concerning the dietary distribution of energy from carbohydrates, fat, and proteins (1, 3, 4). However, carbohydrates are the main energy contributing nutrients in our diet with the highest impact on plasma glucose levels and the total amount of carbohydrates consumed in a meal is a significant predictor for the postprandial glucose response; furthermore, both the quantity and quality (e.g. dietary fibre, added sugar and glycaemic index) of carbohydrates influence plasma glucose levels (5, 6). In contrast, protein, fat, and alcohol have more limited effects on postprandial plasma glucose levels but obviously have a significant impact on the total energy balance (5, 6). Thus, monitoring the dietary intake of carbohydrates is crucial to control postprandial glucose fluctuations, which may lead to clinical benefits such as a reduction in plasma glucose variability, the number of hyperglycaemic episodes and thereby improvements in glycated haemoglobin A1c (HbA1c).

Accordingly, the European and American clinical guidelines recommend that people with T2D receive individualized guidance on self-monitoring carbohydrate intake to optimize meal timing and food choices based on their current dietary intake and glucose-lowering medication (3). This may include carbohydrate counting or similar methods for achieving glycaemic control in people with T2D (5-8).

Two levels of carbohydrate counting have been defined internationally with different learning objectives and increasing complexity: a basic and an advanced level (9-11). Basic carbohydrate counting (BCC) is a method aiming at increasing carbohydrate awareness. People with diabetes are educated in how to manage a consistent carbohydrate intake regarding time and amount, which foods are rich in carbohydrates, and how to read food labels and estimate carbohydrate portion sizes accurately. BCC aims to improve overall glycaemic control. Advanced carbohydrate counting (ACC) is targeted at the individual who ideally masters BCC and is on intensive insulin therapy and prepared to learn how to match mealtime insulin dosing according to carbohydrate intake using carbohydrate-insulin ratios and sensitivity factor. In other words, the ACC concept does not apply to all people with T2D because of the complex treatment regimens (e.g. oral antidiabetic agents or other types of insulin than fast-acting meal insulins), potential patient barriers (e.g. difficulties in implementing the method in a real-life context), lack of motivation to learn the method (e.g. too time consuming to match insulin according to the carbohydrate content in each meal, or do pre- and postprandial plasma glucose monitoring), and low levels of education, literacy and/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. In the clinical guidelines and human studies, the term “carbohydrate counting” is often used synonymously with ACC. Systematic reviews and meta-analyses of randomised controlled trials (RCTs) have shown that ACC can improve HbA1c in people with type 1 diabetes (T1D) (12-14). Only a few RCTs (15, 16) have investigated the effect of ACC in people with T2D on intensive insulin therapy and found limited effects on HbA1c, while only one recent RCT has investigated the effect of BCC in people with T2D and found an effect on HbA1c only in a subgroup of the study population (17). These study results need to be confirmed.

Accurate portion-size estimation is an important skill in BCC to obtain consistency in the daily carbohydrate intake and is also an important component of body weight management. Recent studies suggest that lower

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4 1 literacy and numeracy skills are associated with poorer portion size estimation skills and understanding of food  
5 2 labels, increased body mass index (BMI), and poorer diabetes-related self-management abilities (18-22).  
6 3 Studies have found that people with diabetes frequently assess their intake of carbohydrates inaccurately and  
7 4 this has been associated with a poorer HbA1c (23-25). In particular mixed meals, energy-dense foods, and  
8 5 larger portion sizes resulted in inaccurate carbohydrate estimation. Thus, carbohydrate awareness and  
9 6 monitoring including gram counting, experience-based estimation of high-carbohydrate foods and practising  
10 7 numeracy skills seems to be important for obtaining better plasma glucose control. Increased carbohydrate  
11 8 awareness may also lead to a reduced carbohydrate consumption and thus a reduced energy intake, which has  
12 9 been shown to be an efficient dietary approach in people with T2D for body weight loss and improvement in  
13 10 HbA1c at least in the short term (<1 year) (3). The short-term effects of low-carbohydrate diets may be due to  
14 11 a decline in dietary adherence over time indicating that the recommended intake of carbohydrates should be  
15 12 individualised and based on an assessment of the patient's current eating patterns and preferences as practised  
16 13 in the BCC concept. Diabetes management requires many daily self-management activities including  
17 14 managing dietary intake, and long-term dietary adherence remains a key challenge for most dietary  
18 15 interventions. Nutrition therapy is a fundamental part of diabetes self-management education and support to  
19 16 help empower and support people in managing their diabetes to improve glycaemic control (2). This may be  
20 17 accomplished by including skills training and social support for maintaining dietary changes. Evidence suggest  
21 18 that a hands-on, learning-by-doing approach (problem- and experience-based patient education) can support  
22 19 the development of food skills in general and improve diet quality in particular (26). Adding group-based  
23 20 dietary approaches to individual lifestyle counselling has also been found to improve dietary habits (27).  
24 21 Similarly, adding diabetes self-management approaches to the diabetes education has led to lower dropout  
25 22 rates, increased self-efficacy and improved HbA1c in people with T2D (28). One study also found that  
26 23 perceived competence in managing diabetes as predicted by the degree to which people experienced the health-  
27 24 care climate to be autonomy supportive and the perceived competence predicted HbA1c (29).  
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37 27 The sparse scientific knowledge about the effect of group-approaches with practiced-focused nutrition  
38 28 education and the BCC concept underlines the need for investigating and evaluating this in a practice-based  
39 29 group educational approach and examining the effect on improved metabolic control in people with T2D.  
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#### 42 31 **Aim**

43 32 The aim is to examine the effectiveness of a group-based dietitian-led practise-focused educational approach  
44 33 for dietary self-management compared to the standard nutrition education on glycaemic control in people with  
45 34 T2D.  
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#### 50 36 **Methods and analysis**

##### 51 37 **Study design**

52 38 The study is as a randomised controlled intervention trial with a parallel-group design (figure 1).  
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55 39 For each participant the study duration is 12 months and includes up to nine visits at the study site (figure 2).  
56 40 All participants will be instructed to maintain their habitual lifestyle in all other aspects than their diet, e.g.  
57 41 keeping the same level of physical activity as habitually during the study period. All participants will be  
58 42 instructed to follow their regular diabetes care in the hospital, which usually includes four yearly visits with a  
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4 1 diabetologist (endocrinologist) and one yearly consultation with a diabetes nurse. Participants will be  
5 2 instructed not to receive any further dietary education during the study period. Close relatives can participate  
6 3 in the dietary education in both study groups if the participant needs support to manage dietary changes.

8  
9 4 The study flow is presented in figure 3. The study follows the guidelines of Standard Protocol Items for  
10 5 Randomised Trials (SPIRIT).

#### 11 6 12 7 Setting

13 8 The study will be carried out at the outpatient clinic at Steno Diabetes Center Copenhagen (SDCC) in Gentofte,  
14 9 Denmark.

#### 16 10 Recruitment and consent

17 11 As a temporary supplementary treatment initiative, SDCC offers courses in BCC for people with T2D treated  
18 12 at SDCC. Participants for the current study will be recruited among people signing up for these courses or  
19 13 people directly referred to one of the courses or the study by a health care professional (diabetologist, diabetes  
20 14 nurse or dietitian) from SDCC. A course administrator at SDCC will contact all interested or referred people  
21 15 by telephone and provide information about the study. In addition, potential study participants will be recruited  
22 16 through information on sdcc.dk and other electronic media or patient-related networks. If the person is  
23 17 interested in the study, the person will receive the written information by mail or e-mail. If interested in study  
24 18 participation, the study investigator/study personnel will schedule a personal meeting for oral information,  
25 19 offering the possibility of bringing a confidant. The person will be given time to discuss any questions and will  
26 20 be informed that he/she has at least 24 hours to decide on participation in the study. If the person decides to  
27 21 participate in the study, the person and the study investigator/study personnel will sign the written informed  
28 22 consent, and the investigator/study personnel will perform a screening. If all inclusion criteria are fulfilled and  
29 23 none of the exclusion criteria are met, the person will be included in the study and randomised to one of the  
30 24 groups. People who decline to participate or do not meet the inclusion criteria will continue their usual care in  
31 25 an outpatient diabetes clinic and will be offered to participate on a BCC course if they still wish to do so.  
32 26 Participants will be informed that participation is voluntary, and that they may withdraw their consent at any  
33 27 time.

#### 39 28 40 29 Inclusion criteria

41 30 People with T2D between 18-75 years with a diabetes duration of at least 12 months and baseline HbA1c of  
42 31 53-97 mmol/mol treated with diet or any glucose-lowering medication are eligible for the study.

#### 44 32 45 33 Exclusion criteria

46 34 People are excluded if they have other types of diabetes than T2D, are practicing carbohydrate counting as  
47 35 judged by the investigator, have a low daily intake of carbohydrates (defined as below 25 E% or 100 g/day),  
48 36 have participated in a BCC group program within the last two years, use an automated bolus calculator, have  
49 37 gastroparesis, have uncontrolled medical issues affecting dietary intake as judged by the investigator or a  
50 38 medical expert. Women who are pregnant or breastfeeding or have plans of pregnancy within the study period  
51 39 are also excluded. Furthermore, people who are either participating in other clinical studies or are unable to  
52 40 understand the informed consent and the study procedures will be excluded.



## 1 Randomisation

2 Participants eligible for inclusion in the study will be randomly allocated in a 1:1 ratio to one of the two groups  
3 (BCC or control) using a computer-generated randomization in the software program *REDCap*. The  
4 randomization is done by stratifying participants based on sex (male or female), BMI ( $<30 \text{ kg/m}^2$  or  $\geq 30$   
5  $\text{kg/m}^2$ ) and HbA1c ( $<70 \text{ mmol/mol}$  or  $\geq 70 \text{ mmol/mol}$ ) at baseline. The randomization is done in blocks in to  
6 order to ensure an equal number of participants in each group.

## 7 Intervention group

8 Participants will receive education in BCC in addition to the standard outpatient nutrition education as  
9 described for the control group. The BCC program consists of two sessions of three hours and a follow-up  
10 group session of two hours. The BCC program uses trained dietitians following a planned curriculum which  
11 include experience-based learning with problem-solving exercises, hands-on activities, short theoretical  
12 presentations, discussions of motivational aspects and coping strategies. The BCC program integrates peer  
13 modelling, skills development, goal setting, observational learning and social support into the program content  
14 and activities. The training includes identifying carbohydrates in food, reading carbohydrate tables, calculating  
15 the carbohydrate content from food labels, tables and applications (app) for smartphones and use of a  
16 personalized carbohydrate plan with guiding suggestions for daily intake of carbohydrates at meals based on  
17 personal dietary recordings including plasma glucose measurements. An app from the Danish Diabetes  
18 Association (*Diabetes og Kulhydrattælling*<sup>®</sup>. The Danish Diabetes Association's app, Pragma soft A/S,  
19 available in Google Play<sup>®</sup> and App Store<sup>®</sup> 12/2014, Free) will be introduced to support estimation and  
20 calculation of carbohydrates.  
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## 22 Control group

23 Participants randomised to the control group will receive current standard outpatient nutrition education in  
24 T2D. This includes individual guidance by a trained dietitian, with one initial 60 minutes dietary counselling  
25 session and two individual 30 minutes follow-up session. The individual guidance is based on the overall  
26 treatment goal and the defined personal dietary goals for behavioural change according to personal preferences.  
27 Dietary guidance includes topics such as healthy dietary habits and weight loss approaches for replacement of  
28 energy-dense foods with low energy-dense foods or special attention to carbohydrate quality (e.g. glycaemic  
29 index and dietary fibre intake), fat quality and other dietary recommendations according to personal needs.  
30

## 31 Data collection

32 All study data will be collected at three visits with clinical examination (baseline, after 6 and 12 months). Data  
33 will be obtained from a self-reported questionnaire, electronic medical records and the physical examinations  
34 conducted by the study investigator or study personnel. All questionnaire data will be collected electronically  
35 using the software system *REDCap* according to local standards for research projects in the capital region of  
36 Denmark. In addition, all sources will be registered in this database. Data generated and stored for specific  
37 equipment (e.g. Dual-energy-X-ray absorptiometry (DXA) data stored in the DXA scanner software database),  
38 electronic medical data (blood and urine measurements, glucose- and lipid-lowering medicine), data from  
39 iPro<sup>®</sup>2 a continuous glucose monitor (CMG) using software from Medtronic (Northridge, CA, US) to  
40 download CGM measurements, dietary data on total energy and nutrients based calculations from the software  
41 system *Vitakost* will be added to the database in *REDCap* on an ongoing basis and at the end of study.  
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43 The primary outcome is the difference in mean HbA1c or mean amplitude of glycaemic excursions (MAGE)  
44 from baseline to end of the intervention (6 month) between and within each of the two study groups (BCC and  
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control). MAGE is used as a measure of glycaemic variability to capture mealtime-related glucose excursions. MAGE has been associated with coronary artery disease independent of HbA1c (30, 31).

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 wk	3 mo	6 mo	12 mo
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; mo=months; PG=plasma glucose; Q=Questionnaire; wk=weeks.

\*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 (>10.0 mmol/l) and standard deviation of mean plasma glucose assessed from CGM measurements.

**Blood and urine samples:** HbA1c (after 12 weeks and 12 months), 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 people with diabetes (32). 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

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1 interpreter with a background as a clinical dietitian and an expert panel of six clinical dietitians working with  
2 diabetes. This was followed by a pilot testing by 10 people with diabetes.

