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Study protocol for optimizing glycaemic control in type 1 diabetes treated with multiple daily insulin injections - intermittently scanned continuous glucose monitoring, carbohydrate counting with automated bolus calculation, or both? A randomized controlled trial

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Title

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Short title: The ABC Flash Study

Trial registration

The study is carried out in accordance with the Helsinki Declaration after approval by the Regional Scientific Ethics Committee (H-17040573). The data collection and handling are performed in accordance with the General Data Protection Regulation. The trial is registered at clinical trial.gov (NCT03682237).

Protocol version

Version 1, December 19, 2019.

Funding

The study is investigator initiated and financed by The Capital Region of Denmark. None of the investigators have personal financial interest in the conduct or the outcome of the project.

Roles and responsibilities

KN is the primary investigator of the study. The study concept, trial design and study protocol: ALS, UPB, OLS, BGR, TA, LD and DV.

ABSTRACT

Introduction:

There are beneficial effects of advanced carbohydrate counting with an automatic bolus calculator (ABC) and intermittently scanned continuous glucose monitoring (isCGM) in persons with type 1 diabetes. We aim to compare the effects of isCGM, training in carbohydrate counting with ABC and the combination of the two concepts with standard care in persons with type 1 diabetes.

Methods and analysis:

A multi-centre randomized controlled trial with inclusion criteria; ≥18 years, type 1 diabetes ≥1 year, injection therapy, HbA1c >53 mmol/mol, whereas daily use of carbohydrate counting and/or CGM/isCGM wear are exclusion criteria. Inclusion was initiated in October 2018 and is ongoing. Eligible persons are randomized into 4 groups; standard care, ABC, isCGM, or ABC + isCGM. Devices used are FreeStyle Libre Flash and smart phone diabetes application mySugr. Participants attend group courses according to treatment allocation with different educational contents. Participants are followed for 26 weeks with clinical visits and telephone consultations. At baseline and at study end, participants wear blinded CGM, have blood samples performed and fill in questionnaires on person related outcomes, and at baseline also on personality traits and hypoglycaemia awareness. The primary outcome is the difference in time spent in normoglycaemia (4-10 mmol/l) at study end vs. baseline between the isCGM group and the standard care group. Secondary outcomes will also be analysed. Results are expected in 2020.

Ethics and dissemination:

The study is approved by the Regional Scientific Ethics Committee (H-17040573).

Strengths and limitations of this study:

- Despite its relevance for many persons with diabetes and their caregivers, the topic has not yet been rigorously examined to evaluate efficacy on glycaemic control.
- The study is robustly designed as a large scale randomized controlled trial.
- A possible limitation may be difficulty with recruiting enough participants in order to reach power estimates.

INTRODUCTION

Insulin therapy in type 1 diabetes is generally adjusted according to food intake, physical activity and current blood glucose levels. It typically involves the combination of fast-acting insulin before meals and to correct hyperglycaemia, and long-acting insulin to control blood glucose overnight and in between meals, referred to as multiple daily injections (MDI). In order to obtain optimal glycaemic control it requires dose adjustment based on the amount of carbohydrate ingested at each meal (1) and frequent self-monitoring of blood glucose (SMBG) measurements. Carbohydrate counting is done based on experience or by using either manual or automatic estimates. Several studies have shown improved HbA1c and treatment satisfaction as well as a tendency towards less hypoglycaemia in persons undergoing training in carbohydrate counting and manual bolus calculation compared to insulin dosing based on experience (1–3). In addition, the use of an automatic bolus calculator (ABC) rather than manual bolus calculation has been proved to reduce HbA1c and improve patient satisfaction (2), with unaffected hypoglycaemia rate (4). Even in a routine care setting, group courses of 4 hours in bolus calculation with ABC and follow-up consultations have shown a reduction in HbA1c with maintained effect 12 months post-course (5). Our experience is that many persons with type 1 diabetes have never been trained in carbohydrate counting or the algorithm for insulin dose calculation.

Compared with conventional SMBG, the use of continuous glucose monitoring (CGM) in MDI treated persons reduces HbA1c and the time spent in mild hypoglycaemia and improves treatment satisfaction (6–8). A variation of real-time CGM is the intermittently scanned CGM (isCGM), where the first-generation readers are without glycaemic alerts, and the wearer scans the sensor to transfer glucose data. An early generation of isCGM has been found to decrease time spent in hypoglycaemia and increase treatment satisfaction and other person related outcomes in people with near-optimal HbA1c at baseline (9). A number of observational studies have evaluated isCGM in terms of accuracy and change in HbA1c (10), with positive reports on wearer satisfaction (11). Two recent observational studies including 120 and 900 adults, respectively, mainly on MDI found improved HbA1c levels, however with moderate increase in mild hypoglycaemic events (12,13), but fewer diabetic ketoacidosis admissions (13). The most pronounced reduction in HbA1c was seen in those with higher HbA1c prior to isCGM use (13). To date, however, no randomized controlled trials exist examining the efficacy of isCGM to increase time in range in patients with suboptimal HbA1c.

It also remains unknown which of the two concepts, bolus calculation with ABC or the use of isCGM, is superior and whether there is an additive effect of the two combined. Furthermore, there are no studies on how to structure training and optimize treatment in patients doing bolus calculation with the concomitant use of isCGM.

In the current study, the primary aim is to compare the effect of isCGM with standard care (SMBG) on glycaemic control. The secondary aim is to compare the effect of the combination of training in carbohydrate counting with ABC and the use of isCGM with standard care. We also aim to assess whether isCGM use can outperform training in carbohydrate counting with ABC.

METHODS AND ANALYSIS

Methods: Participants, interventions and outcomes

Participants

The ABC Flash Study is a randomized controlled, open-label, four-arm parallel trial carried out at five sites in The Capital Region of Denmark; Steno Diabetes Center Copenhagen, Rigshospitalet, Amager and Hvidovre Hospital, Nordsjællands Hospital Hillerød, and Bispebjerg and Frederiksberg Hospital. Inclusion criteria are age ≥ 18 years, type 1 diabetes duration ≥ 1 year, HbA1c > 53 mmol/mol, and the use of MDI therapy with basal insulin accounting for ≥ 30 % of the total daily insulin dose. Exclusion criteria are daily use of carbohydrate counting or CGM, use of NPH insulin, pregnancy, breastfeeding, gastroparesis, severe diabetes complications (i.e. proliferative retinopathy, myocardial infarction within the last six months), other medical or psychological conditions judged unsuitable for study participation, participation in other diabetes-related clinical research, the use of other drugs than insulin affecting glucose metabolism, or the inability to understand the individual information and to give informed consent. Hence, participants are adults with type 1 diabetes and suboptimal glycaemic control, treated with basal and bolus insulin and attending an outpatient diabetes clinic in the Capital Region of Denmark. Screening for inclusion was initiated October 1, 2018 and is planned to continue until March 31, 2020.

Intervention

Devices

The automatic bolus calculator

The ABC system used for this trial is the CE-marked mobile telephone diabetes application mySugr available for Android and iPhone. It is a digital logbook designed to support persons with diabetes in their self-management. It consists of an insulin bolus calculator based on the following settings that can be individually adjusted for every half an hour lap though the 24-hours: carbohydrate ratio, insulin sensitivity, target glucose value and insulin duration time. For every meal, the user enters current glucose value and estimated carbohydrate intake into the application and receive a suggestion on insulin bolus dosage. In case of correction of hyperglycaemia, the user enters current glucose value and receive a suggestion on corrective insulin dosage. Data are stored for 3 months.

The intermittently scanned CGM

The isCGM device used in this trial is the FreeStyle Libre Flash CGM system (Abbott Diabetes Care, Alameda, CA, USA). It consists of a 14-day disc sensor to be worn on the upper arm, a reader and/or a mobile phone application to scan and data display. The sensor measures and continuously stores interstitial glucose concentrations every 15 minutes (800 glucose readings / 24 hours). The sensor is inserted into the upper arm skin and placed by a thin needle, which is immediately retracted, leaving a thin and 6 mm long plastic glucose recorder in the skin. To obtain a current glucose value, the wearer scans the sensor with either the reader device or a mobile phone application (FreeStyle Libre Link available for Android and iPhone, Abbott Diabetes Care) producing real-time data. The reader devices used for this study were updated mid-2019 (14). The application was available in Denmark for Android and iPhone from mid-2019 (15). The system is CE-marked and accurate enough for insulin dosing except during fluctuant and low glucose levels. Wearers do not need to calibrate the system but to avoid loss of data, the sensor must be scanned every 8 hours. Scanned glucose data are presented to the wearer on the display as numerical values including glucose trends based on automatically stored data. Both intermittently scanned as well as continuously stored glucose data are displayed as graphs and logbooks and are available as numerical values after download from the reader device/mobile phone to a computer by the software program Diasend (Glooko, USA).

Assignment of interventions

Persons eligible for inclusion draw a centrally prepared, sealed randomization envelope at the screening visit. The envelope is left unopened until after the initial blinded CGM period, where the given intervention is revealed; A (standard care), B (ABC), C (isCGM) or D (ABC and isCGM).

Courses for participants

Four types of group courses for participants are included in the trial (Table 1). Each course includes one to three educational elements according to group allocation. Course length (4-4.5 hours) and group size (4-6 participants) are rather similar between the groups. The educational elements are:

1. General diabetes: Training in general diabetes health issues, how to do experience-based dosing, how to handle sick days, exercise etc. in general terms.
2. ABC: Theoretic and practical training in carbohydrate counting and bolus calculation (5).
3. mySugr diabetes application: The application is downloaded on the participants personal smartphone. The insulin to carbohydrate ratio (the amount of carbohydrates needed to match the glucose lowering effect of 1 unit of subcutaneously injected rapid-acting insulin) and the insulin sensitivity (the decrease in blood glucose in mmol/l caused by 1 unit of subcutaneously injected rapid-acting insulin) are empirically estimated for each participant using the 500- and the 100- rule, respectively (16). The insulin duration time is set at 4 hours. The target glucose value is in general set at 6 mmol/l during daytime and 7 mmol/l during night time.
4. FreeStyle Libre Flash CGM: Participants are instructed to use the system according to our local guideline and those in group D are also instructed in how to incorporate isCGM trend arrows to adjust the mySugr application settings.

All the above-mentioned educational concepts are also practiced during individual consultations throughout the 26-week trial period.

Training of study personnel

The healthcare professionals at the different study sites have been educated in the protocol and different course content and treatment modalities, how to conduct courses and study visits on two separate days before inclusion was initiated. Teachers on these study personnel training sessions

were an endocrinologist (KN), a diabetes nurse and a dietitian from the investigator group with substantial experience in the field.