3  
4 *Perceived Competencies in Diabetes Scale (PCS)*: The PCS is a validated scale (33) which includes four items  
5 that reflect participants' feelings of competence about engaging in a healthier behaviour and participating in a  
6 nutritional education program. Forward and backward linguistic translation from English to Danish has been  
7 done according to standard procedures in 2001 under the guidance of Professor Vibeke Zoffmann.

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

11 *Carbohydrate photographic questionnaire (CPQ)*: The CPQ is an electronic questionnaire assessing skills in  
12 correct estimation of portion sizes of 11 commonly eaten high-carbohydrate foods. The CPQ has been  
13 developed and validated against real food in 87 people with diabetes. The study results by Ewers et al. has  
14 been accepted for publication in Journal of Nutrition and Food Science in September 2019.

15 *Mathematical literacy questionnaire*: A 10-item test with modified questions from the nutrition domain of the  
16 *Diabetes Numeracy Test (DNT)* (34) was designed and feasibility tested to investigate mathematical literacy  
17 including numeracy skills (addition, subtraction, division and multiplication) which are essential for  
18 understanding numbers and applying mathematical skills in daily life e.g. for calculating carbohydrates.

19 *International Physical Activity Questionnaire Short Form (IPAQ SF)*: The Danish version of the IPAQ SF (35)  
20 will be used to assess changes in level of physical activity during the study period.

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

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

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

#### 30 Data analysis plan

31 The trial is ongoing. The recruitment started in October 2018 and is expected to be completed by October  
32 2021.

#### 33 Sample size calculation

34 A power calculation was conducted based on the primary outcome measures HbA1c and MAGE. Allowing  
35 for an estimated drop-out rate of 30% and subgroup analyses the sample size was planned to include a total of  
36 226 people in the study (113 in each arm). This was based on a sample size calculation which suggested that  
37 including 87 participants in each of the study groups would give 80% power to detect a clinically meaningful  
38 difference in change in HbA1c of 3.0 mmol/mol between the BCC group versus the control group with a 5%  
39 significance level using a two-sided test and an estimated standard deviation (SD) of 7 mmol/mol. The used

SD and dropout rate were based on previous BCC courses at SDCC where mean changes and SD of HbA1c after 6 months were calculated based on completers with T2D. MAGE has only been used as an outcome measure of glucose variability in a few randomised controlled dietary intervention studies of people with diabetes (36, 37) showing differences in changes in MAGE up to 4.8 mmol/l (SD: 1.0) after a 12-week carbohydrate counting intervention (36), but is regularly used in other clinical studies evaluating glucose variability. By including 113 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 (6 months) of  $\geq 0.30$  mmol/l (SD 0.7 mmol/l) between the two 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 (38). Results will be presented as means (SD) for normally distributed variables and as medians (inter-quartile range) for non-normally distributed variables. Paired samples t-test will be used to compare baseline data between and within the two study groups 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 6 months, and 12 months 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:** People were involved in developing the educational content of the program in basic carbohydrate counting. People 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-18014918), has been approved for data storage by the Danish Data Protection Agency (journal no VD-2018-233, I-suite no 6474) and has been registered at ClinicalTrials.gov (NCT03623139).

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

6  
7 Data is owned by the investigators who are responsible for publishing the results. Positive and negative as well  
8 as inconclusive study results will be published by the investigators in international peer-reviewed journals, and  
9 all co-authors must comply with the Vancouver rules. BE will be responsible for writing the first draft of the  
10 manuscript based on the main study results as a first author under guidance by TV and JMB. The study results  
11 will be presented at relevant national and international scientific conferences and meetings and will be  
12 published in international peer-reviewed scientific journals.

13 Data sharing: Requests regarding dataset must be send to the corresponding author [bettina.ewers@regionh.dk](mailto:bettina.ewers@regionh.dk)

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4 1 **Authors' contributions:** BE conceived the original idea for this trial, planned the study design, performed the  
5 2 sample size calculations and wrote the first draft of the protocol manuscript. TV and JMB provided valuable  
6 3 input regarding trial design, planning and analytical considerations, and edited the first draft of the protocol  
7 4 manuscript. All authors approved the final version of the clinical trial protocol. BE is the principle investigator  
8 5 and is responsible for correspondence with all authorities regarding the study and is responsible for the data  
9 6 collection (recruitment, screening and clinical study examinations), overall monitoring the trial and for  
10 7 conducting the statistical analyses. TV and JMB are supervisors and coinvestigators of this trial. Should any  
11 8 safety concerns arise during the conduct of the study these will be brought to the attention of TV and JMB by  
12 9 BE and will be carefully reviewed.  
13  
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15 10  
16 11 **Funding statement:** This work was supported by The Beckett Foundation (grant number 17-2-0957), the Axel  
17 12 Muusfeldts Foundation (grant no 2017-856) and the Novo Nordisk Foundation (No assigned grant number) as  
18 13 part of a supplementary treatment initiative at SDCC in 2018-2020.  
19

20  
21 14 **Competing interests:** None of the authors have financial relationships with organizations that might have an  
22 15 interest in the submitted work, or other relationships or activities that could appear to have influenced the  
23 16 submitted work.  
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1 **Figure titles and legends (captions)**

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3 **Figure 1.** Study design

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5 **Figure 2.** Schematic diagram of the intervention

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7 BCC, basic carbohydrate counting; BP, blood pressure; BW, body weight; CGM, Continuous Glucose  
8 Monitoring; DXA, dual-energy-X-ray absorptiometry; V, visit; WHC, waist-hip circumference.

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

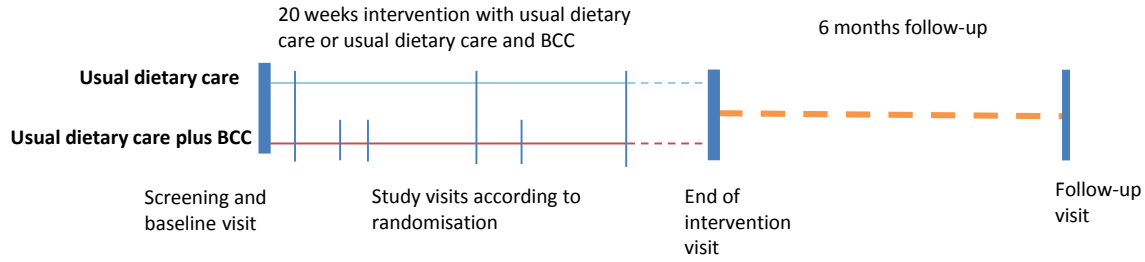
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12 BCC, basic carbohydrate counting.

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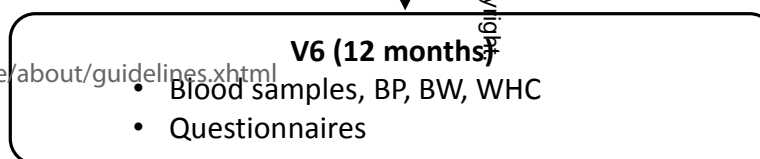
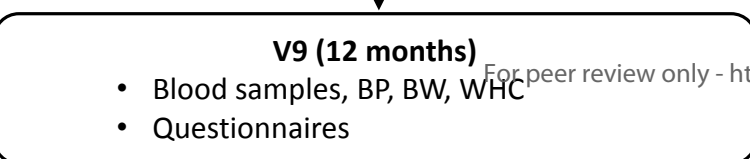
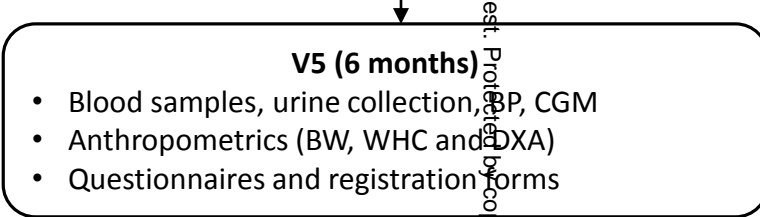
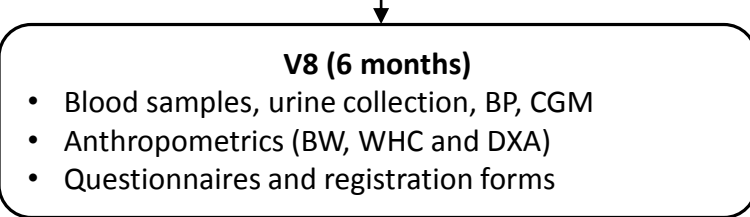
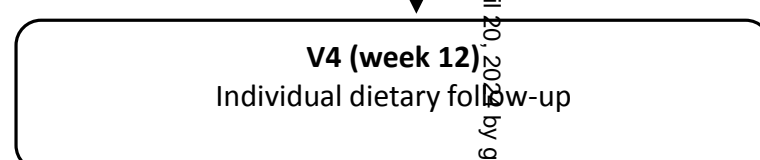
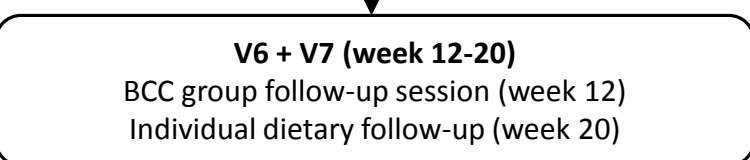
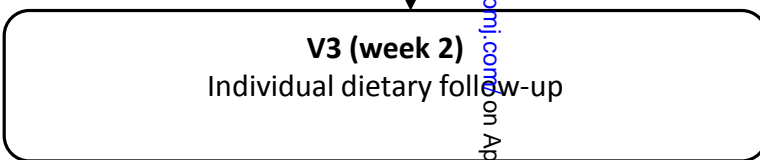
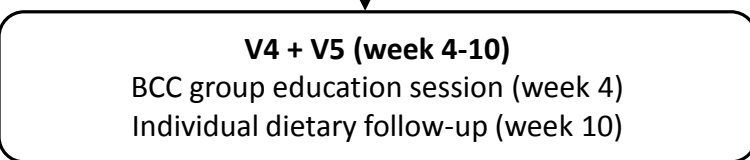
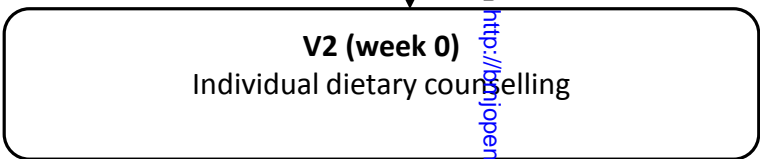
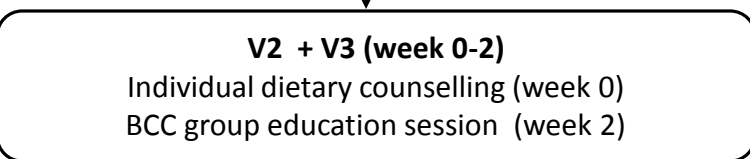
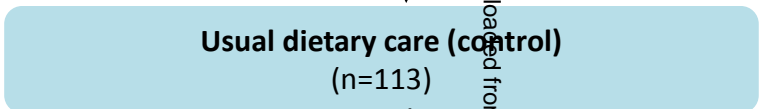
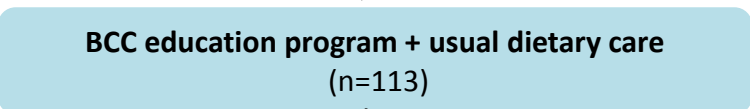
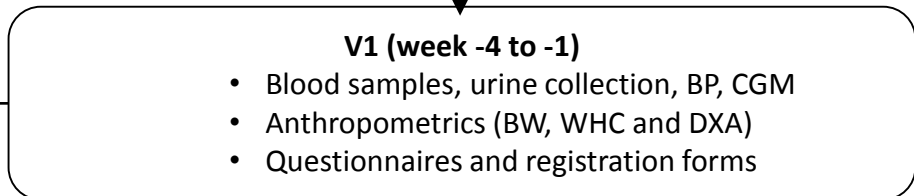
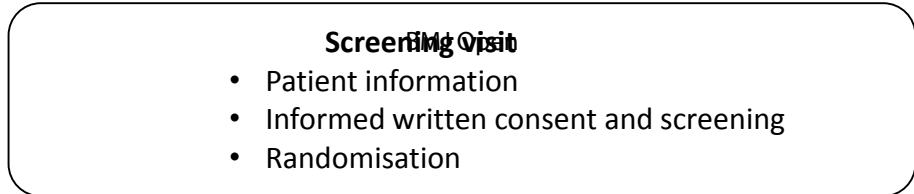
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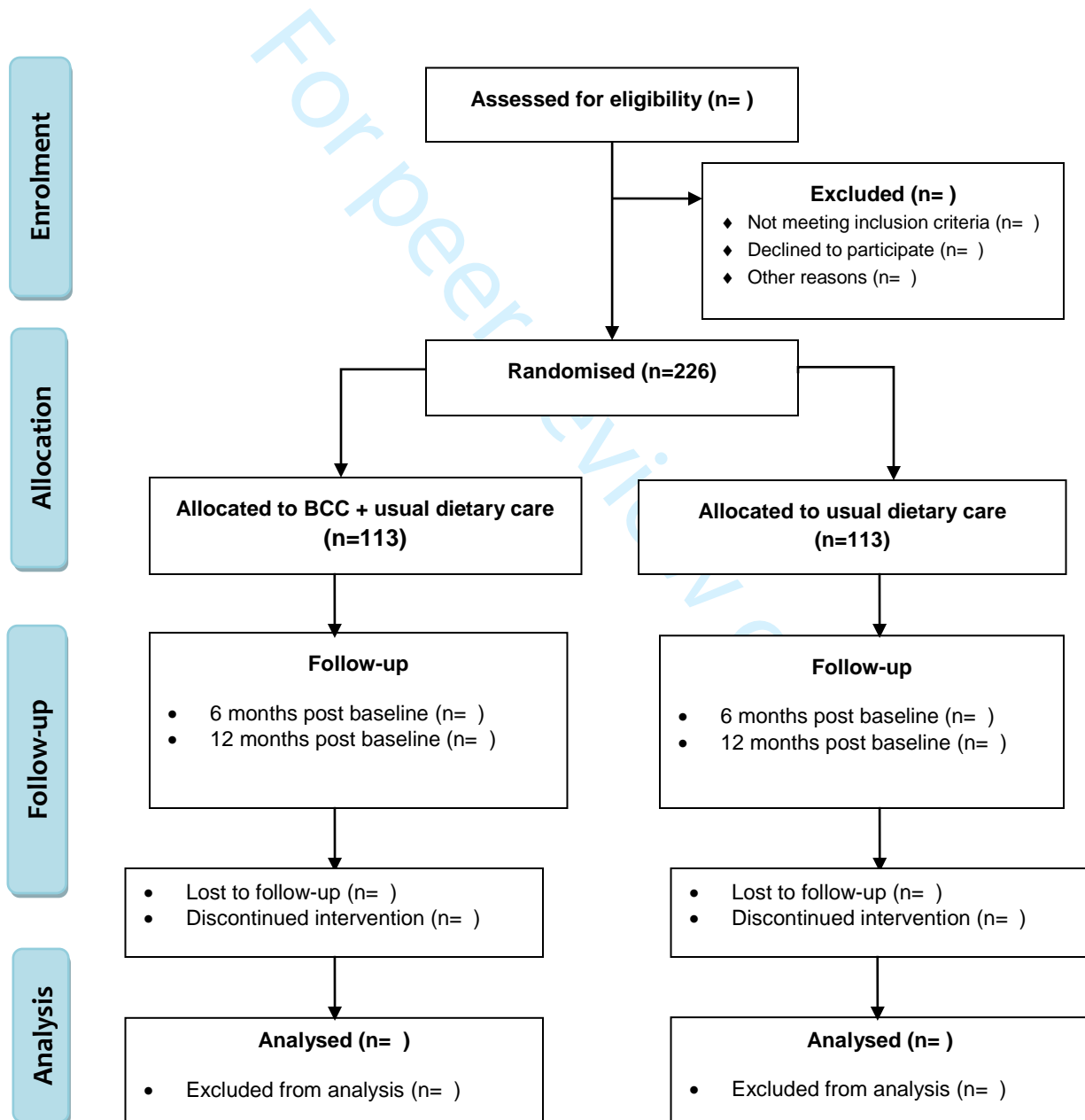
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STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description for the BCC study	Addressed on page number
<b>Administrative information</b>			
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 39___
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	___p 2___
	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___

## 1 Introduction

2			
3	Background and	6a	Description of research question and justification for undertaking the trial, including summary of relevant
4	rationale		studies (published and unpublished) examining benefits and harms for each intervention
5			_____p 9-10_____
6		6b	Explanation for choice of comparators
7			_____
8	Objectives	7	Specific objectives or hypotheses
9			_____p 11_____
10	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial or single group),
11			allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
12			_____p 13_____

## 14 Methods: Participants, interventions, and outcomes

15			
16	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will
17			be collected. Reference to where list of study sites can be obtained
18			_____p 18-19_____
19	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and
20			individuals who will perform the interventions (eg, surgeons, psychotherapists)
21			_____p 16_____
22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be
23			administered
24		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose
25			change in response to harms, participant request, or improving/worsening disease)
26			_____p 16_____
27		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence
28			(eg, drug tablet return, laboratory tests)
29			_____p 15_____
30		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
31			_____p 14_____
32	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood
33			pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg,
34			median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen
35			efficacy and harm outcomes is strongly recommended
36			_____p 12_____
37	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for
38			participants. A schematic diagram is highly recommended (see Figure)
39			Table 1 page 20,
40			Fig 2 page 25



1	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 31___
2				
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4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	___p 15___
5				
6	<b>Methods: Assignment of interventions (for controlled trials)</b>			
7	<b>Allocation:</b>			
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10	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 18___
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16	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___
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20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	___p 36___
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24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	___n/a___
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27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	___n/a___
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31	<b>Methods: Data collection, management, and analysis</b>			
32				
33	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 23-24___
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39		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 16-17___
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1	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 32___
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5	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 31___
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8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	___p 31___
9				
10		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 31___
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14	<b>Methods: Monitoring</b>			
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16	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 32-33___
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22		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 36___
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24				
25	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 33___
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28	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___
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32	<b>Ethics and dissemination</b>			
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34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	___p 32___
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37	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 34___
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	___p 17___
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4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	___p 29-30___
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7	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 32-33___
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10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	___p 39___
11				
12				
13	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 32___
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16	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___
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20	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	___p 37___
21				
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24		31b	Authorship eligibility guidelines and any intended use of professional writers	___p 32___
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26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	___n/a___
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29	<b>Appendices</b>			
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31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix 1, 2, 3, 4, 5
32				
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34	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 28-30___
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\*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](https://creativecommons.org/licenses/by/4.0/)" license. n/a, not relevant.

# BMJ Open

**Effects of basic carbohydrate counting vs. standard outpatient nutritional education (The BCC Study): study protocol for a randomized, parallel open-label, intervention study focusing on HbA1c and glucose variability in patients with type 2 diabetes**

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Keywords:	NUTRITION & DIETETICS, Carbohydrate awareness, Basic carbohydrate counting, Type 2 diabetes, Nutrition education, Randomized controlled trial

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4 Effects of basic carbohydrate counting vs. standard outpatient nutritional education (The BCC Study): study  
5 protocol for a randomised, parallel open-label, intervention study focusing on HbA1c and glucose variability  
6 in patients with type 2 diabetes  
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## Abstract

**Introduction:** Recommendations on energy intake are key in body weight management to improve glycaemic control in people with type 2 diabetes (T2D). International clinical guidelines recommend a variety of eating patterns to promote energy restriction as the primary dietetic approach to body weight control in managing T2D. In addition, individualized guidance on self-monitoring carbohydrate intake to optimize meal timing and food choices (e.g. basic carbohydrate counting (BCC)) is recommended to achieve glycaemic control. However, the evidence for this approach in T2D is limited. The objective of this study is to compare the effect of an educational program in BCC as add-on to the usual dietary care on glycaemic control in people with T2D.

**Methods and analyses:** The study is designed as a randomised, controlled trial with a parallel-group design. The study duration is 12 months with data collection at baseline, and after 6 and 12 months. We plan to include 226 adults with T2D. Participants will be randomised to one of two interventions: 1) BCC as add-on to usual dietary care, or 2) usual dietary care. The primary outcome is changes in glycated haemoglobin A1c (HbA1c) or mean amplitude of glycaemic excursions (MAGE) from baseline and after 6 months intervention between and within study groups. Further outcome measures include changes in 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 diet and 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 NCT03623139.

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### Strengths and limitations of this study

1. The study has a long-term follow-up and will provide knowledge on the effects of BCC in people with T2D
2. The study applies well-documented measures of glycaemic control as effect-parameters
3. The results obtained have applicability beyond Denmark in the Caucasian population and has the potential to be included in the recommendations in future T2D 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 participants in the control group for 1 year
5. The difference in the number of hours and type of dietary education and support between the two groups may also influence the participants’ learning and knowledge.



## 1 Introduction

Body weight management is central in managing people with type 2 diabetes (T2D) and even a modest weight loss is recommended to improve glycaemic control and reduce the need for glucose-lowering medication in people with T2D (1-3). Accordingly, the national and international clinical guidelines for managing T2D recommend energy restriction as the primary dietetic approach for body weight control to improve metabolic control with no recommendations concerning the dietary distribution of energy from carbohydrates, fat, and proteins (1, 3, 4). However, carbohydrates are the main energy contributing nutrients in our diet with the highest impact on plasma glucose levels and the total amount of carbohydrates consumed in a meal is a significant predictor for the postprandial glucose response; furthermore, both the quantity and quality (e.g. dietary fibre, added sugar and glycaemic index) of carbohydrates influence plasma glucose levels (5, 6). In contrast, protein, fat, and alcohol have more limited effects on postprandial plasma glucose levels but obviously have a significant impact on the total energy balance (5, 6). Thus, monitoring the dietary intake of carbohydrates is crucial to control postprandial glucose fluctuations, which may lead to clinical benefits such as a reduction in plasma glucose variability, the number of hyperglycaemic episodes and thereby improvements in glycated haemoglobin A1c (HbA1c).

Accordingly, the European and American clinical guidelines recommend that people with T2D receive individualized guidance on self-monitoring carbohydrate intake to optimize meal timing and food choices based on their current dietary intake and glucose-lowering medication (3). This may include carbohydrate counting or similar methods for achieving glycaemic control in people with T2D (5-8).

Two levels of carbohydrate counting have been defined internationally with different learning objectives and increasing complexity: a basic and an advanced level (9-11). Basic carbohydrate counting (BCC) is a method aiming at increasing carbohydrate awareness. People with diabetes are educated in how to manage a consistent carbohydrate intake regarding time and amount, which foods are rich in carbohydrates, and how to read food labels and estimate carbohydrate portion sizes accurately. BCC aims to improve overall glycaemic control. Advanced carbohydrate counting (ACC) is targeted at the individual who ideally masters BCC and is on intensive insulin therapy and prepared to learn how to match mealtime insulin dosing according to carbohydrate intake using carbohydrate-insulin ratios and sensitivity factor. In other words, the ACC concept does not apply to all people with T2D because of the complex treatment regimens (e.g. oral antidiabetic agents or other types of insulin than fast-acting meal insulins), potential patient barriers (e.g. difficulties in implementing the method in a real-life context), lack of motivation to learn the method (e.g. too time consuming to match insulin according to the carbohydrate content in each meal, or do pre- and postprandial plasma glucose monitoring), and low levels of education, literacy and/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. In the clinical guidelines and human studies, the term "carbohydrate counting" is often used synonymously with ACC. Systematic reviews and meta-analyses of randomised controlled trials (RCTs) have shown that ACC can improve HbA1c in people with type 1 diabetes (T1D) (12-14). Only a few RCTs (15, 16) have investigated the effect of ACC in people with T2D on intensive insulin therapy and found limited effects on HbA1c, while only one recent RCT has investigated the effect of BCC in people with T2D and found an effect on HbA1c only in a subgroup of the study population (17). These study results need to be confirmed.

Accurate portion-size estimation is an important skill in BCC to obtain consistency in the daily carbohydrate intake and is also an important component of body weight management. Recent studies suggest that lower

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4 1 literacy and numeracy skills are associated with poorer portion size estimation skills and understanding of food  
5 2 labels, increased body mass index (BMI), and poorer diabetes-related self-management abilities (18-22).  
6 3 Studies have found that people with diabetes frequently assess their intake of carbohydrates inaccurately and  
7 4 this has been associated with a poorer HbA1c (23-25). In particular mixed meals, energy-dense foods, and  
8 5 larger portion sizes resulted in inaccurate carbohydrate estimation. Thus, carbohydrate awareness and  
9 6 monitoring including gram counting, experience-based estimation of high-carbohydrate foods and practising  
10 7 numeracy skills seems to be important for obtaining better plasma glucose control. Increased carbohydrate  
11 8 awareness may also lead to a reduced carbohydrate consumption and thus a reduced energy intake, which has  
12 9 been shown to be an efficient dietary approach in people with T2D for body weight loss and improvement in  
13 10 HbA1c at least in the short term (<1 year) (3). The short-term effects of low-carbohydrate diets may be due to  
14 11 a decline in dietary adherence over time indicating that the recommended intake of carbohydrates should be  
15 12 individualised and based on an assessment of the patient's current eating patterns and preferences as practised  
16 13 in the BCC concept. Diabetes management requires many daily self-management activities including  
17 14 managing dietary intake, and long-term dietary adherence remains a key challenge for most dietary  
18 15 interventions. Nutrition therapy is a fundamental part of diabetes self-management education and support to  
19 16 help empower and support people in managing their diabetes to improve glycaemic control (2). This may be  
20 17 accomplished by including skills training and social support for maintaining dietary changes. Evidence suggest  
21 18 that a hands-on, learning-by-doing approach (problem- and experience-based patient education) can support  
22 19 the development of food skills in general and improve diet quality in particular (26). Adding group-based  
23 20 dietary approaches to individual lifestyle counselling has also been found to improve dietary habits (27).  
24 21 Similarly, adding diabetes self-management approaches to the diabetes education has led to lower dropout  
25 22 rates, increased self-efficacy and improved HbA1c in people with T2D (28). One study also found that  
26 23 perceived competence in managing diabetes as predicted by the degree to which people experienced the health-  
27 24 care climate to be autonomy supportive and the perceived competence predicted HbA1c (29).  
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37 27 The sparse scientific knowledge about the effect of group-approaches with practiced-focused nutrition  
38 28 education and the BCC concept underlines the need for investigating and evaluating this in a practice-based  
39 29 group educational approach and examining the effect on improved metabolic control in people with T2D.  
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#### 42 31 **Aim**

43 32 The aim is to examine the effectiveness of a group-based dietitian-led practise-focused educational approach  
44 33 for dietary self-management compared to the standard nutrition education on glycaemic control in people with  
45 34 T2D.  
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#### 50 36 **Methods and analysis**

##### 51 37 **Study design**

52 38 The study is as a randomised controlled intervention trial with a parallel-group design (figure 1).  
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55 39 For each participant the study duration is 12 months and includes up to nine visits at the study site (figure 2).  
56 40 All participants will be instructed to maintain their habitual lifestyle in all other aspects than their diet, e.g.  
57 41 keeping the same level of physical activity as habitually during the study period. All participants will be  
58 42 instructed to follow their regular diabetes care in the hospital, which usually includes four yearly visits with a  
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4 1 diabetologist (endocrinologist) and one yearly consultation with a diabetes nurse. Participants will be  
5 2 instructed not to receive any further dietary education during the study period. Close relatives can participate  
6 3 in the dietary education in both study groups if the participant needs support to manage dietary changes.