Diabetes care

In line with national guidelines (17), the overall aim in term of diabetes management is to obtain fasting and pre-prandial glucose values of 4-6 mmol/l, post-prandial glucose values lower than 10 mmol/l, to avoid any glucose values lower than 3 mmol/l and keep the number of glucose values below 4 mmol/l at an absolute minimum. At baseline and up to the last study visit, all participants fill in work sheets for daily reporting of basal insulin units, insulin boluses and SMBG values during the two weeks of blinded CGM wear to adjust insulin therapy. Moreover, participants receive a hypoglycaemia diary to fill in symptoms of hypoglycaemia and/or glucose values below 3.9 mmol/l, throughout the trial which is also used for insulin adjustments.

Participants in groups A (standard care) and B (ABC) are encouraged to measure SMBG at least four times daily with their personally preferred glucose meter. Participants in group C (isCGM) and D (isCGM and ABC) are instructed to use the isCGM system according to a local guideline based on manufacturer's guideline (18) and in line with recent publications on the topic (19–21). During both study visits and telephone consultations (see below) study personnel titrate insulin doses based on the different types of glucose values provided and other clinical information i.e. hypoglycaemic events, planned physical activity etc. For participants in group B and D, the carbohydrate ratio, the insulin sensitivity and the target glucose settings are evaluated and, if needed, adjusted (2).

Outcomes

The primary outcome is the difference in change from baseline to end of study between groups C (isCGM) and A (standard care) in time spent in normoglycaemia (defined as glucose of 4-10 mmol/l, minutes/24 hours and percentage of time, obtained by blinded CGM (22)).

Secondary outcomes are; difference in change from baseline to end of study between groups in HbA1c (mmol/mol), difference between groups in severe hypoglycaemia occurrence during the study period (defined as hypoglycaemic events requiring assistance from another person), difference between groups in symptomatic and confirmed hypoglycaemia occurrence during the study period (defined as glucose (SMBG or isCGM) < 3 mmol/l), difference in change between baseline and end of study between groups in diabetes distress, diabetes treatment satisfaction,

diabetes empowerment, diabetes quality of life, time spent in hypo- (blinded CGM glucose <3 mmol/l, <4 mmol/l, minutes/day), hyperglycaemia (>10 mmol/l, minutes/day) and glycaemic variability (standard deviation), total insulin dose (recorded as a mean of 2 weeks during blinded CGM (insulin units (IU)/day/kg, total basal insulin dose (IU/day/kg and insulin boluses (number/24 hours), body weight (kg), urinary albumin/excretion rate (mg/24 hours) and the association between personality traits scoring at baseline with any outcome measures in the groups.

Methods: data collection, management, and analysis

Data collection

Blinded CGM

After screening for inclusion (before opening the randomization envelope), and at study end, all participants are asked to wear a blinded (non-real-time) CGM (The FreeStyle Libre Professional CGM system, Abbott Diabetes Care, Oxon, UK) to obtain glucose data. The sensor is inserted by a health care professional (see above for details on the isCGM). While wearing the sensor, users do not need to enter any fingerstick data or carry around a receiver, since the device collects all glucose data automatically. Following two weeks of sensor wear, data are downloaded in office by a reader device and a manufacturer-provided computer software program (LibreLink, Abbott Diabetes Care). These data are collected between screening visit and course participation (baseline data) and the two last study visits (final data), respectively.

Glucose and automatic bolus calculator data

Glucose (SMBG or isCGM) are downloaded to a computer (software Diasend, Glooko, USA) and data from the ABC are sent by e-mail from the user to the project health care professional at study visit 2, 4 and 6. The average number of symptomatic mild hypoglycaemic episodes per week and any severe hypoglycaemic episode are consecutively recorded throughout the trial.

Questionnaires

At screening and last study visit, all participants fill in the following validated questionnaires; Problem Areas in Diabetes Questionnaire (PAID), Diabetes Treatment Satisfaction Questionnaire (DTSQs at baseline and DTSQs and DTSQc at last visit) (23), Diabetes empowerment test (DES

short form) and Diabetes quality of life (ADDQoL-19). At screening, they also fill in the questionnaire Neuroticism Extraversion Openness Agreeableness Conscientiousness Five-Factor Invertory-3 (NEO-FFI-3) and hypo-awareness assessment (24–27).

Blood and urine sampling and body weight

Blood and urine sampling are performed at screening and last study visit for analysis of HbA1c (mmol/mol) and general health/safety. Midways through the study, HbA1c is measured. Body weight (kg) is measured at screening and last study visit on the same scale in the laboratory.

Study visits and telephone consultations

There are in total five clinical follow-up study visits (visit 2-6) at 2, 4, 12, 24 and 26 weeks planned during the 26 weeks trial participation (see Figure 1). Participants in group A (standard care) and C (isCGM) have appointments with the project nurse, whereas participants in group B (ABC) and D (isCGM and ABC) have joint appointments with both the project nurse and the project dietician. All participants have appointments with the project physician at first visit (screening) and midways throughout participation (visit 4). Visit 3 is not mandatory but proposed to participants in need of extra support or renewed teaching in the allocated intervention. In between the clinical study visits, there are three telephone consultations (1-3) at 0, 8 and 17 weeks where the project nurse contact the participants.

Data management

The data management is performed in accordance with the General Data Protection Regulation. Data are consecutively collected and stored in a browser-based software and workflow database (REDCap). The database is password protected and only the local and primary investigators have access to the data.

Data analysis

A sample size of 160 (40 per group) was calculated to have 80% power to detect a difference in mean time in target glycaemic range (4-10 mmol/l) between treatment group A and C of 75 minutes per day with a standard deviation of 120 minutes, and a 2-sided α-level of 0.05. Sample size is increased to 180 (45 per group) to account for a potential drop out of approximately 10%.

Changes in primary and secondary outcomes over the intervention period and effects of the treatments will be modelled by linear mixed-effects models with a patient-specific random intercept to account for the correlation of repeated measurements within patients and a random intercept for centre to account for the clustering effect of study centre. The exact times of measurements will be used. All analyses will be performed as an intention to treat analysis. Statistical significance will be inferred at a two-tailed $P < 0.05$. The p-values for secondary outcomes will be corrected by the Benjamini-Hochberg method for multiple comparisons (28).

Public and patient involvement

Persons with type 1 diabetes were not involved in the initial phases of the study. Already recruited participants, however, are asked to assess the burden of the intervention and time required to participate in the research. This has resulted in a supplementary document that is presented to possible participants to give a realistic picture of time spent on participation over time. Persons with type 1 diabetes will be sought involved in the dissemination plan of the results by for example commenting on written information with regards to language and form.

ETHICS AND DISSEMINATION

The study is carried out in accordance with the Helsinki Declaration after approval by the Regional Scientific Ethics Committee (H-17040573) and is registered at clinical trial.gov (NCT03682237).

Until now, an early generation isCGM has been found to improve time spent in hypoglycaemia, treatment satisfaction and other person related outcomes in people with near-optimal HbA1c (9). A number of observational studies have evaluated isCGM in broader populations with regards to change in HbA1c and accuracy and satisfaction among wearers (10–13). To date, however, no randomized controlled trials have been performed to examine the efficacy of isCGM to increase time in range in patients with suboptimal HbA1c. In addition, carbohydrate counting with ABC has been proved to improve HbA1c and patient satisfaction (2) and nutritional therapy has an integral role in diabetes management (29). Which one of the two treatment concepts that is superior to the other, and whether there is an additive effect of the two combined, has to our knowledge not previously been evaluated. Most important, however, no randomized controlled trials have been

performed to examine the efficacy of isCGM to increase time in range in patients with suboptimal HbA1c.

The investigators expect that the current study results will help guiding persons with type 1 diabetes treated with MDI and their health care professionals in choosing evidence-based methods for optimal glycaemic control. We believe that the possible risks and side effects among participants are outweighed by the potential benefits from the conduct of this study. The overall individual risk of side effects is expected to be modest and is mainly related to the time spent on learning how to count carbohydrates and use the mySugr application and/or using the isCGM system. With regards to all other planned study procedures, the risk of complications or adverse events is negligible and outweighed by the possible beneficial effects of conducting the study. The occurrence of any adverse events will be assessed at every visit and telephone contact during the study period. All participants are covered by the mandatory individual insurance at each local hospital in The Capital Region of Denmark. Blood samples are analysed directly after sampling without the establishment of a biobank. If the study is prematurely terminated, the investigators will promptly inform the Regional Scientific Ethics Committee and the participants to assure appropriate therapy and follow-up.

The study results are expected to be disseminated at international and national diabetes conferences and meetings and published in international journals with considerable impact. All participants who at first study visit expressed an interest in the results will receive a short version of the main findings expressed in lay terms and will be invited to a short oral presentation at the main study site. The results will also be sought presented via the Danish Diabetes Association and communicated to the public by a press release.

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AUTHOR´S CONTRIBUTION

ALS wrote the first draft of the manuscript. Critical revision of the manuscript: UPB, OLS, BGR, TA, LD, DV and KN.

FUNDING STATEMENT

The study is investigator-initiated and -driven, financed by The Capital Region of Denmark. None of the investigators have personal financial interest in the conduct or the outcome of the project.

COMPETING INTEREST STATEMENTS

KN is a shareholder of Novo Nordisk; has received research support from Novo Nordisk, Roche Diagnostics, Dexcom and Zealand Pharma; has received lecture fees from Medtronic, Roche Diagnostics, Rubin Medical, Sanofi, Zealand Pharma, Novo Nordisk, and Dexcom; and has served on advisory panels for Medtronic, Abbott, and Novo Nordisk. UPB has served on advisory boards for AstraZeneca, Bristol-Myers Squibb, Sanofi-Aventis, Novo Nordisk and Zealand Pharma and has received lecture fees from AstraZeneca, Bristol-Myers Squibb, Sanofi-Aventis and Novo Nordisk. TA holds stocks in Novo Nordisk. ALS, OLS, BGR, LD and DV do not have any competing interests.