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9 4 The study flow is presented in figure 3. The study follows the guidelines of Standard Protocol Items for  
10 5 Randomised Trials (SPIRIT).

#### 11 6 12 7 Setting

13 8 The study will be carried out at the outpatient clinic at Steno Diabetes Center Copenhagen (SDCC) in Gentofte,  
14 9 Denmark.

#### 16 10 Recruitment and consent

17 11 As a temporary supplementary treatment initiative, SDCC offers courses in BCC for people with T2D treated  
18 12 at SDCC. Participants for the current study will be recruited among people signing up for these courses or  
19 13 people directly referred to one of the courses or the study by a health care professional (diabetologist, diabetes  
20 14 nurse or dietitian) from SDCC. A course administrator at SDCC will contact all interested or referred people  
21 15 by telephone and provide information about the study. In addition, potential study participants will be recruited  
22 16 through information on sdcc.dk and other electronic media or patient-related networks. If the person is  
23 17 interested in the study, the person will receive the written information by mail or e-mail. If interested in study  
24 18 participation, the study investigator/study personnel will schedule a personal meeting for oral information,  
25 19 offering the possibility of bringing a confidant. The person will be given time to discuss any questions and will  
26 20 be informed that he/she has at least 24 hours to decide on participation in the study. If the person decides to  
27 21 participate in the study, the person and the study investigator/study personnel will sign the written informed  
28 22 consent, and the investigator/study personnel will perform a screening. If all inclusion criteria are fulfilled and  
29 23 none of the exclusion criteria are met, the person will be included in the study and randomised to one of the  
30 24 groups. People who decline to participate or do not meet the inclusion criteria will continue their usual care in  
31 25 an outpatient diabetes clinic and will be offered to participate on a BCC course if they still wish to do so.  
32 26 Participants will be informed that participation is voluntary, and that they may withdraw their consent at any  
33 27 time.

#### 39 28 40 29 Inclusion criteria

41 30 People with T2D between 18-75 years with a diabetes duration of at least 12 months and baseline HbA1c of  
42 31 53-97 mmol/mol treated with diet or any glucose-lowering medication are eligible for the study.

#### 44 32 45 33 Exclusion criteria

46 34 People are excluded if they have other types of diabetes than T2D, are practicing carbohydrate counting as  
47 35 judged by the investigator, have a low daily intake of carbohydrates (defined as below 25 E% or 100 g/day),  
48 36 have participated in a BCC group program within the last two years, use an automated bolus calculator, have  
49 37 gastroparesis, have uncontrolled medical issues affecting dietary intake as judged by the investigator or a  
50 38 medical expert. Women who are pregnant or breastfeeding or have plans of pregnancy within the study period  
51 39 are also excluded. Furthermore, people who are either participating in other clinical studies or are unable to  
52 40 understand the informed consent and the study procedures will be excluded.

## 1 Randomisation

2 Participants eligible for inclusion in the study will be randomly allocated in a 1:1 ratio to one of the two groups  
3 (BCC or control) using a computer-generated randomization in the software program *REDCap*. The  
4 randomization is done by stratifying participants based on sex (male or female), BMI (<30 kg/m<sup>2</sup> or ≥ 30  
5 kg/m<sup>2</sup>) and HbA1c (<70 mmol/mol or ≥ 70 mmol/mol) at baseline. The randomization is done in blocks in to  
6 order to ensure an equal number of participants in each group.

## 7 Intervention group

8 Participants will receive education in BCC in addition to the standard outpatient nutrition education as  
9 described for the control group. The BCC program consists of two sessions of three hours and a follow-up  
10 group session of two hours. The BCC program uses trained dietitians following a planned curriculum which  
11 include experience-based learning with problem-solving exercises, hands-on activities, short theoretical  
12 presentations, discussions of motivational aspects and coping strategies. The BCC program integrates peer  
13 modelling, skills development, goal setting, observational learning and social support into the program content  
14 and activities. The training includes identifying carbohydrates in food, reading carbohydrate tables, calculating  
15 the carbohydrate content from food labels, tables and applications (app) for smartphones and use of a  
16 personalized carbohydrate plan with guiding suggestions for daily intake of carbohydrates at meals based on  
17 personal dietary recordings including plasma glucose measurements. An app from the Danish Diabetes  
18 Association (*Diabetes og Kulhydrattælling*<sup>®</sup>. The Danish Diabetes Association's app, Pragma soft A/S,  
19 available in Google Play<sup>®</sup> and App Store<sup>®</sup> 12/2014, Free) will be introduced to support estimation and  
20 calculation of carbohydrates.

## 21 Control group

22 Participants randomised to the control group will receive current standard outpatient nutrition education in  
23 T2D. This includes individual guidance by a trained dietitian, with one initial 60 minutes dietary counselling  
24 session and two individual 30 minutes follow-up session. The individual guidance is based on the overall  
25 treatment goal and the defined personal dietary goals for behavioural change according to personal preferences.  
26 Dietary guidance includes topics such as healthy dietary habits and weight loss approaches for replacement of  
27 energy-dense foods with low energy-dense foods or special attention to carbohydrate quality (e.g. glycaemic  
28 index and dietary fibre intake), fat quality and other dietary recommendations according to personal needs.

## 29 Data collection

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

40 The primary outcome is the difference in mean HbA1c or mean amplitude of glycaemic excursions (MAGE)  
41 from baseline to end of the intervention (6 month) between and within each of the two study groups (BCC and  
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control). MAGE is used as a measure of glycaemic variability to capture mealtime-related glucose excursions. MAGE has been associated with coronary artery disease independent of HbA1c (30, 31).

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 wk	3 mo	6 mo	12 mo
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; mo=months; PG=plasma glucose; Q=Questionnaire; wk=weeks.

\*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 (>10.0 mmol/l) and standard deviation of mean plasma glucose assessed from CGM measurements.

**Blood and urine samples:** HbA1c (after 12 weeks and 12 months), 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 people with diabetes (32). 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



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1 interpreter with a background as a clinical dietitian and an expert panel of six clinical dietitians working with  
2 diabetes. This was followed by a pilot testing by 10 people with diabetes.

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4 *Perceived Competencies in Diabetes Scale (PCS)*: The PCS is a validated scale (33) which includes four items  
5 that reflect participants' feelings of competence about engaging in a healthier behaviour and participating in a  
6 nutritional education program. Forward and backward linguistic translation from English to Danish has been  
7 done according to standard procedures in 2001 under the guidance of Professor Vibeke Zoffmann.

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

11 *Carbohydrate photographic questionnaire (CPQ)*: The CPQ is an electronic questionnaire assessing skills in  
12 correct estimation of portion sizes of 11 commonly eaten high-carbohydrate foods. The CPQ has been  
13 developed and validated against real food in 87 people with diabetes. The study results by Ewers et al. has  
14 been accepted for publication in Journal of Nutrition and Food Science in September 2019.

15 *Mathematical literacy questionnaire*: A 10-item test with modified questions from the nutrition domain of the  
16 *Diabetes Numeracy Test (DNT)* (34) was designed and feasibility tested to investigate mathematical literacy  
17 including numeracy skills (addition, subtraction, division and multiplication) which are essential for  
18 understanding numbers and applying mathematical skills in daily life e.g. for calculating carbohydrates.

19 *International Physical Activity Questionnaire Short Form (IPAQ SF)*: The Danish version of the IPAQ SF (35)  
20 will be used to assess changes in level of physical activity during the study period.

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

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

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

#### 30 Data analysis plan

31 The trial is ongoing. The recruitment started in October 2018 and is expected to be completed by October  
32 2021.

#### 33 Sample size calculation

34 A power calculation was conducted based on the primary outcome measures HbA1c and MAGE. Allowing  
35 for an estimated drop-out rate of 30% and subgroup analyses the sample size was planned to include a total of  
36 226 people in the study (113 in each arm). This was based on a sample size calculation which suggested that  
37 including 87 participants in each of the study groups would give 80% power to detect a difference in change  
38 in HbA1c of 3.0 mmol/mol between the BCC group versus the control group with a 5% significance level  
39 using a two-sided test and an estimated standard deviation (SD) of 7 mmol/mol. The used SD and dropout rate

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4 1 were based on previous BCC courses at SDCC where mean changes and SD of HbA1c after 6 months were  
5 2 calculated based on completers with T2D. MAGE has only been used as an outcome measure of glucose  
6 3 variability in a few randomised controlled dietary intervention studies of people with diabetes (36, 37) showing  
7 4 differences in changes in MAGE up to 4.8 mmol/l (SD: 1.0) after a 12-week carbohydrate counting  
8 5 intervention (36), but is regularly used in other clinical studies evaluating glucose variability. By including  
9 6 113 participants in each study group we will have a power of 80% (alpha level of 0.05) in a two-sided test to  
10 7 detect a difference in the change in MAGE during the intervention period (6 months) of  $\geq 0.30$  mmol/l (SD 0.7  
11 8 mmol/l) between the two study groups.  
12 9

#### 16 10 Statistical methods

17 11 Analysis and reporting of the study results will follow the CONSORT (Consolidated Standards of Reporting  
18 12 Trials) guidelines for reporting parallel group randomised trials (38). Results will be presented as means (SD)  
19 13 for normally distributed variables and as medians (inter-quartile range) for non-normally distributed variables.  
20 14 Paired samples t-test will be used to compare baseline data between and within the two study groups for normal  
21 15 data and Wilcoxon signed rank test for non-normal data. Mixed-effect models will be used to test differences  
22 16 in outcomes from baseline to follow-up to take repeated measurements into account. If model assumptions  
23 17 cannot be met even after logarithmic transformation, non-parametric tests will be used. Examinations of the  
24 18 relevant diagnostic plots, including QQ-plots, will be used to evaluate normality of the residuals.  
25 19

26 20 The baseline demographics as well as clinical and diabetes-related characteristics of the intervention and the  
27 21 control groups will be presented and compared. The average changes between baseline and 6 months, and 12  
28 22 months in primary and secondary outcomes will be calculated for each of the groups. Intention-to-treat (ITT)  
29 23 analysis will be performed as the primary analysis on all primary and secondary outcomes after the last  
30 24 participant has ended participation. Missing values will be handled with a last observation carried forward  
31 25 approach for ITT analysis with the use of the multiple imputation approach in a sensitivity analysis. Per-  
32 26 protocol (PP) analysis will only be performed in case of sensitivity testing. Metabolic patterns will be tested  
33 27 with multivariate statistics. Adjustment for relevant confounders will be performed including adjustment for  
34 28 the stratified variables. Heterogeneity in responsiveness to the interventions will be tested by dividing each  
35 29 intervention group into smaller groups based on data distribution (medians) or clinically meaningful cut-points.  
36 30 Two-sided tests will be used. *P* values of  $< 0.05$  are considered significant. The statistical programs SPSS and  
37 31 SAS will be used for data analysis.  
38 32

39 33 **Patient and public involvement:** People were involved in developing the educational content of the program  
40 34 in basic carbohydrate counting. People were not involved in setting the research questions or the outcome  
41 35 measures, nor were they involved in developing the study design. Information may be disseminated to the  
42 36 public via any media coverage of study findings.  
43 37

#### 44 38 Ethics and dissemination

45 39 The study will be conducted in accordance with the ethical principles in the Declaration of Helsinki and to the  
46 40 regulations for Good Clinical Practice (GCP) to the extent that this is relevant for non-medical studies. The  
47 41 study has been approved by the Ethics Committee of the Capital Region, Copenhagen (#H-18014918), has  
48 42 been approved for data storage by the Danish Data Protection Agency (journal no VD-2018-233, I-suite no  
49 43 6474) and has been registered at ClinicalTrials.gov (NCT03623139).  
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1 All health-related matters and sensitive personal data will be handled in accordance with the Danish “Act on  
2 Processing of Personal Data”. All health-related matters and sensitive personal data (blood test results etc.)  
3 will be depersonalized. All participants will be given a study number referring to their personal information,  
4 which will be stored securely and separately. Data will be stored in coded form for 10 years after last participant  
5 has attended the last visit, after which the data will be fully anonymised.

6  
7 Data is owned by the investigators who are responsible for publishing the results. Positive and negative as well  
8 as inconclusive study results will be published by the investigators in international peer-reviewed journals, and  
9 all co-authors must comply with the Vancouver rules. BE will be responsible for writing the first draft of the  
10 manuscript based on the main study results as a first author under guidance by TV and JMB. The study results  
11 will be presented at relevant national and international scientific conferences and meetings and will be  
12 published in international peer-reviewed scientific journals.