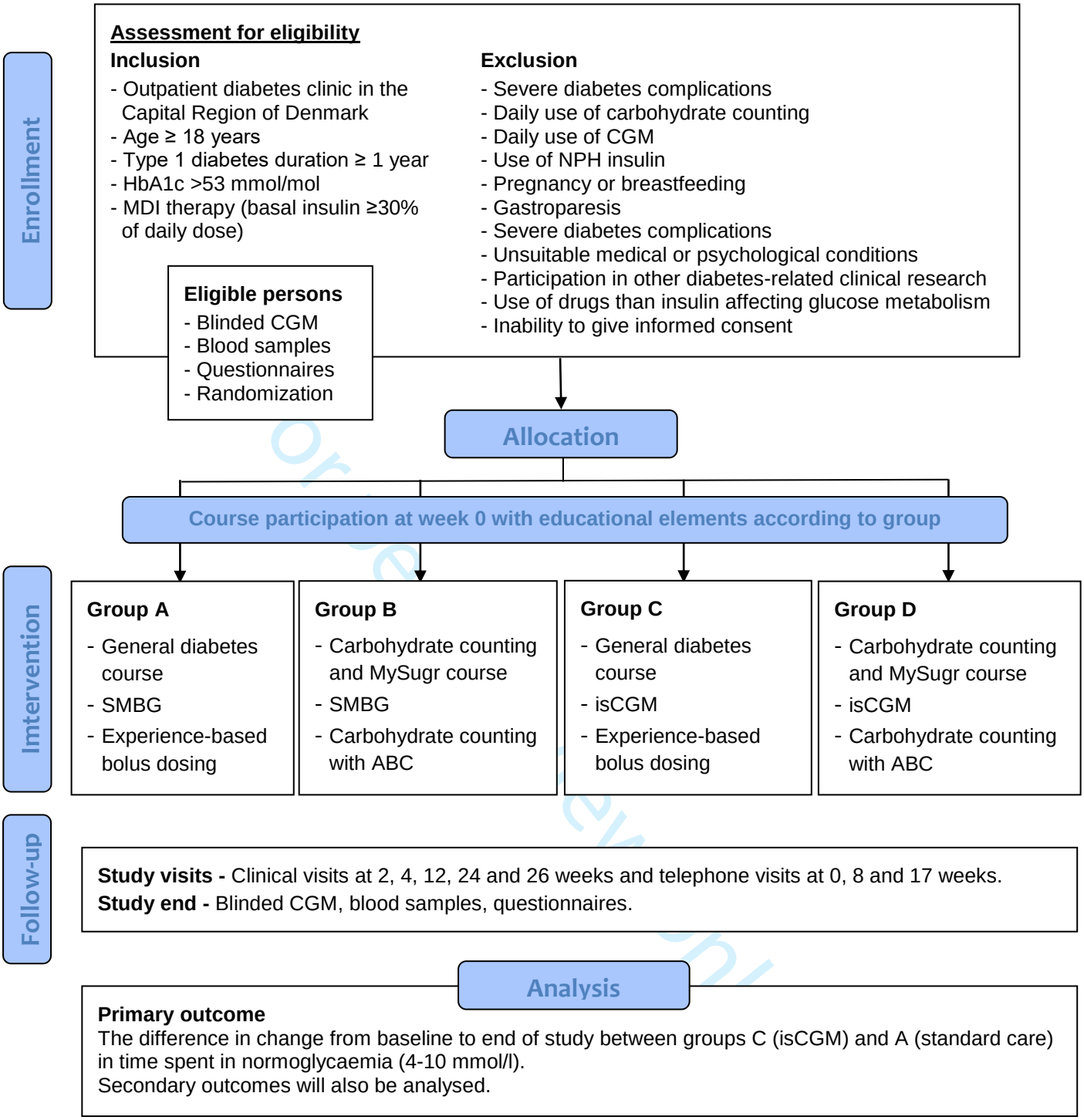
WORD COUNT

Abstract 296 words, full text 3,157 of 4,000 allowed words.

Table 1. Overview of glucose measurement methods, decision on insulin bolus and educational element in course according to group allocation. Abbreviations: SMBG (self-monitored blood glucose), isCGM (intermittently scanned glucose monitoring).

Intervention group	Glucose measurement method	Decision on insulin bolus	Educational element in course
A	SMBG	Experience-based	• General diabetes
B	SMBG	Carbohydrate counting with automatic bolus calculator	• Training in carbohydrate counting • Training in the use of the application mySugr
C	isCGM	Experience-based	• General diabetes • Training in FreeStyle Libre Flash use
D	isCGM	Carbohydrate counting with automatic bolus calculator	• Training in carbohydrate counting • Training in the use of the application mySugr • Training in FreeStyle Libre Flash use and how to incorporate glucose trend arrows to adjust the mySugr application settings

Figure legend, figure 1. Flow chart of participants throughout the trial.


Enrollment
Assessment for eligibility
Inclusion
- Outpatient diabetes clinic in the Capital Region of Denmark
- Age ≥ 18 years
- Type 1 diabetes duration ≥ 1 year
- HbA1c >53 mmol/mol
- MDI therapy (basal insulin ≥30% of daily dose)
Exclusion
- Severe diabetes complications
- Daily use of carbohydrate counting
- Daily use of CGM
- Use of NPH insulin
- Pregnancy or breastfeeding
- Gastroparesis
- Severe diabetes complications
- Unsuitable medical or psychological conditions
- Participation in other diabetes-related clinical research
- Use of drugs than insulin affecting glucose metabolism
- Inability to give informed consent
Eligible persons
- Blinded CGM
- Blood samples
- Questionnaires
- Randomization
Allocation
Course participation at week 0 with educational elements according to group
Imtervention
Group A
- General diabetes course
- SMBG
- Experience-based bolus dosing
Group B
- Carbohydrate counting and MySugr course
- SMBG
- Carbohydrate counting with ABC
Group C
- General diabetes course
- isCGM
- Experience-based bolus dosing
Group D
- Carbohydrate counting and MySugr course
- isCGM
- Carbohydrate counting with ABC
Follow-up
Study visits - Clinical visits at 2, 4, 12, 24 and 26 weeks and telephone visits at 0, 8 and 17 weeks.
Study end - Blinded CGM, blood samples, questionnaires.
Analysis
Primary outcome
The difference in change from baseline to end of study between groups C (isCGM) and A (standard care) in time spent in normoglycaemia (4-10 mmol/l).
Secondary outcomes will also be analysed.

BMJ Open

Study protocol for optimising glycaemic control in type 1 diabetes treated with multiple daily insulin injections - intermittently scanned continuous glucose monitoring, carbohydrate counting with automated bolus calculation, or both? A randomised controlled trial

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Title

Original title: Study protocol for optimising glycaemic control in type 1 diabetes treated with multiple daily insulin injections - intermittently scanned continuous glucose monitoring, carbohydrate counting with automated bolus calculation, or both? A randomised controlled trial

Short title: The ABC Flash Study

Trial registration

The study is carried out in accordance with the Helsinki Declaration after approval by the Regional Scientific Ethics Committee (H-17040573). The data collection and handling are performed in accordance with the General Data Protection Regulation. The trial is registered at www.clinicaltrial.gov (NCT03682237).

Protocol version

Version 2, February 17, 2020.

Funding

The study is investigator initiated and financed by The Capital Region of Denmark. None of the investigators have personal financial interest in the conduct or the outcome of the project.

Roles and responsibilities

KN is the primary investigator of the study. The study concept, trial design and study protocol: ALS, UPB, OLS, BGR, TA, LD and DV.

ABSTRACT

Introduction:

There are beneficial effects of advanced carbohydrate counting with an automatic bolus calculator (ABC) and intermittently scanned continuous glucose monitoring (isCGM) in persons with type 1 diabetes. We aim to compare the effects of isCGM, training in carbohydrate counting with ABC and the combination of the two concepts with standard care in persons with type 1 diabetes.

Methods and analysis:

A multi-centre randomised controlled trial with inclusion criteria; ≥18 years, type 1 diabetes ≥1 year, injection therapy, HbA1c >53 mmol/mol, whereas daily use of carbohydrate counting and/or CGM/isCGM wear are exclusion criteria. Inclusion was initiated in October 2018 and is ongoing. Eligible persons are randomised into 4 groups; standard care, ABC, isCGM, or ABC + isCGM. Devices used are FreeStyle Libre Flash and smart phone diabetes application mySugr. Participants attend group courses according to treatment allocation with different educational contents. Participants are followed for 26 weeks with clinical visits and telephone consultations. At baseline and at study end, participants wear blinded CGM, have blood samples performed and fill in questionnaires on person related outcomes, and at baseline also on personality traits and hypoglycaemia awareness. The primary outcome is the difference in time spent in normoglycaemia (4-10 mmol/l) at study end vs. baseline between the isCGM group and the standard care group. Secondary outcomes will also be analysed. Results are expected in 2020.

Ethics and dissemination:

The study is approved by the Regional Scientific Ethics Committee (H-17040573).

Strengths and limitations of this study:

- Despite its relevance for many persons with diabetes and their caregivers, the topic has not yet been rigorously examined to evaluate efficacy on glycaemic control.
- The study is robustly designed as a large scale randomised controlled trial.
- A possible limitation may be difficulty with recruiting enough participants in order to reach power estimates.

INTRODUCTION

Insulin therapy in type 1 diabetes is generally adjusted according to food intake, physical activity and current blood glucose levels. It typically involves the combination of fast-acting insulin before meals and to correct hyperglycaemia, and long-acting insulin to control blood glucose overnight and in between meals, referred to as multiple daily injections (MDI). In order to obtain optimal glycaemic control it requires dose adjustment based on the amount of carbohydrate ingested at each meal (1) and frequent self-monitoring of blood glucose (SMBG) measurements. Carbohydrate counting is done based on experience or by using either manual or automatic estimates. Several studies have shown improved HbA1c and treatment satisfaction as well as a tendency towards less hypoglycaemia in persons undergoing training in carbohydrate counting and manual bolus calculation compared to insulin dosing based on experience (1–3). In addition, the use of an automatic bolus calculator (ABC) rather than manual bolus calculation has been proved to reduce HbA1c and improve patient satisfaction (2), with unaffected hypoglycaemia rate (4). Even in a routine care setting, group courses of 4 hours in bolus calculation with ABC and follow-up consultations have shown a reduction in HbA1c with maintained effect 12 months post-course (5). Our experience is that many persons with type 1 diabetes have never been trained in carbohydrate counting or the algorithm for insulin dose calculation.

Compared with conventional SMBG, the use of continuous glucose monitoring (CGM) in MDI treated persons reduces HbA1c and the time spent in mild hypoglycaemia and improves treatment satisfaction (6–8). A variation of real-time CGM is the intermittently scanned CGM (isCGM), where the first-generation readers are without glycaemic alerts, and the wearer scans the sensor to transfer glucose data. An early generation of isCGM has been found to decrease time spent in hypoglycaemia and increase treatment satisfaction and other person related outcomes in people with near-optimal HbA1c at baseline (9). A number of observational studies have evaluated isCGM in terms of accuracy and change in HbA1c (10), with positive reports on wearer satisfaction (11). Two recent observational studies including 120 and 900 adults, respectively, mainly on MDI found improved HbA1c levels, however with moderate increase in mild hypoglycaemic events (12,13), but fewer diabetic ketoacidosis admissions (13). The most pronounced reduction in HbA1c was seen in those with higher HbA1c prior to isCGM use (13). To date, however, no randomised controlled trials exist examining the efficacy of isCGM to increase time in range in patients with suboptimal HbA1c.

It also remains unknown which of the two concepts, bolus calculation with ABC or the use of isCGM, is superior and whether there is an additive effect of the two combined. Furthermore, there are no studies on how to structure training and optimise treatment in patients doing bolus calculation with the concomitant use of isCGM.

In the current study, the primary aim is to compare the effect of isCGM with standard care (SMBG) on glycaemic control. The secondary aim is to compare the effect of the combination of training in carbohydrate counting with ABC and the use of isCGM with standard care. We also aim to assess whether isCGM use can outperform training in carbohydrate counting with ABC.