13 Data sharing: Requests regarding dataset must be send to the corresponding author [bettina.ewers@regionh.dk](mailto:bettina.ewers@regionh.dk)

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4 1 **Authors' contributions:** BE conceived the original idea for this trial, planned the study design, performed the  
5 2 sample size calculations and wrote the first draft of the protocol manuscript. TV and JMB provided valuable  
6 3 input regarding trial design, planning and analytical considerations, and edited the first draft of the protocol  
7 4 manuscript. All authors approved the final version of the clinical trial protocol. BE is the principle investigator  
8 5 and is responsible for correspondence with all authorities regarding the study and is responsible for the data  
9 6 collection (recruitment, screening and clinical study examinations), overall monitoring the trial and for  
10 7 conducting the statistical analyses. TV and JMB are supervisors and coinvestigators of this trial. Should any  
11 8 safety concerns arise during the conduct of the study these will be brought to the attention of TV and JMB by  
12 9 BE and will be carefully reviewed.  
13  
14

15 10  
16 11 **Funding statement:** This work was supported by The Beckett Foundation (grant number 17-2-0957), the Axel  
17 12 Muusfeldts Foundation (grant no 2017-856) and the Novo Nordisk Foundation (No assigned grant number) as  
18 13 part of a supplementary treatment initiative at SDCC in 2018-2020.  
19  
20

21 14 **Competing interests:** None of the authors have financial relationships with organizations that might have an  
22 15 interest in the submitted work, or other relationships or activities that could appear to have influenced the  
23 16 submitted work.  
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1 **Figure titles and legends (captions)**

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3 **Figure 1.** Study design

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5 **Figure 2.** Schematic diagram of the intervention

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7 BCC, basic carbohydrate counting; BP, blood pressure; BW, body weight; CGM, Continuous Glucose  
8 Monitoring; DXA, dual-energy-X-ray absorptiometry; V, visit; WHC, waist-hip circumference.

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

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12 BCC, basic carbohydrate counting.

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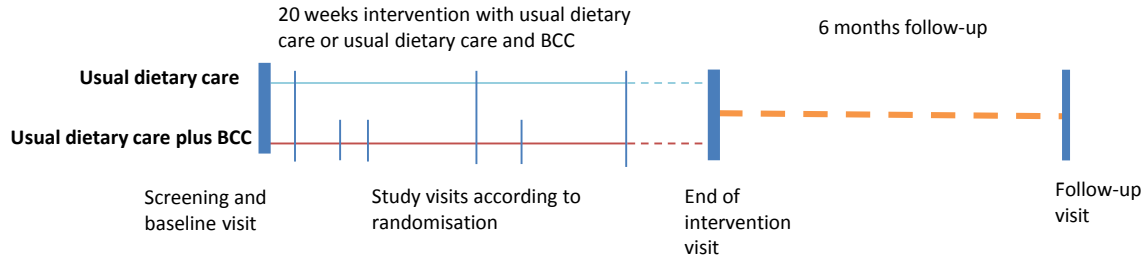
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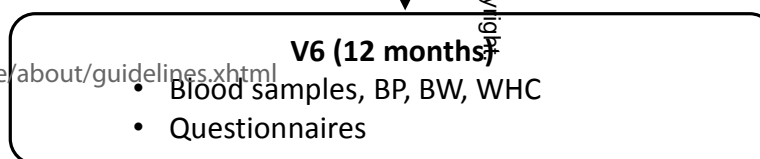
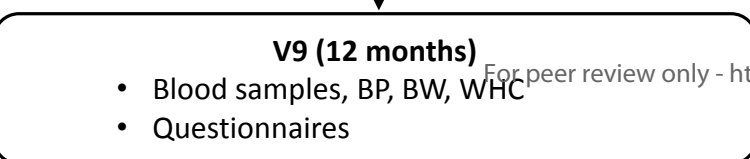
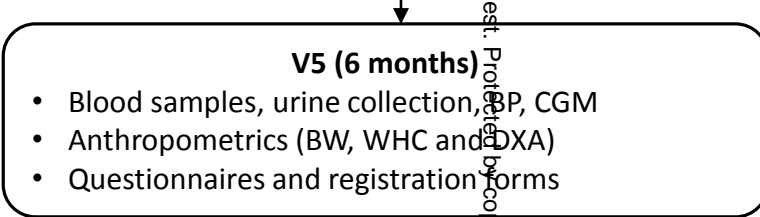
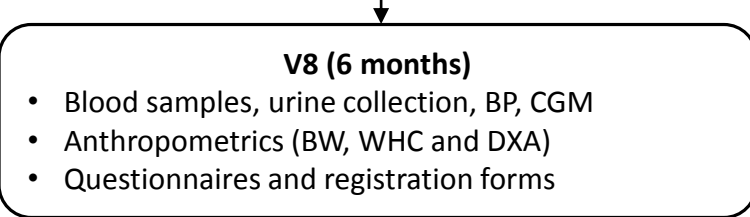
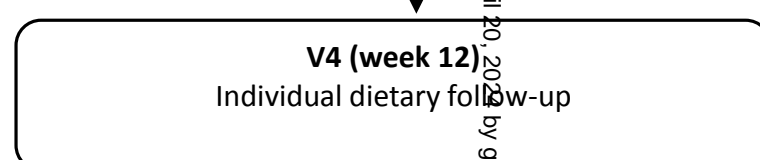
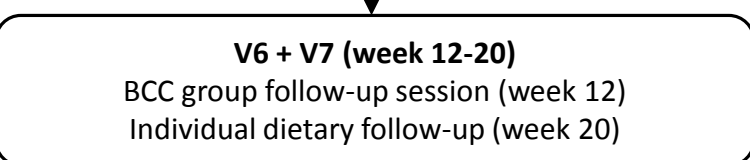
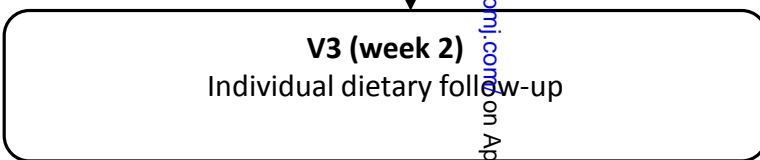
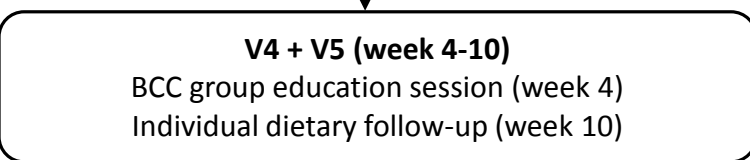
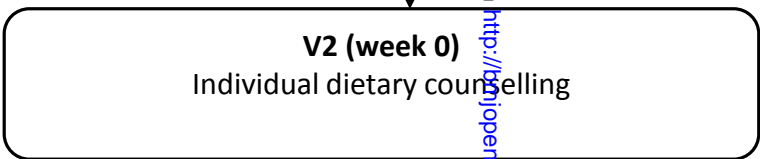
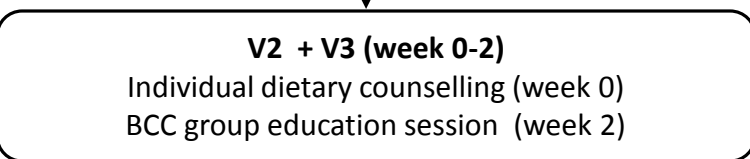
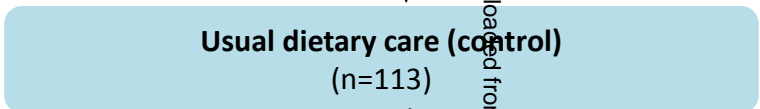
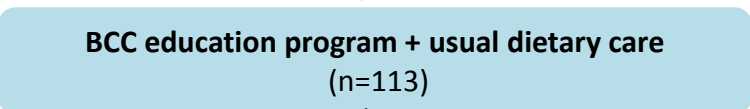
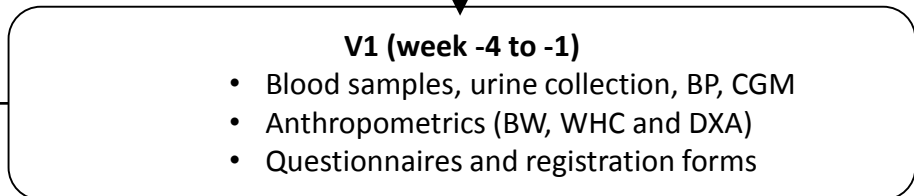
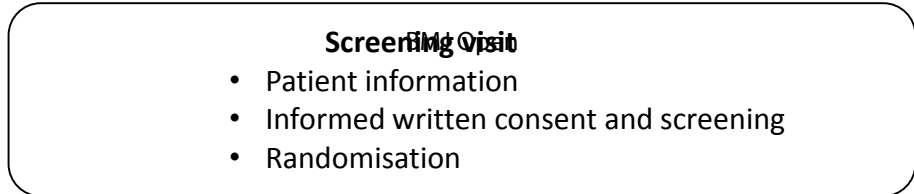
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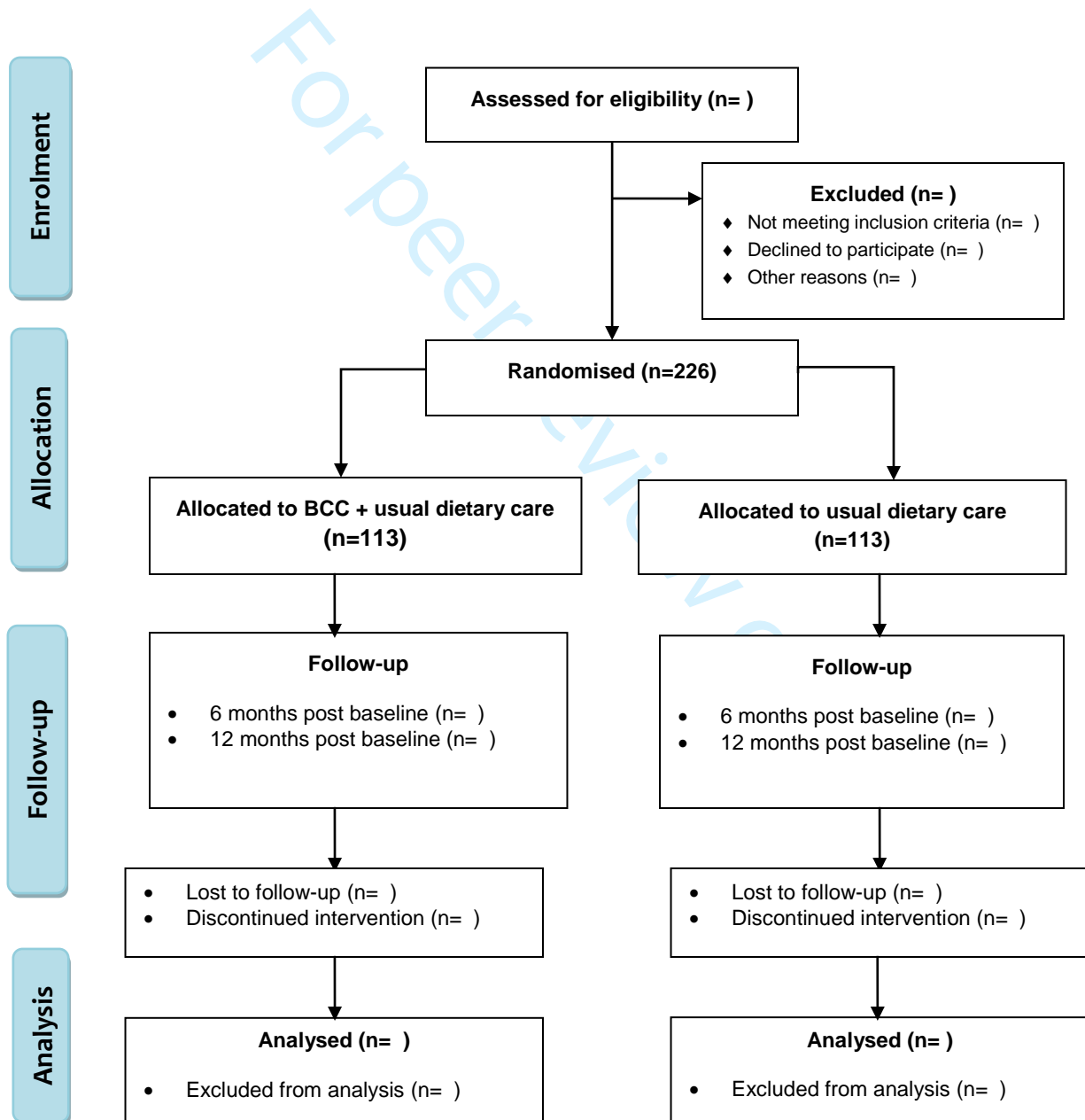
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STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description for the BCC study	Addressed on page number
<b>Administrative information</b>			
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 39___
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	___p 2___
	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___

## 1 Introduction

2			
3	Background and	6a	Description of research question and justification for undertaking the trial, including summary of relevant
4	rationale		studies (published and unpublished) examining benefits and harms for each intervention
5			_____p 9-10_____
6		6b	Explanation for choice of comparators
7			_____
8	Objectives	7	Specific objectives or hypotheses
9			_____p 11_____
10	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial or single group),
11			allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
12			_____p 13_____

## 14 Methods: Participants, interventions, and outcomes

15			
16	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will
17			be collected. Reference to where list of study sites can be obtained
18			_____p 18-19_____
19	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and
20			individuals who will perform the interventions (eg, surgeons, psychotherapists)
21			_____p 16_____
22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be
23			administered
24		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose
25			change in response to harms, participant request, or improving/worsening disease)
26			_____p 16_____
27		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence
28			(eg, drug tablet return, laboratory tests)
29			_____p 15_____
30		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
31			_____p 14_____
32	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood
33			pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg,
34			median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen
35			efficacy and harm outcomes is strongly recommended
36			_____p 12_____
37	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for
38			participants. A schematic diagram is highly recommended (see Figure)
39			Table 1 page 20,
40			Fig 2 page 25

1	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 31___
2				
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4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	___p 15___
5				
6	<b>Methods: Assignment of interventions (for controlled trials)</b>			
7	<b>Allocation:</b>			
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10	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 18___
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16	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___
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20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	___p 36___
21				
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24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	___n/a___
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27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	___n/a___
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31	<b>Methods: Data collection, management, and analysis</b>			
32				
33	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 23-24___
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39		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 16-17___
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1	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 32___
2				
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5	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 31___
6				
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8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	___p 31___
9				
10		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 31___
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14	<b>Methods: Monitoring</b>			
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16	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 32-33___
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22		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 36___
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25	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 33___
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28	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___
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32	<b>Ethics and dissemination</b>			
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34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	___p 32___
35				
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37	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 34___
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	___p 17___
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4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	___p 29-30___
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7	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 32-33___
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10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	___p 39___
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13	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 32___
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16	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___
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20	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	___p 37___
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24		31b	Authorship eligibility guidelines and any intended use of professional writers	___p 32___
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26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	___n/a___
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29	<b>Appendices</b>			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix 1, 2, 3, 4, 5
32				
33				
34	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 28-30___
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\*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](https://creativecommons.org/licenses/by/4.0/)" license. n/a, not relevant.

# BMJ Open

**Effects of basic carbohydrate counting vs. standard outpatient nutritional education (The BCC Study): study protocol for a randomized, parallel open-label, intervention study focusing on HbA1c and glucose variability in patients with type 2 diabetes**

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4 Effects of basic carbohydrate counting vs. standard outpatient nutritional education (The BCC Study): study  
5 protocol for a randomised, parallel open-label, intervention study focusing on HbA1c and glucose variability  
6 in patients with type 2 diabetes  
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## Abstract

**Introduction:** Recommendations on energy intake are key in body weight management to improve glycaemic control in people with type 2 diabetes (T2D). International clinical guidelines recommend a variety of eating patterns to promote energy restriction as the primary dietetic approach to body weight control in managing T2D. In addition, individualized guidance on self-monitoring carbohydrate intake to optimize meal timing and food choices (e.g. basic carbohydrate counting (BCC)) is recommended to achieve glycaemic control. However, the evidence for this approach in T2D is limited. The objective of this study is to compare the effect of an educational program in BCC as add-on to the usual dietary care on glycaemic control in people with T2D.

**Methods and analyses:** The study is designed as a randomised, controlled trial with a parallel-group design. The study duration is 12 months with data collection at baseline, and after 6 and 12 months. We plan to include 226 adults with T2D. Participants will be randomised to one of two interventions: 1) BCC as add-on to usual dietary care, or 2) usual dietary care. The primary outcome is changes in glycated haemoglobin A1c (HbA1c) or mean amplitude of glycaemic excursions (MAGE) from baseline and after 6 months intervention between and within study groups. Further outcome measures include changes in 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 diet and 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 NCT03623139.

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### Strengths and limitations of this study

1. The study has a long-term follow-up and will provide knowledge on the effects of BCC in people with T2D
2. The study applies well-documented measures of glycaemic control as effect-parameters
3. The results obtained have applicability beyond Denmark in the Caucasian population and has the potential to be included in the recommendations in future T2D 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 participants in the control group for 1 year
5. The difference in the number of hours and type of dietary education and support between the two groups may also influence the participants’ learning and knowledge.

## 1 Introduction

Body weight management is central in managing people with type 2 diabetes (T2D) and even a modest weight loss is recommended to improve glycaemic control and reduce the need for glucose-lowering medication in people with T2D (1-3). Accordingly, the national and international clinical guidelines for managing T2D recommend energy restriction as the primary dietetic approach for body weight control to improve metabolic control with no recommendations concerning the dietary distribution of energy from carbohydrates, fat, and proteins (1, 3, 4). However, carbohydrates are the main energy contributing nutrients in our diet with the highest impact on plasma glucose levels and the total amount of carbohydrates consumed in a meal is a significant predictor for the postprandial glucose response; furthermore, both the quantity and quality (e.g. dietary fibre, added sugar and glycaemic index) of carbohydrates influence plasma glucose levels (5, 6). In contrast, protein, fat, and alcohol have more limited effects on postprandial plasma glucose levels but obviously have a significant impact on the total energy balance (5, 6). Thus, monitoring the dietary intake of carbohydrates is crucial to control postprandial glucose fluctuations, which may lead to clinical benefits such as a reduction in plasma glucose variability, the number of hyperglycaemic episodes and thereby improvements in glycated haemoglobin A1c (HbA1c).

Accordingly, the European and American clinical guidelines recommend that people with T2D receive individualized guidance on self-monitoring carbohydrate intake to optimize meal timing and food choices based on their current dietary intake and glucose-lowering medication (3). This may include carbohydrate counting or similar methods for achieving glycaemic control in people with T2D (5-8).

Two levels of carbohydrate counting have been defined internationally with different learning objectives and increasing complexity: a basic and an advanced level (9-11). Basic carbohydrate counting (BCC) is a method aiming at increasing carbohydrate awareness. People with diabetes are educated in how to manage a consistent carbohydrate intake regarding time and amount, which foods are rich in carbohydrates, and how to read food labels and estimate carbohydrate portion sizes accurately. BCC aims to improve overall glycaemic control. Advanced carbohydrate counting (ACC) is targeted at the individual who ideally masters BCC and is on intensive insulin therapy and prepared to learn how to match mealtime insulin dosing according to carbohydrate intake using carbohydrate-insulin ratios and sensitivity factor. In other words, the ACC concept does not apply to all people with T2D because of the complex treatment regimens (e.g. oral antidiabetic agents or other types of insulin than fast-acting meal insulins), potential patient barriers (e.g. difficulties in implementing the method in a real-life context), lack of motivation to learn the method (e.g. too time consuming to match insulin according to the carbohydrate content in each meal, or do pre- and postprandial plasma glucose monitoring), and low levels of education, literacy and/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. In the clinical guidelines and human studies, the term “carbohydrate counting” is often used synonymously with ACC. Systematic reviews and meta-analyses of randomised controlled trials (RCTs) have shown that ACC can improve HbA1c in people with type 1 diabetes (T1D) (12-14). Only a few RCTs (15, 16) have investigated the effect of ACC in people with T2D on intensive insulin therapy and found limited effects on HbA1c, while only one recent RCT has investigated the effect of BCC in people with T2D and found an effect on HbA1c only in a subgroup of the study population (17). These study results need to be confirmed.

Accurate portion-size estimation is an important skill in BCC to obtain consistency in the daily carbohydrate intake and is also an important component of body weight management. Recent studies suggest that lower

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4 1 literacy and numeracy skills are associated with poorer portion size estimation skills and understanding of food  
5 2 labels, increased body mass index (BMI), and poorer diabetes-related self-management abilities (18-22).  
6 3 Studies have found that people with diabetes frequently assess their intake of carbohydrates inaccurately and  
7 4 this has been associated with a poorer HbA1c (23-25). In particular mixed meals, energy-dense foods, and  
8 5 larger portion sizes resulted in inaccurate carbohydrate estimation. Thus, carbohydrate awareness and  
9 6 monitoring including gram counting, experience-based estimation of high-carbohydrate foods and practising  
10 7 numeracy skills seems to be important for obtaining better plasma glucose control. Increased carbohydrate  
11 8 awareness may also lead to a reduced carbohydrate consumption and thus a reduced energy intake, which has  
12 9 been shown to be an efficient dietary approach in people with T2D for body weight loss and improvement in  
13 10 HbA1c at least in the short term (<1 year) (3). The short-term effects of low-carbohydrate diets may be due to  
14 11 a decline in dietary adherence over time indicating that the recommended intake of carbohydrates should be  
15 12 individualised and based on an assessment of the patient's current eating patterns and preferences as practised  
16 13 in the BCC concept. Diabetes management requires many daily self-management activities including  
17 14 managing dietary intake, and long-term dietary adherence remains a key challenge for most dietary  
18 15 interventions. Nutrition therapy is a fundamental part of diabetes self-management education and support to  
19 16 help empower and support people in managing their diabetes to improve glycaemic control (2). This may be  
20 17 accomplished by including skills training and social support for maintaining dietary changes. Evidence suggest  
21 18 that a hands-on, learning-by-doing approach (problem- and experience-based patient education) can support  
22 19 the development of food skills in general and improve diet quality in particular (26). Adding group-based  
23 20 dietary approaches to individual lifestyle counselling has also been found to improve dietary habits (27).  
24 21 Similarly, adding diabetes self-management approaches to the diabetes education has led to lower dropout  
25 22 rates, increased self-efficacy and improved HbA1c in people with T2D (28). One study also found that  
26 23 perceived competence in managing diabetes as predicted by the degree to which people experienced the health-  
27 24 care climate to be autonomy supportive and the perceived competence predicted HbA1c (29).  
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37 27 The sparse scientific knowledge about the effect of group-approaches with practiced-focused nutrition  
38 28 education and the BCC concept underlines the need for investigating and evaluating this in a practice-based  
39 29 group educational approach and examining the effect on improved metabolic control in people with T2D.  
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#### 42 31 **Aim**

43 32 The aim is to examine the effectiveness of a group-based dietitian-led practise-focused educational approach  
44 33 for dietary self-management compared to the standard nutrition education on glycaemic control in people with  
45 34 T2D.  
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#### 50 36 **Methods and analysis**

##### 51 37 **Study design**

52 38 The study is as a randomised controlled intervention trial with a parallel-group design (figure 1).  
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55 39 For each participant the study duration is 12 months and includes up to nine visits at the study site (figure 2).  
56 40 All participants will be instructed to maintain their habitual lifestyle in all other aspects than their diet, e.g.  
57 41 keeping the same level of physical activity as habitually during the study period. All participants will be  
58 42 instructed to follow their regular diabetes care in the hospital, which usually includes four yearly visits with a  
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4 1 diabetologist (endocrinologist) and one yearly consultation with a diabetes nurse. Participants will be  
5 2 instructed not to receive any further dietary education during the study period. Close relatives can participate  
6 3 in the dietary education in both study groups if the participant needs support to manage dietary changes.

8  
9 4 The study flow is presented in figure 3. The study follows the guidelines of Standard Protocol Items for  
10 5 Randomised Trials (SPIRIT).

#### 11 6 12 7 Setting

13 8 The study will be carried out at the outpatient clinic at Steno Diabetes Center Copenhagen (SDCC) in Gentofte,  
14 9 Denmark.

#### 16 10 Recruitment and consent

17 11 As a temporary supplementary treatment initiative, SDCC offers courses in BCC for people with T2D treated  
18 12 at SDCC. Participants for the current study will be recruited among people signing up for these courses or  
19 13 people directly referred to one of the courses or the study by a health care professional (diabetologist, diabetes  
20 14 nurse or dietitian) from SDCC. A course administrator at SDCC will contact all interested or referred people  
21 15 by telephone and provide information about the study. In addition, potential study participants will be recruited  
22 16 through information on sdcc.dk and other electronic media or patient-related networks. If the person is  
23 17 interested in the study, the person will receive the written information by mail or e-mail. If interested in study  
24 18 participation, the study investigator/study personnel will schedule a personal meeting for oral information,  
25 19 offering the possibility of bringing a confidant. The person will be given time to discuss any questions and will  
26 20 be informed that he/she has at least 24 hours to decide on participation in the study. If the person decides to  
27 21 participate in the study, the person and the study investigator/study personnel will sign the written informed  
28 22 consent, and the investigator/study personnel will perform a screening. If all inclusion criteria are fulfilled and  
29 23 none of the exclusion criteria are met, the person will be included in the study and randomised to one of the  
30 24 groups. People who decline to participate or do not meet the inclusion criteria will continue their usual care in  
31 25 an outpatient diabetes clinic and will be offered to participate on a BCC course if they still wish to do so.  
32 26 Participants will be informed that participation is voluntary, and that they may withdraw their consent at any  
33 27 time.

#### 39 28 40 29 Inclusion criteria

41 30 People with T2D between 18-75 years with a diabetes duration of at least 12 months and baseline HbA1c of  
42 31 53-97 mmol/mol treated with diet or any glucose-lowering medication are eligible for the study.

#### 44 32 45 33 Exclusion criteria

46 34 People are excluded if they have other types of diabetes than T2D, are practicing carbohydrate counting as  
47 35 judged by the investigator, have a low daily intake of carbohydrates (defined as below 25 E% or 100 g/day),  
48 36 have participated in a BCC group program within the last two years, use an automated bolus calculator, have  
49 37 gastroparesis, have uncontrolled medical issues affecting dietary intake as judged by the investigator or a  
50 38 medical expert. Women who are pregnant or breastfeeding or have plans of pregnancy within the study period  
51 39 are also excluded. Furthermore, people who are either participating in other clinical studies or are unable to  
52 40 understand the informed consent and the study procedures will be excluded.



## 1 Randomisation

2 Participants eligible for inclusion in the study will be randomly allocated in a 1:1 ratio to one of the two groups  
3 (BCC or control) using a computer-generated randomization in the software program *REDCap*. The  
4 randomization is done by stratifying participants based on sex (male or female), BMI ( $<30 \text{ kg/m}^2$  or  $\geq 30$   
5  $\text{kg/m}^2$ ) and HbA1c ( $<70 \text{ mmol/mol}$  or  $\geq 70 \text{ mmol/mol}$ ) at baseline. The randomization is done in blocks in to  
6 order to ensure an equal number of participants in each group.