METHODS AND ANALYSIS

Methods: Participants, interventions and outcomes

Participants

The ABC Flash Study is a randomised controlled, open-label, four-arm parallel trial carried out at five sites in The Capital Region of Denmark; Steno Diabetes Center Copenhagen, Rigshospitalet, Amager and Hvidovre Hospital, Nordsjællands Hospital Hillerød, and Bispebjerg and Frederiksberg Hospital. Inclusion criteria are age ≥ 18 years, type 1 diabetes duration ≥ 1 year, HbA1c > 53 mmol/mol, and the use of MDI therapy with basal insulin accounting for ≥ 30 % of the total daily insulin dose. Exclusion criteria are daily use of carbohydrate counting or CGM, use of NPH insulin, pregnancy, breastfeeding, gastroparesis, severe diabetes complications (i.e. proliferative retinopathy, myocardial infarction within the last six months), other medical or psychological conditions judged unsuitable for study participation, participation in other diabetes-related clinical research, the use of other drugs than insulin affecting glucose metabolism, or the inability to understand the individual information and to give informed consent. Hence, participants are adults with type 1 diabetes and suboptimal glycaemic control, treated with basal and bolus insulin and attending an outpatient diabetes clinic in the Capital Region of Denmark. Screening for inclusion was initiated October 1, 2018 and is planned to continue until March 31, 2020.

Intervention

Devices

The automatic bolus calculator

The ABC system used for this trial is the CE-marked mobile telephone diabetes application mySugr available for Android and iPhone. It is a digital logbook designed to support persons with diabetes in their self-management. It consists of an insulin bolus calculator based on the following settings that can be individually adjusted for every half an hour lap though the 24-hours: carbohydrate ratio, insulin sensitivity, target glucose value and insulin duration time. For every meal, the user enters current glucose value and estimated carbohydrate intake and receives a suggestion on insulin bolus dosage. In case of correction of hyperglycaemia, the user enters current glucose value and receives a suggestion on corrective insulin dosage. Data are stored for 3 months.

The intermittently scanned CGM

The isCGM device used in this trial is the FreeStyle Libre Flash CGM system (Abbott Diabetes Care, Alameda, CA, USA). It consists of a 14-day disc sensor to be worn on the upper arm, a reader and/or a mobile phone application to scan and display data. The sensor measures and continuously stores interstitial glucose concentrations every 15 minutes (800 glucose readings / 24 hours). The sensor is inserted into the upper arm skin and placed by a thin needle, which is immediately retracted, leaving a thin 6 mm long plastic glucose recorder in the skin. To obtain a current glucose value, the wearer scans the sensor with either the reader device or a mobile phone application (FreeStyle Libre Link available for Android and iPhone, Abbott Diabetes Care) producing real-time data. The reader devices used for this study were updated mid-2019 (14). The application was available in Denmark for Android and iPhone from mid-2019 (15). The system is CE-marked and accurate enough for insulin dosing except during fluctuant and low glucose levels. Wearers do not need to calibrate the system but to avoid loss of data, the sensor must be scanned every 8 hours. Scanned glucose data are presented to the wearer on the display as numerical values including glucose trends based on automatically stored data. Both intermittently scanned as well as continuously stored glucose data are displayed as graphs and logbooks and are available as numerical values after download from the reader device/mobile phone to a computer by the software program Diasend (Glooko, USA).

Assignment of interventions

Persons eligible for inclusion are randomised 1:1:1:1 by drawing a sealed and opaque randomisation envelope at the screening visit. The envelopes were centrally prepared by a person without relation to the specific trial. The main site was assigned to screen 72 participants, while the four remaining sites were each assigned to screen 32 participants. There is equal distribution of group assignments at each site (18 at the main site; 8 at each of the other four sites). The envelope is left unopened until after the initial blinded CGM period, where the given intervention is revealed; A (standard care), B (ABC), C (isCGM) or D (ABC and isCGM). In case of drop-out, the participant´s allocation is not to be replaced in the remaining randomisation envelopes.

Courses for participants

Four types of group courses for participants are included in the trial (Table 1). Each course includes one to three educational elements according to group allocation. Course length (4-4.5 hours) and group size (4-6 participants) are rather similar between the groups. The educational elements are:

1. General diabetes: Training in general diabetes health issues, how to do experience-based dosing, how to handle sick days, exercise etc. in general terms.
2. ABC: Theoretic and practical training in carbohydrate counting and bolus calculation (5).
3. mySugr diabetes application: The application is downloaded on the participants personal smartphone. The insulin to carbohydrate ratio (the amount of carbohydrates needed to match the glucose lowering effect of 1 unit of subcutaneously injected rapid-acting insulin) and the insulin sensitivity (the decrease in blood glucose in mmol/l caused by 1 unit of subcutaneously injected rapid-acting insulin) are empirically estimated for each participant using the 500- and the 100- rule, respectively (16). The insulin duration time is set at 4 hours. The target glucose value is in general set at 6 mmol/l during daytime and 7 mmol/l during night time.
4. FreeStyle Libre Flash CGM: Participants are instructed to use the system according to our local guideline and those in group D are also instructed in how to incorporate isCGM trend arrows to adjust the mySugr application settings.

All the above-mentioned educational concepts are also practiced during individual consultations throughout the 26-week trial period.

Training of study personnel

The healthcare professionals at the different study sites have been educated in the protocol and different course content and treatment modalities, how to conduct courses and study visits on two separate days before inclusion was initiated. Teachers on these study personnel training sessions were an endocrinologist (KN), a diabetes nurse and a dietitian from the investigator group with substantial experience in the field.

Diabetes care

In line with national guidelines (17), the overall aim in term of diabetes management is to obtain fasting and pre-prandial glucose values of 4-6 mmol/l, post-prandial glucose values lower than 10 mmol/l, to avoid any glucose values lower than 3 mmol/l and keep the number of glucose values below 4 mmol/l at an absolute minimum. At baseline and up to the last study visit, all participants fill in work sheets for daily reporting of basal insulin units, insulin boluses and SMBG values during the two weeks of blinded CGM wear to adjust insulin therapy. Moreover, participants receive a hypoglycaemia diary to fill in symptoms of hypoglycaemia and/or glucose values below 3.9 mmol/l, throughout the trial which is also used for insulin adjustments.

Participants in groups A (standard care) and B (ABC) are encouraged to measure SMBG at least four times daily with their personally preferred glucose meter. Participants in group C (isCGM) and D (isCGM and ABC) are instructed to use the isCGM system according to a local guideline based on manufacturer's guideline (18) and in line with recent publications on the topic (19–21). During both study visits and telephone consultations (see below) study personnel titrate insulin doses based on the different types of glucose values provided and other clinical information i.e. hypoglycaemic events, planned physical activity etc. For participants in group B and D, both the basal insulin dose and the ABC settings (primarily carbohydrate ratio and insulin sensitivity) are evaluated and, if needed, adjusted according to a local guideline based on previous publications and clinical experience (2,22).

Outcomes

The primary outcome is the difference in change from baseline to end of study between groups C (isCGM) and A (standard care) in time spent in normoglycaemia (defined as glucose of 4-10 mmol/l, minutes/24 hours, obtained by blinded CGM (23)).

Secondary outcomes are; difference in change from baseline to end of study between groups in HbA1c (mmol/mol), difference between groups in severe hypoglycaemia occurrence during the study period (defined as hypoglycaemic events requiring assistance from another person), difference between groups in symptomatic and confirmed hypoglycaemia occurrence during the study period (defined as glucose (SMBG or isCGM) < 3 mmol/l), difference in change between baseline and end of study between groups in diabetes distress, diabetes treatment satisfaction, diabetes empowerment, diabetes quality of life, time spent in hypo- (blinded CGM glucose <3 mmol/l, <4 mmol/l, minutes/day) and hyperglycaemia (>10 mmol/l, minutes/day), glycaemic variability (standard deviation), total insulin dose (recorded as a mean of 2 weeks during blinded CGM (insulin units (IU)/day/kg), total basal insulin dose (IU/day/kg), insulin boluses (number/24 hours), body weight (kg), urinary albumin/excretion rate (mg/24 hours) and the association between personality traits scoring at baseline with any outcome measures in the groups.

Methods: data collection, management, and analysis

Data collection

Blinded CGM

After screening for inclusion (before opening the randomisation envelope), and at study end, all participants are asked to wear a blinded (non-real-time) CGM (The FreeStyle Libre Professional CGM system, Abbott Diabetes Care, Oxon, UK) to obtain glucose data. The sensor is inserted by a health care professional (see above for details on the isCGM). While wearing the sensor, users do not need to enter any fingerstick data or carry around a receiver, since the device collects all glucose data automatically. Following two weeks of sensor wear, data are downloaded in office by a reader device and a manufacturer-provided computer software program (LibreLink, Abbott Diabetes Care). These data are collected between screening visit and course participation (baseline data) and the two last study visits (final data), respectively.

Glucose and automatic bolus calculator data

Glucose (SMBG or isCGM) are downloaded to a computer (software Diasend, Glooko, USA) and data from the ABC are sent by e-mail from the user to the project health care professional at study

visit 2, 4 and 6. The average number of symptomatic mild hypoglycaemic episodes per week and any severe hypoglycaemic episode are consecutively recorded throughout the trial.

Questionnaires

At screening and last study visit, all participants fill in the following validated questionnaires; Problem Areas in Diabetes Questionnaire (PAID), Diabetes Treatment Satisfaction Questionnaire (DTSQs at baseline and DTSQs and DTSQc at last visit) (24), Diabetes empowerment test (DES short form) and Diabetes quality of life (ADDQoL-19). At screening, they also fill in the questionnaire Neuroticism Extraversion Openness Agreeableness Conscientiousness Five-Factor Invertory-3 (NEO-FFI-3) and hypo-awareness assessment (25–28).

General health, blood and urine sampling and body weight

A general health/safety assessment, including full objective examination (cardiac and pulmonal auscultation, blood pressure measurement, inspection of insulin injection sites etc.) and information on history of severe hypoglycaemia is performed at screening. At both screening and last visit, all participants have blood and urine samples taken, as well as body weight measured (kg), which is done using the same scale every time. HbA1c (mmol/mol) is measured at screening, midway through the study, and again at last visit.

Study visits and telephone consultations

There are in total five clinical follow-up study visits (visit 2-6) at 2, 4, 12, 24 and 26 weeks planned during the 26 weeks trial participation (see Figure 1). Participants in group A (standard care) and C (isCGM) have appointments with the project nurse, whereas participants in group B (ABC) and D (isCGM and ABC) have joint appointments with both the project nurse and the project dietician. All participants have appointments with the project physician at first visit (screening) and midways throughout participation (visit 4). Visit 3 is not mandatory but proposed to participants in need of extra support or renewed teaching in the allocated intervention. In between the clinical study visits, there are three telephone consultations (1-3) at 0, 8 and 17 weeks where the project nurse contact the participants.