## 7 Intervention group

8 Participants will receive education in BCC in addition to the standard outpatient nutrition education as  
9 described for the control group. The BCC program consists of two sessions of three hours and a follow-up  
10 group session of two hours. The BCC program uses trained dietitians following a planned curriculum which  
11 include experience-based learning with problem-solving exercises, hands-on activities, short theoretical  
12 presentations, discussions of motivational aspects and coping strategies. The BCC program integrates peer  
13 modelling, skills development, goal setting, observational learning and social support into the program content  
14 and activities. The training includes identifying carbohydrates in food, reading carbohydrate tables, calculating  
15 the carbohydrate content from food labels, tables and applications (app) for smartphones and use of a  
16 personalized carbohydrate plan with guiding suggestions for daily intake of carbohydrates at meals based on  
17 personal dietary recordings including plasma glucose measurements. An app from the Danish Diabetes  
18 Association (*Diabetes og Kulhydrattælling*<sup>®</sup>. The Danish Diabetes Association's app, Pragma soft A/S,  
19 available in Google Play<sup>®</sup> and App Store<sup>®</sup> 12/2014, Free) will be introduced to support estimation and  
20 calculation of carbohydrates.

## 21 Control group

22 Participants randomised to the control group will receive current standard outpatient nutrition education in  
23 T2D. This includes individual guidance by a trained dietitian, with one initial 60 minutes dietary counselling  
24 session and two individual 30 minutes follow-up session. The individual guidance is based on the overall  
25 treatment goal and the defined personal dietary goals for behavioural change according to personal preferences.  
26 Dietary guidance includes topics such as healthy dietary habits and weight loss approaches for replacement of  
27 energy-dense foods with low energy-dense foods or special attention to carbohydrate quality (e.g. glycaemic  
28 index and dietary fibre intake), fat quality and other dietary recommendations according to personal needs.

## 29 Data collection

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

40 The primary outcome is the difference in mean HbA1c or mean amplitude of glycaemic excursions (MAGE)  
41 from baseline to end of the intervention (6 month) between and within each of the two study groups (BCC and  
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control). MAGE is used as a measure of glycaemic variability to capture mealtime-related glucose excursions. MAGE has been associated with coronary artery disease independent of HbA1c (30, 31).

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 wk	3 mo	6 mo	12 mo
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; mo=months; PG=plasma glucose; Q=Questionnaire; wk=weeks.

\*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 % of time in range (3.9-10.0 mmol/l), % time spent in hypoglycaemia (<3.9 mmol/l), % time spent in hyperglycaemia (>10.0 mmol/l) and standard deviation of mean plasma glucose assessed from CGM measurements. Percentages of time in ranges (target, hypoglycaemia, and hyperglycaemia) according to the described thresholds have been recommended by a large expert group in an international consensus report on the use of CGM (32).

**Blood and urine samples:** HbA1c (after 12 weeks and 12 months), 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 people with diabetes (33). The scale is designed to determine patient satisfaction with the diet, the degree of daily life and social life limitations due to dietary changes, and the impact of food insecurity

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4 1 on dietary adherence and self-management due to limited financial resources. A forward translation and  
5 2 cultural adaption of the DDRQOL was done by a Japanese-Danish interpreter with a background as a clinical  
6 3 dietitian and an expert panel of six clinical dietitians working with diabetes. This was followed by a pilot  
7 4 testing by 10 people with diabetes.  
8 5

9 6  
10 7 *Perceived Competencies in Diabetes Scale (PCS)*: The PCS is a validated scale (34) which includes four items  
11 8 that reflect participants' feelings of competence about engaging in a healthier behaviour and participating in a  
12 9 nutritional education program. Forward and backward linguistic translation from English to Danish has been  
13 10 done according to standard procedures in 2001 under the guidance of Professor Vibeke Zoffmann.  
14 11

15 12  
16 13 *Health-Care Climate Questionnaire (HCCQ)*: The HCCQ chosen in this study is a 5-item short form of the  
17 14 originally validated 15-item measure that assesses people's perceptions of the degree to which dietitians are  
18 15 autonomy supportive versus controlling in providing dietary treatment.  
19 16

20 17  
21 18 *Carbohydrate photographic questionnaire (CPQ)*: The CPQ is an electronic questionnaire assessing skills in  
22 19 correct estimation of portion sizes of 11 commonly eaten high-carbohydrate foods. The CPQ has been  
23 20 developed and validated against real food in 87 people with diabetes. The study results by Ewers et al. has  
24 21 been accepted for publication in Journal of Nutrition and Food Science in September 2019.  
25 22

26 23  
27 24 *Mathematical literacy questionnaire*: A 10-item test with modified questions from the nutrition domain of the  
28 25 *Diabetes Numeracy Test (DNT)* (35) was designed and feasibility tested to investigate mathematical literacy  
29 26 including numeracy skills (addition, subtraction, division and multiplication) which are essential for  
30 27 understanding numbers and applying mathematical skills in daily life e.g. for calculating carbohydrates.  
31 28

32 29  
33 30 *International Physical Activity Questionnaire Short Form (IPAQ SF)*: The Danish version of the IPAQ SF (36)  
34 31 will be used to assess changes in level of physical activity during the study period.  
35 32

36 33  
37 34 Self-reported demographic questions include level of education, occupation, marital status, household  
38 35 composition and yearly income.  
39 36

40 37  
41 38 *Dietary data*: Four days of weighed dietary food records collected at baseline and six months after baseline.  
42 39 Dietary records will be calculated using the software system *Vitakost* (Vitakost Aps, Kolding) where nutrient  
43 40 and energy calculations are based on the Danish national food database. The dietary food records are used to  
44 41 estimate total energy intake (kJ/d), intake of carbohydrates, protein and fat (g/day and g/meal), added sugar  
45 42 (g/d) and total dietary fibre intake (g/d).  
46 43

47 44  
48 45 *Baseline data (from the electronic medical record)*: type of diabetes, gender, age, smoking status, medical  
49 46 conditions, total number of visits at a diabetologist and diabetes nurse and dietician during the study period.  
50 47

#### 50 48 Data analysis plan

51 49 The trial is ongoing. The recruitment started in October 2018 and is expected to be completed by October  
52 50 2021.  
53 51

#### 54 52 Sample size calculation

55 53 A power calculation was conducted based on the primary outcome measures HbA1c and MAGE. Allowing  
56 54 for an estimated drop-out rate of 30% and subgroup analyses the sample size was planned to include a total of  
57 55 226 people in the study (113 in each arm). This was based on a sample size calculation which suggested that  
58 56 including 87 participants in each of the study groups would give 80% power to detect a difference in change  
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4 1 in HbA1c of 3.0 mmol/mol between the BCC group versus the control group with a 5% significance level  
5 2 using a two-sided test and an estimated standard deviation (SD) of 7 mmol/mol. The used SD and dropout rate  
6 3 were based on previous BCC courses at SDCC where mean changes and SD of HbA1c after 6 months were  
7 4 calculated based on completers with T2D. MAGE has only been used as an outcome measure of glucose  
8 5 variability in a few randomised controlled dietary intervention studies of people with diabetes (37, 38) showing  
9 6 differences in changes in MAGE up to 4.8 mmol/l (SD: 1.0) after a 12-week carbohydrate counting  
10 7 intervention (37), but is regularly used in other clinical studies evaluating glucose variability. By including  
11 8 113 participants in each study group we will have a power of 80% (alpha level of 0.05) in a two-sided test to  
12 9 detect a difference in the change in MAGE during the intervention period (6 months) of  $\geq 0.30$  mmol/l (SD 0.7  
13 10 mmol/l) between the two study groups.  
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## 19 12 Statistical methods

20 13 Analysis and reporting of the study results will follow the CONSORT (Consolidated Standards of Reporting  
21 14 Trials) guidelines for reporting parallel group randomised trials (39). Results will be presented as means (SD)  
22 15 for normally distributed variables and as medians (inter-quartile range) for non-normally distributed variables.  
23 16 Paired samples t-test will be used to compare baseline data between and within the two study groups for normal  
24 17 data and Wilcoxon signed rank test for non-normal data. Mixed-effect models will be used to test differences  
25 18 in outcomes from baseline to follow-up to take repeated measurements into account. If model assumptions  
26 19 cannot be met even after logarithmic transformation, non-parametric tests will be used. Examinations of the  
27 20 relevant diagnostic plots, including QQ-plots, will be used to evaluate normality of the residuals.  
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30 21  
31 22 The baseline demographics as well as clinical and diabetes-related characteristics of the intervention and the  
32 23 control groups will be presented and compared. The average changes between baseline and 6 months, and 12  
33 24 months in primary and secondary outcomes will be calculated for each of the groups. Intention-to-treat (ITT)  
34 25 analysis will be performed as the primary analysis on all primary and secondary outcomes after the last  
35 26 participant has ended participation. Missing values will be handled with a last observation carried forward  
36 27 approach for ITT analysis with the use of the multiple imputation approach in a sensitivity analysis. Per-  
37 28 protocol (PP) analysis will only be performed in case of sensitivity testing. Metabolic patterns will be tested  
38 29 with multivariate statistics. Adjustment for relevant confounders will be performed including adjustment for  
39 30 the stratified variables. Heterogeneity in responsiveness to the interventions will be tested by dividing each  
40 31 intervention group into smaller groups based on data distribution (medians) or clinically meaningful cut-points.  
41 32 Two-sided tests will be used. *P* values of  $< 0.05$  are considered significant. The statistical programs SPSS and  
42 33 SAS will be used for data analysis.  
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46 35 **Patient and public involvement:** People were involved in developing the educational content of the program  
47 36 in basic carbohydrate counting. People were not involved in setting the research questions or the outcome  
48 37 measures, nor were they involved in developing the study design. Information may be disseminated to the  
49 38 public via any media coverage of study findings.  
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## 52 40 Ethics and dissemination

53 41 The study will be conducted in accordance with the ethical principles in the Declaration of Helsinki and to the  
54 42 regulations for Good Clinical Practice (GCP) to the extent that this is relevant for non-medical studies. The  
55 43 study has been approved by the Ethics Committee of the Capital Region, Copenhagen (#H-18014918), has  
56 44 been approved for data storage by the Danish Data Protection Agency (journal no VD-2018-233, I-suite no  
57 45 6474) and has been registered at ClinicalTrials.gov (NCT03623139).  
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2 All health-related matters and sensitive personal data will be handled in accordance with the Danish “Act on  
3 Processing of Personal Data”. All health-related matters and sensitive personal data (blood test results etc.)  
4 will be depersonalized. All participants will be given a study number referring to their personal information,  
5 which will be stored securely and separately. Data will be stored in coded form for 10 years after last participant  
6 has attended the last visit, after which the data will be fully anonymised.

7  
8 Data is owned by the investigators who are responsible for publishing the results. Positive and negative as well  
9 as inconclusive study results will be published by the investigators in international peer-reviewed journals, and  
10 all co-authors must comply with the Vancouver rules. BE will be responsible for writing the first draft of the  
11 manuscript based on the main study results as a first author under guidance by TV and JMB. The study results  
12 will be presented at relevant national and international scientific conferences and meetings and will be  
13 published in international peer-reviewed scientific journals.

14 Data sharing: Requests regarding dataset must be send to the corresponding author [bettina.ewers@regionh.dk](mailto:bettina.ewers@regionh.dk)

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4 1 **Authors' contributions:** BE conceived the original idea for this trial, planned the study design, performed the  
5 2 sample size calculations and wrote the first draft of the protocol manuscript. TV and JMB provided valuable  
6 3 input regarding trial design, planning and analytical considerations, and edited the first draft of the protocol  
7 4 manuscript. All authors approved the final version of the clinical trial protocol. BE is the principle investigator  
8 5 and is responsible for correspondence with all authorities regarding the study and is responsible for the data  
9 6 collection (recruitment, screening and clinical study examinations), overall monitoring the trial and for  
10 7 conducting the statistical analyses. TV and JMB are supervisors and coinvestigators of this trial. Should any  
11 8 safety concerns arise during the conduct of the study these will be brought to the attention of TV and JMB by  
12 9 BE and will be carefully reviewed.  
13  
14

15 10  
16 11 **Funding statement:** This work was supported by The Beckett Foundation (grant number 17-2-0957), the Axel  
17 12 Muusfeldts Foundation (grant no 2017-856) and the Novo Nordisk Foundation (No assigned grant number) as  
18 13 part of a supplementary treatment initiative at SDCC in 2018-2020.  
19  
20

21 14 **Competing interests:** None of the authors have financial relationships with organizations that might have an  
22 15 interest in the submitted work, or other relationships or activities that could appear to have influenced the  
23 16 submitted work.  
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1 **Figure titles and legends (captions)**

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3 **Figure 1.** Study design

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5 **Figure 2.** Schematic diagram of the intervention

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7 BCC, basic carbohydrate counting; BP, blood pressure; BW, body weight; CGM, Continuous Glucose  
8 Monitoring; DXA, dual-energy-X-ray absorptiometry; V, visit; WHC, waist-hip circumference.

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

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12 BCC, basic carbohydrate counting.

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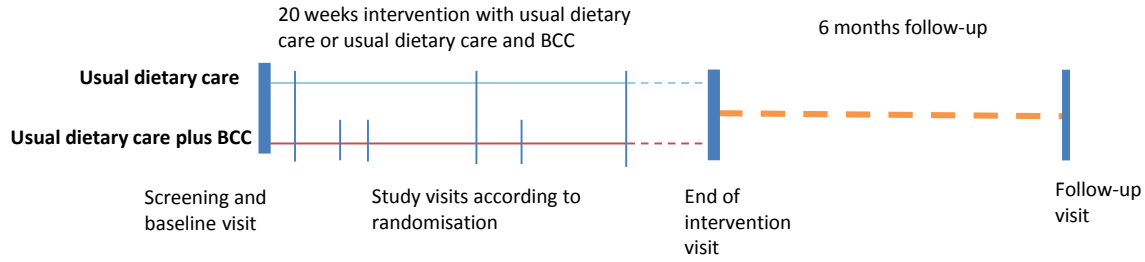
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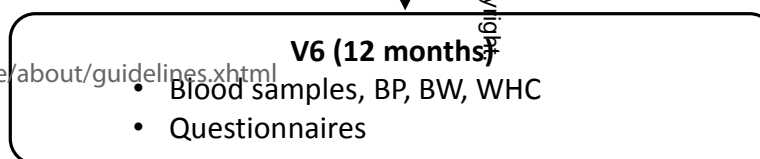
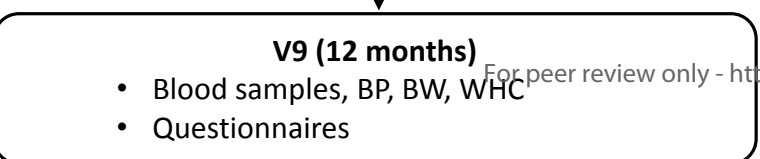
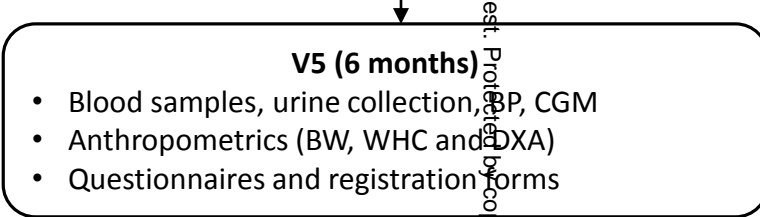
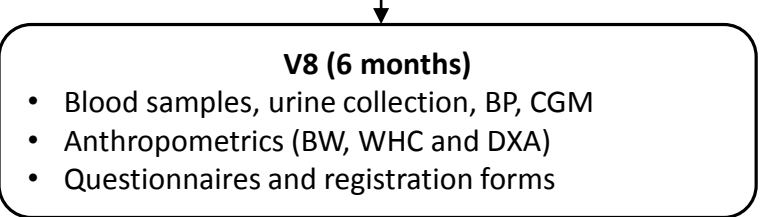
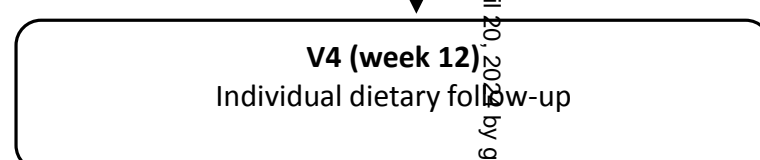
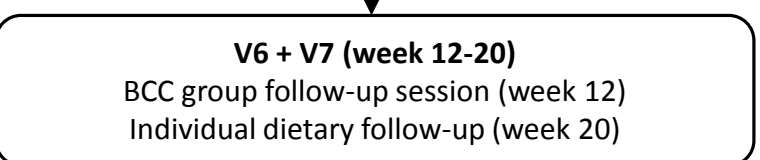
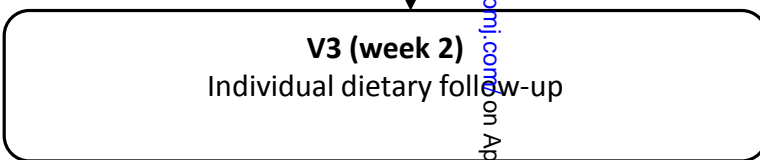
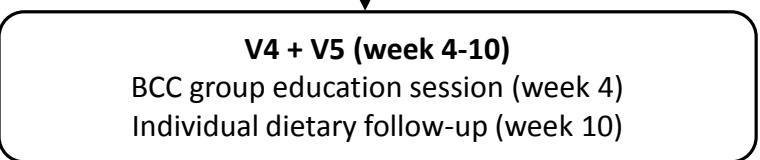
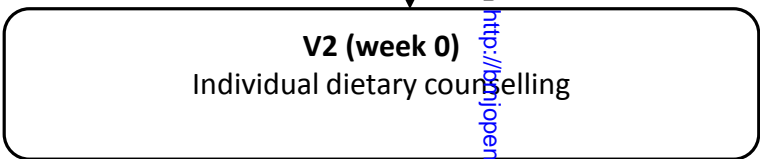
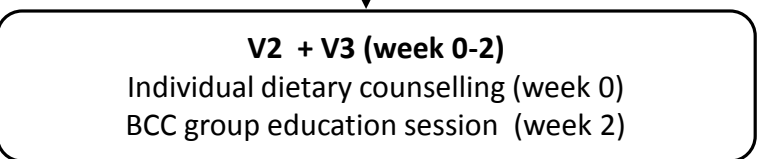
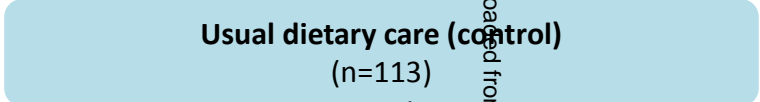
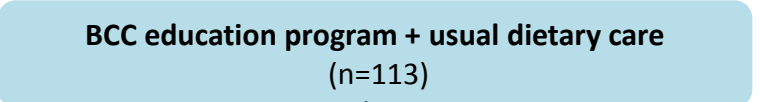
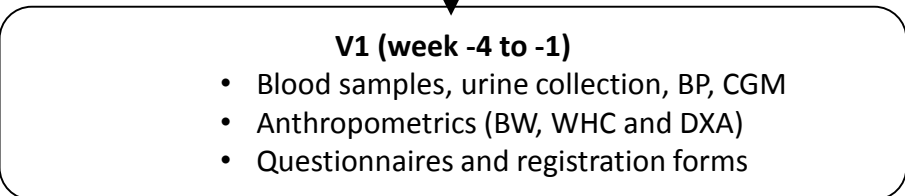
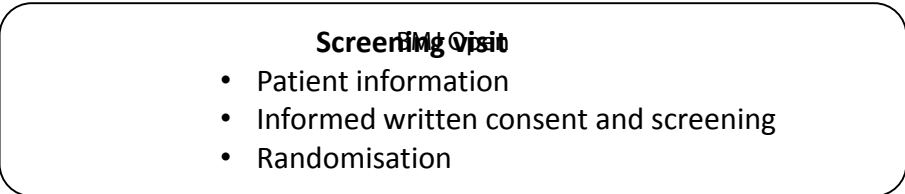
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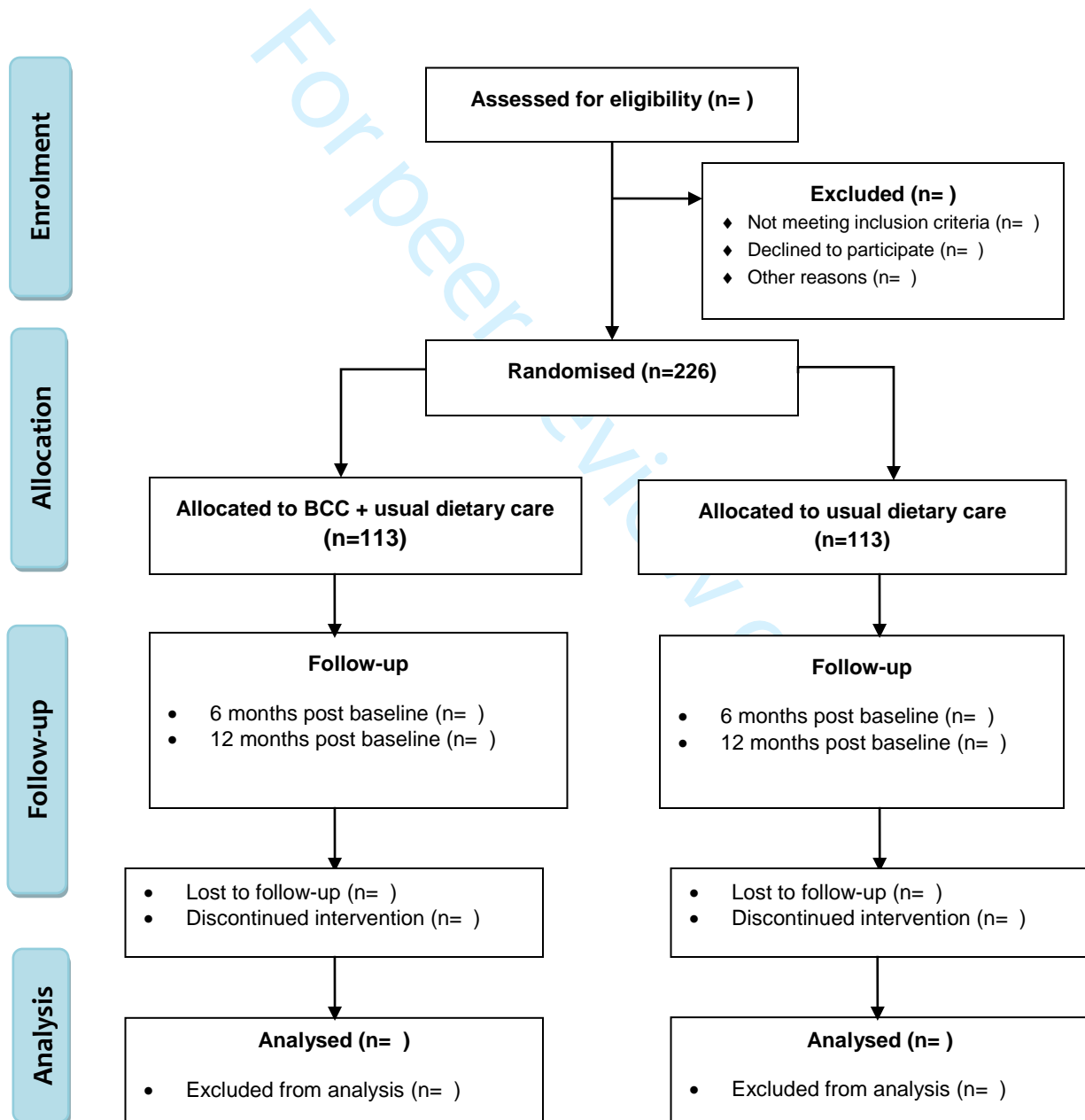
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STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description for the BCC study	Addressed on page number
<b>Administrative information</b>			
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 39___
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	___p 2___
	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___

## 1 Introduction

2			
3	Background and	6a	Description of research question and justification for undertaking the trial, including summary of relevant
4	rationale		studies (published and unpublished) examining benefits and harms for each intervention
5			_____p 9-10_____
6		6b	Explanation for choice of comparators
7			_____
8	Objectives	7	Specific objectives or hypotheses
9			_____p 11_____
10	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial or single group),
11			allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
12			_____p 13_____

## 14 Methods: Participants, interventions, and outcomes

15			
16	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will
17			be collected. Reference to where list of study sites can be obtained
18			_____p 18-19_____
19	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and
20			individuals who will perform the interventions (eg, surgeons, psychotherapists)
21			_____p 16_____
22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be
23			administered
24			_____p 13-14_____
25		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose
26			change in response to harms, participant request, or improving/worsening disease)
27			_____p 16_____
28		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence
29			(eg, drug tablet return, laboratory tests)
30			_____p 15_____
31		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
32			_____p 14_____
33	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood
34			pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg,
35			median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen
36			efficacy and harm outcomes is strongly recommended
37			_____p 12_____
38	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for
39			participants. A schematic diagram is highly recommended (see Figure)
40			Table 1 page 20,
41			Fig 2 page 25
42			

1	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 31___
2				
3				
4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	___p 15___
5				
6	<b>Methods: Assignment of interventions (for controlled trials)</b>			
7	<b>Allocation:</b>			
8				
9				
10	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 18___
11				
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15				
16	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___
17				
18				
19				
20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	___p 36___
21				
22				
23				
24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	___n/a___
25				
26				
27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	___n/a___
28				
29				
30				
31	<b>Methods: Data collection, management, and analysis</b>			
32				
33	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 23-24___
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39		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 16-17___
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1	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 32___
2				
3				
4				
5	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 31___
6				
7				
8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	___p 31___
9				
10		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 31___
11				
12				
13				
14	<b>Methods: Monitoring</b>			
15				
16	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 32-33___
17				
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22		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 36___
23				
24				
25	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 33___
26				
27				
28	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___
29				
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32	<b>Ethics and dissemination</b>			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	___p 32___
35				
36				
37	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 34___
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	___p 17___
2				
3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	___p 29-30___
5				
6				
7	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 32-33___
8				
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10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	___p 39___
11				
12				
13	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 32___
14				
15				
16	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___
17				
18				
19				
20	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	___p 37___
21				
22				
23				
24		31b	Authorship eligibility guidelines and any intended use of professional writers	___p 32___
25				
26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	___n/a___
27				
28				
29	<b>Appendices</b>			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix 1, 2, 3, 4, 5
32				
33				
34	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 28-30___
35				
36				

\*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](https://creativecommons.org/licenses/by/4.0/)" license. n/a, not relevant.