Data management

The data management is performed in accordance with the General Data Protection Regulation. Data are consecutively collected and stored in a browser-based software and workflow database

(REDCap). The database is password protected and only the local and primary investigators have access to the data.

Data analysis

A sample size of 160 (40 per group) was calculated to have 80% power to detect a difference in mean time in target glycaemic range (4-10 mmol/l) between treatment group A and C of 75 minutes per day with a standard deviation of 120 minutes, and a 2-sided α-level of 0.05. Sample size is increased to 180 (45 per group) to account for a potential drop out of approximately 10%.

Changes in primary and secondary outcomes over the intervention period and effects of the treatments will be modelled by linear mixed-effects models with a patient-specific random intercept to account for the correlation of repeated measurements within patients and a random intercept for centre to account for the clustering effect of study centre. The exact times of measurements will be used. All analyses will be performed as an intention to treat analysis. Statistical significance will be inferred at a two-tailed $P < 0.05$. The p-values for secondary outcomes will be corrected by the Benjamini-Hochberg method for multiple comparisons (29).

Public and patient involvement

Persons with type 1 diabetes were not involved in the initial phases of the study. Already recruited participants, however, are asked to assess the burden of the intervention and time required to participate in the research. This has resulted in a supplementary document that is presented to possible participants to give a realistic picture of time spent on participation over time. Persons with type 1 diabetes will be sought to be involved in the dissemination plan of the results by for example commenting on written information with regards to language and form.

ETHICS AND DISSEMINATION

The study is carried out in accordance with the Helsinki Declaration after approval by the Regional Scientific Ethics Committee (H-17040573) and is registered at clinical trial.gov (NCT03682237).

Until now, an early generation isCGM has been found to improve time spent in hypoglycaemia, treatment satisfaction and other person related outcomes in people with near-optimal HbA1c (9). A

number of observational studies have evaluated isCGM in broader populations with regards to change in HbA1c and accuracy and satisfaction among wearers (10–13). To date, however, no randomised controlled trials have been performed to examine the efficacy of isCGM to increase time in range in patients with suboptimal HbA1c. In addition, carbohydrate counting with ABC has been proved to improve HbA1c and patient satisfaction (2) and nutritional therapy has an integral role in diabetes management (30). Which one of the two treatment concepts that is superior to the other, and whether there is an additive effect of the two combined, has to our knowledge not previously been evaluated. Most important, however, no randomised controlled trials have been performed to examine the efficacy of isCGM to increase time in range in patients with suboptimal HbA1c. A possible limitation may be difficulty with recruiting enough participants in order to reach power estimates.

The investigators expect that the current study results will help guiding persons with type 1 diabetes treated with MDI and their health care professionals in choosing evidence-based methods for optimal glycaemic control. We believe that the possible risks and side effects among participants are outweighed by the potential benefits from the conduct of this study. The overall individual risk of side effects is expected to be modest and is mainly related to the time spent on learning how to count carbohydrates and use the mySugr application and/or using the isCGM system. With regards to all other planned study procedures, the risk of complications or adverse events is negligible and outweighed by the possible beneficial effects of conducting the study. The occurrence of any adverse events will be assessed at every visit and telephone contact during the study period. All participants are covered by the mandatory individual insurance at each local hospital in The Capital Region of Denmark. Blood samples are analysed directly after sampling without the establishment of a biobank. If the study is prematurely terminated, the investigators will promptly inform the Regional Scientific Ethics Committee and the participants to assure appropriate therapy and follow-up.

The study results are expected to be disseminated at international and national diabetes conferences and meetings and published in international journals with considerable impact. All participants who at first study visit expressed an interest in the results will receive a short version of the main findings expressed in lay terms and will be invited to a short oral presentation at the main study site. The results will also be sought presented to the Danish Diabetes Association and communicated to the public by a press release.

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AUTHOR´S CONTRIBUTION

ALS wrote the first draft of the manuscript. Critical revision of the manuscript: UPB, OLS, BGR, TA, LD, DV and KN.

FUNDING STATEMENT

The study is investigator-initiated and -driven, financed by The Capital Region of Denmark. None of the investigators have personal financial interest in the conduct or the outcome of the project.

COMPETING INTEREST STATEMENTS

KN is a shareholder of Novo Nordisk; has received research support from Novo Nordisk, Roche Diagnostics, Dexcom and Zealand Pharma; has received lecture fees from Medtronic, Roche Diagnostics, Rubin Medical, Sanofi, Zealand Pharma, Novo Nordisk, and Dexcom; and has served on advisory panels for Medtronic, Abbott, and Novo Nordisk. UPB has served on advisory boards for AstraZeneca, Bristol-Myers Squibb, Sanofi-Aventis, Novo Nordisk and Zealand Pharma and has received lecture fees from AstraZeneca, Bristol-Myers Squibb, Sanofi-Aventis and Novo Nordisk. TA holds stocks in Novo Nordisk. ALS, OLS, BGR, LD and DV do not have any competing interests.

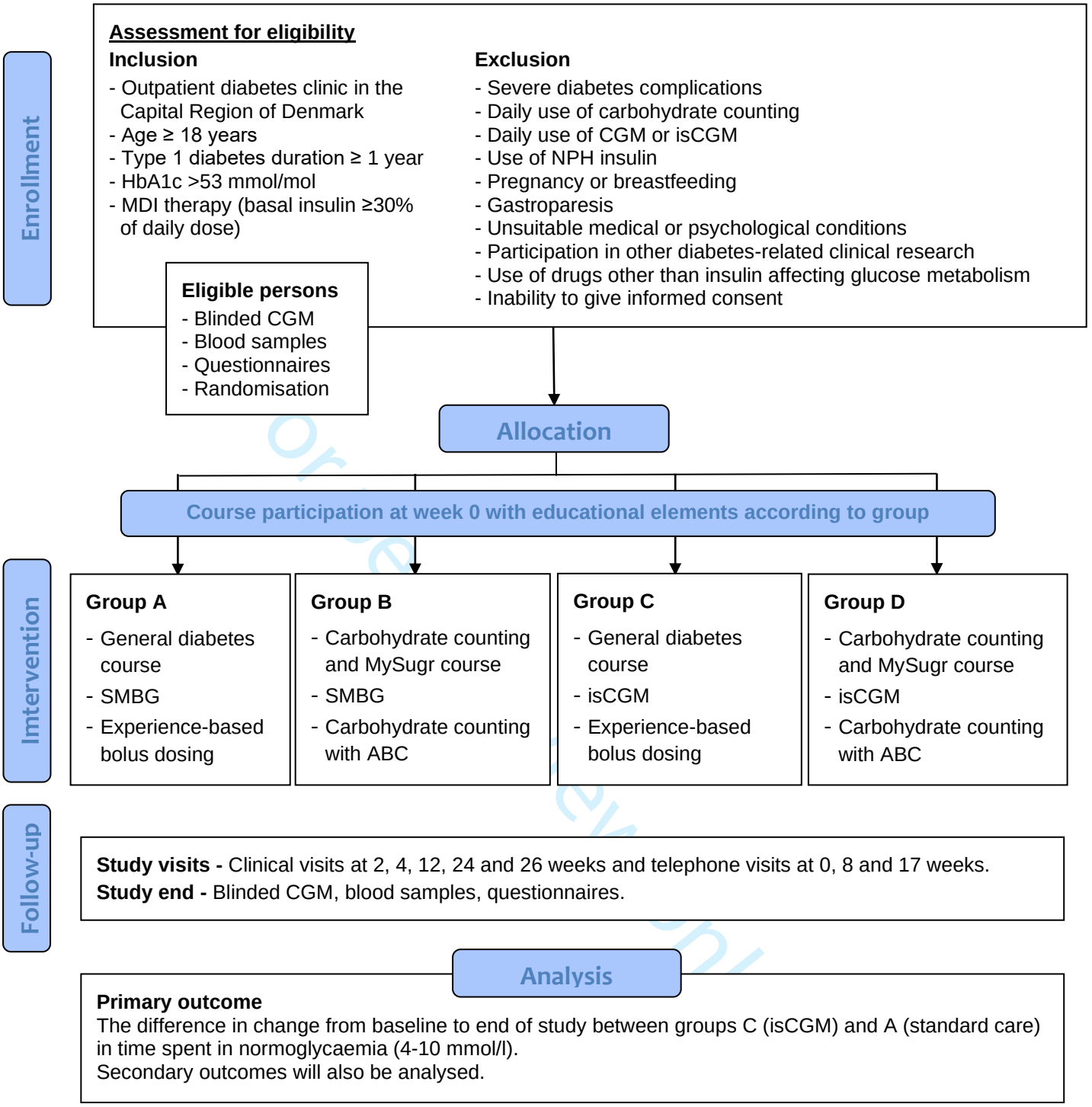
WORD COUNT

Abstract 296 words, full text 3,295 of 4,000 allowed words.

Table 1. Overview of glucose measurement methods, decision on insulin bolus and educational element in course according to group allocation. Abbreviations: SMBG (self-monitored blood glucose), isCGM (intermittently scanned glucose monitoring).

Intervention group	Glucose measurement method	Decision on insulin bolus	Educational element in course
A	SMBG	Experience-based	• General diabetes
B	SMBG	Carbohydrate counting with automatic bolus calculator	• Training in carbohydrate counting • Training in the use of the application mySugr
C	isCGM	Experience-based	• General diabetes • Training in FreeStyle Libre Flash use
D	isCGM	Carbohydrate counting with automatic bolus calculator	• Training in carbohydrate counting • Training in the use of the application mySugr • Training in FreeStyle Libre Flash use and how to incorporate glucose trend arrows to adjust the mySugr application settings

Figure legend, figure 1. Flow chart of participants throughout the trial.


Enrollment
Assessment for eligibility
Inclusion
- Outpatient diabetes clinic in the Capital Region of Denmark
- Age ≥ 18 years
- Type 1 diabetes duration ≥ 1 year
- HbA1c >53 mmol/mol
- MDI therapy (basal insulin ≥30% of daily dose)
Exclusion
- Severe diabetes complications
- Daily use of carbohydrate counting
- Daily use of CGM or isCGM
- Use of NPH insulin
- Pregnancy or breastfeeding
- Gastroparesis
- Unsuitable medical or psychological conditions
- Participation in other diabetes-related clinical research
- Use of drugs other than insulin affecting glucose metabolism
- Inability to give informed consent
Eligible persons
- Blinded CGM
- Blood samples
- Questionnaires
- Randomisation
Allocation
Course participation at week 0 with educational elements according to group
Imtervention
Group A
- General diabetes course
- SMBG
- Experience-based bolus dosing
Group B
- Carbohydrate counting and MySugr course
- SMBG
- Carbohydrate counting with ABC
Group C
- General diabetes course
- isCGM
- Experience-based bolus dosing
Group D
- Carbohydrate counting and MySugr course
- isCGM
- Carbohydrate counting with ABC
Follow-up
Study visits - Clinical visits at 2, 4, 12, 24 and 26 weeks and telephone visits at 0, 8 and 17 weeks.
Study end - Blinded CGM, blood samples, questionnaires.
Analysis
Primary outcome
The difference in change from baseline to end of study between groups C (isCGM) and A (standard care) in time spent in normoglycaemia (4-10 mmol/l).
Secondary outcomes will also be analysed.

(S1)

Informeret samtykke til deltagelse i et sundhedsvidenskabeligt forskningsprojekt.

Forskningsprojektets titel:

Optimizing metabolic control in type 1 diabetes treated with multiple daily insulin injections - flash glucose monitoring, carbohydrate counting with automated bolus calculation, or both?

Dansk:

Forbedring af diabeteskontrollen hos Type 1 diabetes patienter - Flash glukose måling, kulhydrattælling med automatisk bolus-beregning eller begge dele?

Erklæring fra forsøgspersonen:

Jeg har fået skriftlig og mundtlig information og jeg ved nok om formål, metode, fordele og ulemper til at sige ja til at deltage.

Jeg ved, at det er frivilligt at deltage, og at jeg altid kan trække mit samtykke tilbage uden at miste mine nuværende eller fremtidige rettigheder til behandling.

Jeg giver samtykke til, at deltage i forskningsprojektet, og har fået en kopi af dette samtykkeark samt en kopi af den skriftlige information om projektet til eget brug.

Forsøgspersonens navn: _____

Dato: _____ Underskrift: _____

Ønsker du at blive informeret om forskningsprojektets resultat samt eventuelle konsekvenser for dig?:

Ja _____ (sæt x) Nej _____ (sæt x)

Erklæring fra den, der afgiver information:

Jeg erklærer, at forsøgspersonen har modtaget mundtlig og skriftlig information om forsøget.

Efter min overbevisning er der givet tilstrækkelig information til, at der kan træffes beslutning om deltagelse i forsøget.

Navnet på den, der har afgivet information:

Dato: _____ Underskrift: _____

Projektidentifikation: (ABC/Flash version 1.0)

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym (page 1)0
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry page (page 1)
	2b	All items from the World Health Organization Trial Registration Data Set (not relevant)
Protocol version	3	Date and version identifier (page 1)
Funding	4	Sources and types of financial, material, and other support (pages 2, 16)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors (pages 1-2)
	5b	Name and contact information for the trial sponsor (not relevant)
	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 (not relevant)
	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) (not relevant)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention (pages 4-5)
	6b	Explanation for choice of comparators (pages 4-5)
Objectives	7	Specific objectives or hypotheses (page 5)

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) (pages 5, 7)
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained (page 5)
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) (page 5)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered (pages 6-8)
	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) (pages 5-8)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) (page 7)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial (pages 6-8)
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 (pages 8-9)
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) (pages 9-10 and Figure 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 (page 11)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size (page 5)
Methods: Assignment of interventions (for controlled trials)		
Allocation:		

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions (page 7)
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 (page 7)
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions (page 7)
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how (not relevant)
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial (not relevant)
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol (pages 9-11)
	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 (pages 9-11)
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 (pages 10-11)
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 (pages 10-11)
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) (pages 10-11)
	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) (pages 10-11)

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed (not relevant)
	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 (not relevant)
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 (pages 9-10, 11-12)
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor (not relevant)

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval (not relevant, is approved)
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) (pages 11-12)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) (pages 5, 11-12)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable (not relevant)
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 (pages 10-11)
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site (page 16)
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 (not applicable currently)

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 (pages 11-12)
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions (not relevant)
	31b	Authorship eligibility guidelines and any intended use of professional writers (not relevant)
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code (not applicable currently)
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates (not relevant, it is a protocol manuscript)
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 (not applicable)

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

BMJ Open

Study protocol for optimising glycaemic control in type 1 diabetes treated with multiple daily insulin injections - intermittently scanned continuous glucose monitoring, carbohydrate counting with automated bolus calculation, or both? A randomised controlled trial

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Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Diabetes and endocrinology
Keywords:	General diabetes < DIABETES & ENDOCRINOLOGY, NUTRITION & DIETETICS, BIOTECHNOLOGY & BIOINFORMATICS

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Title

Original title: Study protocol for optimising glycaemic control in type 1 diabetes treated with multiple daily insulin injections - intermittently scanned continuous glucose monitoring, carbohydrate counting with automated bolus calculation, or both? A randomised controlled trial

Short title: The ABC Flash Study

Trial registration

The study is carried out in accordance with the Helsinki Declaration after approval by the Regional Scientific Ethics Committee (H-17040573). The data collection and handling are performed in accordance with the General Data Protection Regulation. The trial is registered at www.clinicaltrial.gov (NCT03682237).

Protocol version

Version 3, March 18, 2020.

Funding

The study is investigator initiated and financed by The Capital Region of Denmark. None of the investigators have personal financial interest in the conduct or the outcome of the project.

Roles and responsibilities

KN is the primary investigator of the study. The study concept, trial design and study protocol: ALS, UPB, OLS, BGR, TA, LD and DV.

ABSTRACT

Introduction:

There are beneficial effects of advanced carbohydrate counting with an automatic bolus calculator (ABC) and intermittently scanned continuous glucose monitoring (isCGM) in persons with type 1 diabetes. We aim to compare the effects of isCGM, training in carbohydrate counting with ABC and the combination of the two concepts with standard care.

Methods and analysis:

A multi-centre randomised controlled trial with inclusion criteria; ≥18 years, type 1 diabetes ≥1 year, injection therapy, HbA1c >53 mmol/mol, whereas daily use of carbohydrate counting and/or CGM/isCGM wear are exclusion criteria. Inclusion was initiated in October 2018 and is ongoing. Eligible persons are randomised into 4 groups; standard care, ABC, isCGM, or ABC + isCGM. Devices used are FreeStyle Libre Flash and smart phone diabetes application mySugr. Participants attend group courses according to treatment allocation with different educational contents. Participants are followed for 26 weeks with clinical visits and telephone consultations. At baseline and at study end, participants wear blinded CGM, have blood samples performed and fill in questionnaires on person related outcomes, and at baseline also on personality traits and hypoglycaemia awareness. The primary outcome is the difference in time spent in normoglycaemia (4-10 mmol/l) at study end vs. baseline between the isCGM group and the standard care group. Secondary outcomes will also be analysed. Results are expected in 2020.

Ethics and dissemination:

Regional Scientific Ethics Committee approval (H-17040573). Results will be sought disseminated at conferences and in high impact journals.

Strengths and limitations of this study:

- Despite its relevance for many persons with diabetes and their caregivers, the topic has not yet been rigorously examined to evaluate efficacy on glycaemic control.
- Robustly designed randomised controlled trial.
- A possible limitation may be difficulty with recruiting enough participants in order to reach power estimates. Unbalanced withdrawal and basal insulin reductions may affect the results.

INTRODUCTION

Insulin therapy in type 1 diabetes is generally adjusted according to food intake, physical activity and current blood glucose levels. It typically involves the combination of fast-acting insulin before meals and to correct hyperglycaemia, and long-acting insulin to control blood glucose overnight and in between meals, referred to as multiple daily injections (MDI). In order to obtain optimal glycaemic control it requires dose adjustment based on the amount of carbohydrate ingested at each meal (1) and frequent self-monitoring of blood glucose (SMBG) measurements. Carbohydrate counting is done based on experience or by using either manual or automatic estimates. Several studies have shown improved HbA1c and treatment satisfaction as well as a tendency towards less hypoglycaemia in persons undergoing training in carbohydrate counting and manual bolus calculation compared to insulin dosing based on experience (1–3). In addition, the use of an automatic bolus calculator (ABC) rather than manual bolus calculation has been proved to reduce HbA1c and improve patient satisfaction (2), with unaffected hypoglycaemia rate (4). Even in a routine care setting, group courses of 4 hours in bolus calculation with ABC and follow-up consultations have shown a reduction in HbA1c with maintained effect 12 months post-course (5). Our experience is that many persons with type 1 diabetes have never been trained in carbohydrate counting or the algorithm for insulin dose calculation.

Compared with conventional SMBG, the use of continuous glucose monitoring (CGM) in MDI treated persons reduces HbA1c and the time spent in mild hypoglycaemia and improves treatment satisfaction (6–8). A variation of real-time CGM is the intermittently scanned CGM (isCGM), where the first-generation readers are without glycaemic alerts, and the wearer scans the sensor to transfer glucose data. An early generation of isCGM has been found to decrease time spent in hypoglycaemia and increase treatment satisfaction and other person related outcomes in people with near-optimal HbA1c at baseline (9). A number of observational studies have evaluated isCGM in terms of accuracy and change in HbA1c (10), with positive reports on wearer satisfaction (11). Two recent observational studies including 120 and 900 adults, respectively, mainly on MDI found improved HbA1c levels, however with moderate increase in mild hypoglycaemic events (12,13), but fewer diabetic ketoacidosis admissions (13). The most pronounced reduction in HbA1c was seen in those with higher HbA1c prior to isCGM use (13). To date, however, no randomised controlled trials exist examining the efficacy of isCGM to increase time in range in patients with suboptimal HbA1c.

It also remains unknown which of the two concepts, bolus calculation with ABC or the use of isCGM, is superior and whether there is an additive effect of the two combined. Furthermore, there are no studies on how to structure training and optimise treatment in patients doing bolus calculation with the concomitant use of isCGM.

In the current study, the primary aim is to compare the effect of isCGM with standard care (SMBG) on glycaemic control. The secondary aim is to compare the effect of the combination of training in carbohydrate counting with ABC and the use of isCGM with standard care. We also aim to assess whether isCGM use can outperform training in carbohydrate counting with ABC.

METHODS AND ANALYSIS

Methods: Participants, interventions and outcomes

Participants

The ABC Flash Study is a randomised controlled, open-label, four-arm parallel trial carried out at five sites in The Capital Region of Denmark; Steno Diabetes Center Copenhagen, Rigshospitalet, Amager and Hvidovre Hospital, Nordsjællands Hospital Hillerød, and Bispebjerg and Frederiksberg Hospital. Inclusion criteria are age ≥ 18 years, type 1 diabetes duration ≥ 1 year, HbA1c > 53 mmol/mol, and the use of MDI therapy with basal insulin accounting for ≥ 30 % of the total daily insulin dose. Exclusion criteria are daily use of carbohydrate counting or CGM, use of NPH insulin, pregnancy, breastfeeding, gastroparesis, severe diabetes complications (i.e. proliferative retinopathy, myocardial infarction within the last six months), other medical or psychological conditions judged unsuitable for study participation, participation in other diabetes-related clinical research, the use of other drugs than insulin affecting glucose metabolism, or the inability to understand the individual information and to give informed consent. Hence, participants are adults with type 1 diabetes and suboptimal glycaemic control, treated with basal and bolus insulin and attending an outpatient diabetes clinic in the Capital Region of Denmark. Screening for inclusion was initiated October 1, 2018 and is planned to continue until March 31, 2020.

Intervention

Devices

The automatic bolus calculator

The ABC system used for this trial is the CE-marked mobile telephone diabetes application mySugr available for Android and iPhone. It is a digital logbook designed to support persons with diabetes in their self-management. It consists of an insulin bolus calculator based on the following settings that can be individually adjusted for every half an hour lap though the 24-hours: carbohydrate ratio, insulin sensitivity, target glucose value and insulin duration time. For every meal, the user enters current glucose value and estimated carbohydrate intake and receives a suggestion on insulin bolus dosage. In case of correction of hyperglycaemia, the user enters current glucose value and receives a suggestion on corrective insulin dosage. Data are stored for 3 months.

The intermittently scanned CGM

The isCGM device used in this trial is the FreeStyle Libre Flash CGM system (Abbott Diabetes Care, Alameda, CA, USA). It consists of a 14-day disc sensor to be worn on the upper arm, a reader and/or a mobile phone application to scan and display data. The sensor measures and continuously stores interstitial glucose concentrations every 15 minutes (800 glucose readings / 24 hours). The sensor is inserted into the upper arm skin and placed by a thin needle, which is immediately retracted, leaving a thin 6 mm long plastic glucose recorder in the skin. To obtain a current glucose value, the wearer scans the sensor with either the reader device or a mobile phone application (FreeStyle Libre Link available for Android and iPhone, Abbott Diabetes Care) producing real-time data. The reader devices used for this study were updated mid-2019 (14). The application was available in Denmark for Android and iPhone from mid-2019 (15). The system is CE-marked and accurate enough for insulin dosing except during fluctuant and low glucose levels. Wearers do not need to calibrate the system but to avoid loss of data, the sensor must be scanned every 8 hours. Scanned glucose data are presented to the wearer on the display as numerical values including glucose trends based on automatically stored data. Both intermittently scanned as well as continuously stored glucose data are displayed as graphs and logbooks and are available as numerical values after download from the reader device/mobile phone to a computer by the software program Diasend (Glooko, USA).

Assignment of interventions

Persons eligible for inclusion are randomised 1:1:1:1 by drawing a sealed and opaque randomisation envelope at the screening visit. The envelopes were centrally prepared by a person without relation to the specific trial. The main site was assigned to screen 72 participants, while the four remaining sites were each assigned to screen 32 participants. There is equal distribution of group assignments at each site (18 at the main site; 8 at each of the other four sites). The envelope is left unopened until after the initial blinded CGM period, where the given intervention is revealed; A (standard care), B (ABC), C (isCGM) or D (ABC and isCGM). In case of drop-out, the participant´s allocation is not to be replaced in the remaining randomisation envelopes.

Courses for participants

Four types of group courses for participants are included in the trial (Table 1). Each course includes one to three educational elements according to group allocation. Course length (4-4.5 hours) and group size (4-6 participants) are rather similar between the groups. The educational elements are:

1. General diabetes: Training in general diabetes health issues, how to do experience-based dosing, how to handle sick days, exercise etc. in general terms.
2. ABC: Theoretic and practical training in carbohydrate counting and bolus calculation (5).
3. mySugr diabetes application: The application is downloaded on the participants personal smartphone. The insulin to carbohydrate ratio (the amount of carbohydrates needed to match the glucose lowering effect of 1 unit of subcutaneously injected rapid-acting insulin) and the insulin sensitivity (the decrease in blood glucose in mmol/l caused by 1 unit of subcutaneously injected rapid-acting insulin) are empirically estimated for each participant using the 500- and the 100- rule, respectively (16). The insulin duration time is set at 4 hours. The target glucose value is in general set at 6 mmol/l during daytime and 7 mmol/l during night time.
4. FreeStyle Libre Flash CGM: Participants are instructed to use the system according to our local guideline and those in group D are also instructed in how to incorporate isCGM trend arrows to adjust the mySugr application settings.

All the above-mentioned educational concepts are also practiced during individual consultations throughout the 26-week trial period.

Training of study personnel

The healthcare professionals at the different study sites have been educated in the protocol and different course content and treatment modalities, how to conduct courses and study visits on two separate days before inclusion was initiated. Teachers on these study personnel training sessions were an endocrinologist (KN), a diabetes nurse and a dietitian from the investigator group with substantial experience in the field.

Diabetes care

In line with national guidelines (17), the overall aim in term of diabetes management is to obtain fasting and pre-prandial glucose values of 4-6 mmol/l, post-prandial glucose values lower than 10 mmol/l, to avoid any glucose values lower than 3 mmol/l and keep the number of glucose values below 4 mmol/l at an absolute minimum. At baseline and up to the last study visit, all participants fill in work sheets for daily reporting of basal insulin units, insulin boluses and SMBG values during the two weeks of blinded CGM wear to adjust insulin therapy. Moreover, participants receive a hypoglycaemia diary to fill in symptoms of hypoglycaemia and/or glucose values below 3.9 mmol/l, throughout the trial which is also used for insulin adjustments.

Participants in groups A (standard care) and B (ABC) are encouraged to measure SMBG at least four times daily with their personally preferred glucose meter. Participants in group C (isCGM) and D (isCGM and ABC) are instructed to use the isCGM system according to a local guideline based on manufacturer's guideline (18) and in line with recent publications on the topic (19–21). During both study visits and telephone consultations (see below) study personnel titrate insulin doses based on the different types of glucose values provided and other clinical information i.e. hypoglycaemic events, planned physical activity etc. For participants in group B and D, both the basal insulin dose and the ABC settings (primarily carbohydrate ratio and insulin sensitivity) are evaluated and, if needed, adjusted according to a local guideline based on previous publications and clinical experience (2,22).

Outcomes

The primary outcome is the difference in change from baseline to end of study between groups C (isCGM) and A (standard care) in time spent in normoglycaemia (defined as glucose of 4-10 mmol/l, minutes/24 hours, obtained by blinded CGM (23)).

Secondary outcomes are; difference in change from baseline to end of study between groups in HbA1c (mmol/mol), difference between groups in severe hypoglycaemia occurrence during the study period (defined as an event requiring assistance of another person, plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal, number of events during study period), difference between groups in symptomatic and confirmed hypoglycaemia occurrence during the study period (defined as glucose (SMBG or isCGM) < 3 mmol/l, number of events per week), difference in change between baseline and end of study between groups in diabetes distress, diabetes treatment satisfaction, diabetes empowerment, diabetes quality of life, time spent in hypo- (blinded CGM glucose <3 mmol/l, <4 mmol/l, minutes/day) and hyperglycaemia (>10 mmol/l, minutes/day), glycaemic variability (standard deviation), total insulin dose (recorded as a mean of 2 weeks during blinded CGM (insulin units (IU)/day/kg), total basal insulin dose (IU/day/kg), insulin boluses (number/24 hours), body weight (kg) and urinary albumin/excretion rate (mg/24 hours), and last the association between personality traits scoring at baseline with any outcome measures in the groups.

Methods: data collection, management, and analysis

Data collection

Blinded CGM

After screening for inclusion (before opening the randomisation envelope), and at study end, all participants are asked to wear a blinded (non-real-time) CGM (The FreeStyle Libre Professional CGM system, Abbott Diabetes Care, Oxon, UK) to obtain glucose data. The sensor is inserted by a health care professional (see above for details on the isCGM). While wearing the sensor, users do not need to enter any fingerstick data or carry around a receiver, since the device collects all glucose data automatically. Following two weeks of sensor wear, data are downloaded in office by a reader device and a manufacturer-provided computer software program (LibreLink, Abbott Diabetes Care). These data are collected between screening visit and course participation (baseline data) and the two last study visits (final data), respectively.

Glucose and automatic bolus calculator data

Glucose (SMBG or isCGM) are downloaded to a computer (software Diasend, Glooko, USA) and data from the ABC are sent by e-mail from the user to the project health care professional at study visit 2, 4 and 6. The average number of symptomatic mild hypoglycaemic episodes per week and any severe hypoglycaemic episode are consecutively recorded throughout the trial.

Questionnaires

At screening and last study visit, all participants fill in the following validated questionnaires; Problem Areas in Diabetes Questionnaire (PAID), Diabetes Treatment Satisfaction Questionnaire (DTSQs at baseline and DTSQs and DTSQc at last visit) (24), Diabetes empowerment test (DES short form) and Diabetes quality of life (ADDQoL-19). At screening, they also fill in the questionnaire Neuroticism Extraversion Openness Agreeableness Conscientiousness Five-Factor Invertory-3 (NEO-FFI-3) and hypo-awareness assessment (25–28).

General health, blood and urine sampling and body weight

A general health/safety assessment, including full objective examination (cardiac and pulmonal auscultation, blood pressure measurement, inspection of insulin injection sites etc.) and information on history of severe hypoglycaemia is performed at screening. At both screening and last visit, all participants have blood and urine samples taken, as well as body weight measured (kg), which is done using the same scale every time. HbA1c (mmol/mol) is measured at screening, midway through the study, and again at last visit.

Study visits and telephone consultations

There are in total five clinical follow-up study visits (visit 2-6) at 2, 4, 12, 24 and 26 weeks planned during the 26 weeks trial participation (see Figure 1). Participants in group A (standard care) and C (isCGM) have appointments with the project nurse, whereas participants in group B (ABC) and D (isCGM and ABC) have joint appointments with both the project nurse and the project dietician. All participants have appointments with the project physician at first visit (screening) and midways throughout participation (visit 4). Visit 3 is not mandatory but proposed to participants in need of extra support or renewed teaching in the allocated intervention. In between the clinical study visits, there are three telephone consultations (1-3) at 0, 8 and 17 weeks where the project nurse contact the participants.

Data management

The data management is performed in accordance with the General Data Protection Regulation. Data are consecutively collected and stored in a browser-based software and workflow database (REDCap). The database is password protected and only the local and primary investigators have access to the data.

Data analysis

A sample size of 160 (40 per group) was calculated to have 80% power to detect a difference in mean time in target glycaemic range (4-10 mmol/l) between treatment group A and C of 75 minutes per day with a standard deviation of 120 minutes, and a 2-sided α-level of 0.05. Sample size is increased to 180 (45 per group) to account for a potential drop out of approximately 10%.

Changes in primary and secondary outcomes over the intervention period and effects of the treatments will be modelled by linear mixed-effects models with a patient-specific random intercept to account for the correlation of repeated measurements within patients and a random intercept for centre to account for the clustering effect of study centre. The exact times of measurements will be used. All analyses will be performed as an intention to treat analysis. Statistical significance will be inferred at a two-tailed $P < 0.05$. The p-values for secondary outcomes will be corrected by the Benjamini-Hochberg method for multiple comparisons (29).

Public and patient involvement

Persons with type 1 diabetes were not involved in the initial phases of the study. Already recruited participants, however, are asked to assess the burden of the intervention and time required to participate in the research. This has resulted in a supplementary document that is presented to possible participants to give a realistic picture of time spent on participation over time. Persons with type 1 diabetes will be sought to be involved in the dissemination plan of the results by for example commenting on written information with regards to language and form.

ETHICS AND DISSEMINATION

The study is carried out in accordance with the Helsinki Declaration after approval by the Regional Scientific Ethics Committee (H-17040573) and is registered at clinical trial.gov (NCT03682237).

Until now, an early generation isCGM has been found to improve time spent in hypoglycaemia, treatment satisfaction and other person related outcomes in people with near-optimal HbA1c (9). A number of observational studies have evaluated isCGM in broader populations with regards to change in HbA1c and accuracy and satisfaction among wearers (10–13). To date, however, no randomised controlled trials have been performed to examine the efficacy of isCGM to increase time in range in patients with suboptimal HbA1c. In addition, carbohydrate counting with ABC has been proved to improve HbA1c and patient satisfaction (2) and nutritional therapy has an integral role in diabetes management (30). Which one of the two treatment concepts that is superior to the other, and whether there is an additive effect of the two combined, has to our knowledge not previously been evaluated. Most important, however, no randomised controlled trials have been performed to examine the efficacy of isCGM to increase time in range in patients with suboptimal HbA1c. A possible limitation may be difficulty with recruiting enough participants in order to reach power estimates. Unbalanced withdrawal may be a risk, as we believe that the demands are higher on participants allocated to one of the two carbohydrate counting groups. Furthermore, as isCGM us not fully reimbursed in Denmark, some participants may sign up for the study with the hope of being randomised to isCGM. Basal insulin reductions may also play a role in achieving glycaemic aims.

The investigators expect that the current study results will help guiding persons with type 1 diabetes treated with MDI and their health care professionals in choosing evidence-based methods for optimal glycaemic control. We believe that the possible risks and side effects among participants are outweighed by the potential benefits from the conduct of this study. The overall individual risk of side effects is expected to be modest and is mainly related to the time spent on learning how to count carbohydrates and use the mySugr application and/or using the isCGM system. With regards to all other planned study procedures, the risk of complications or adverse events is negligible and outweighed by the possible beneficial effects of conducting the study. The occurrence of any adverse events will be assessed at every visit and telephone contact during the study period. All participants are covered by the mandatory individual insurance at each local hospital in The Capital Region of Denmark. Blood samples are analysed directly after sampling without the establishment

of a biobank. If the study is prematurely terminated, the investigators will promptly inform the Regional Scientific Ethics Committee and the participants to assure appropriate therapy and follow-up.

The study results are expected to be disseminated at international and national diabetes conferences and meetings and published in international journals with considerable impact. All participants who at first study visit expressed an interest in the results will receive a short version of the main findings expressed in lay terms and will be invited to a short oral presentation at the main study site. The results will also be sought presented to the Danish Diabetes Association and communicated to the public by a press release.

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AUTHOR´S CONTRIBUTION

ALS wrote the first draft of the manuscript. Critical revision of the manuscript: UPB, OLS, BGR, TA, LD, DV and KN.

FUNDING STATEMENT

The study is investigator-initiated and -driven, financed by The Capital Region of Denmark. None of the investigators have personal financial interest in the conduct or the outcome of the project.

COMPETING INTEREST STATEMENTS

KN is a shareholder of Novo Nordisk; has received research support from Novo Nordisk, Roche Diagnostics, Dexcom and Zealand Pharma; has received lecture fees from Medtronic, Roche Diagnostics, Rubin Medical, Sanofi, Zealand Pharma, Novo Nordisk, and Dexcom; and has served on advisory panels for Medtronic, Abbott, and Novo Nordisk. UPB has served on advisory boards for AstraZeneca, Bristol-Myers Squibb, Sanofi-Aventis, Novo Nordisk and Zealand Pharma and has received lecture fees from AstraZeneca, Bristol-Myers Squibb, Sanofi-Aventis and Novo Nordisk. TA holds stocks in Novo Nordisk. ALS, OLS, BGR, LD and DV do not have any competing interests.

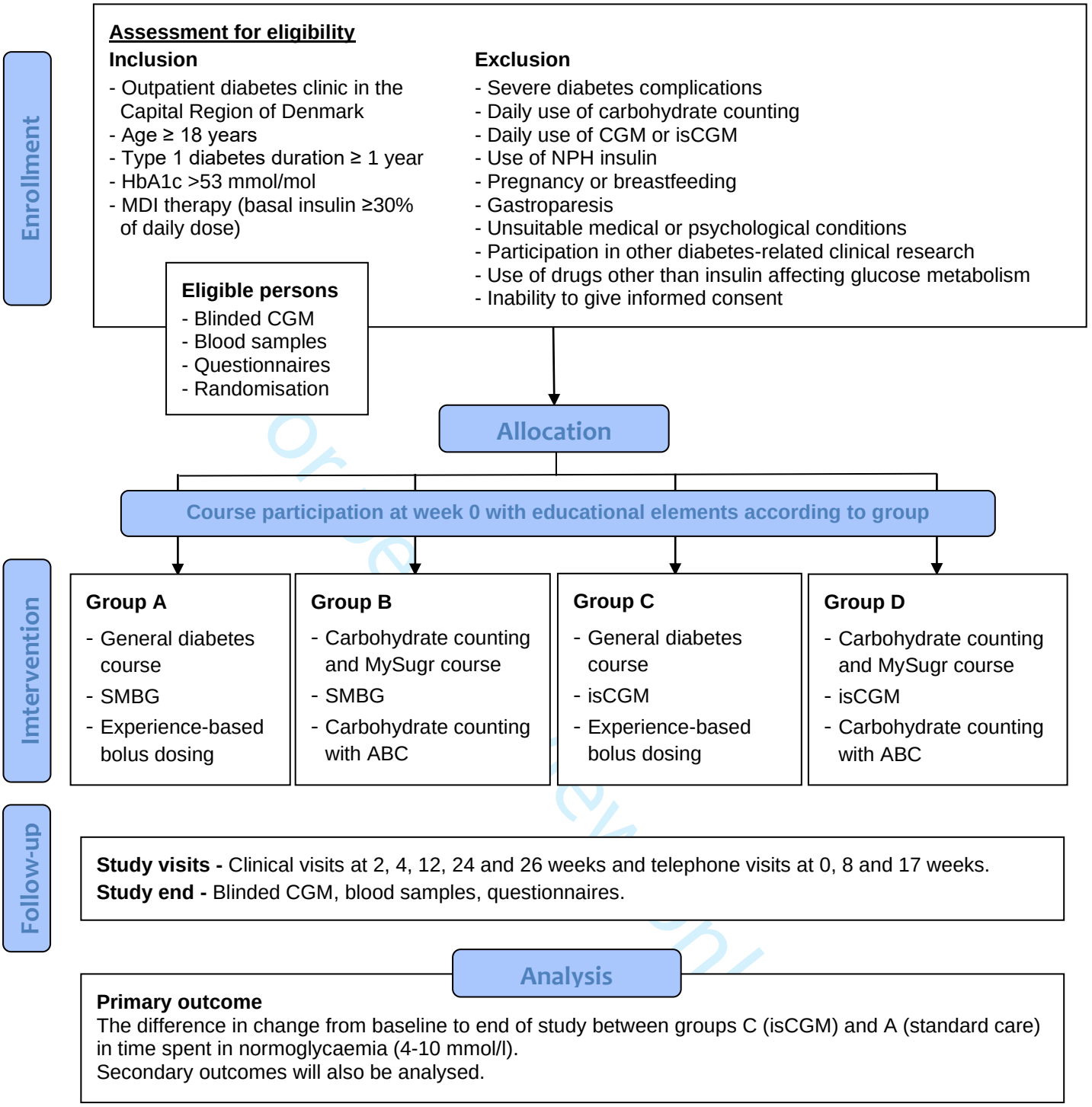
WORD COUNT

Abstract 300 words, full text 3,391 of 4,000 allowed words.

Table 1. Overview of glucose measurement methods, decision on insulin bolus and educational element in course according to group allocation. Abbreviations: SMBG (self-monitored blood glucose), isCGM (intermittently scanned glucose monitoring).

Intervention group	Glucose measurement method	Decision on insulin bolus	Educational element in course
A	SMBG	Experience-based	• General diabetes
B	SMBG	Carbohydrate counting with automatic bolus calculator	• Training in carbohydrate counting • Training in the use of the application mySugr
C	isCGM	Experience-based	• General diabetes • Training in FreeStyle Libre Flash use
D	isCGM	Carbohydrate counting with automatic bolus calculator	• Training in carbohydrate counting • Training in the use of the application mySugr • Training in FreeStyle Libre Flash use and how to incorporate glucose trend arrows to adjust the mySugr application settings

Figure legend, figure 1. Flow chart of participants throughout the trial.


Enrollment
Assessment for eligibility
Inclusion
- Outpatient diabetes clinic in the Capital Region of Denmark
- Age ≥ 18 years
- Type 1 diabetes duration ≥ 1 year
- HbA1c >53 mmol/mol
- MDI therapy (basal insulin ≥30% of daily dose)
Exclusion
- Severe diabetes complications
- Daily use of carbohydrate counting
- Daily use of CGM or isCGM
- Use of NPH insulin
- Pregnancy or breastfeeding
- Gastroparesis
- Unsuitable medical or psychological conditions
- Participation in other diabetes-related clinical research
- Use of drugs other than insulin affecting glucose metabolism
- Inability to give informed consent
Eligible persons
- Blinded CGM
- Blood samples
- Questionnaires
- Randomisation
Allocation
Course participation at week 0 with educational elements according to group
Imtervention
Group A
- General diabetes course
- SMBG
- Experience-based bolus dosing
Group B
- Carbohydrate counting and MySugr course
- SMBG
- Carbohydrate counting with ABC
Group C
- General diabetes course
- isCGM
- Experience-based bolus dosing
Group D
- Carbohydrate counting and MySugr course
- isCGM
- Carbohydrate counting with ABC
Follow-up
Study visits - Clinical visits at 2, 4, 12, 24 and 26 weeks and telephone visits at 0, 8 and 17 weeks.
Study end - Blinded CGM, blood samples, questionnaires.
Analysis
Primary outcome
The difference in change from baseline to end of study between groups C (isCGM) and A (standard care) in time spent in normoglycaemia (4-10 mmol/l).
Secondary outcomes will also be analysed.

(S1)

Informeret samtykke til deltagelse i et sundhedsvidenskabeligt forskningsprojekt.

Forskningsprojektets titel:

Optimizing metabolic control in type 1 diabetes treated with multiple daily insulin injections - flash glucose monitoring, carbohydrate counting with automated bolus calculation, or both?

Dansk:

Forbedring af diabeteskontrollen hos Type 1 diabetes patienter - Flash glukose måling, kulhydrattælling med automatisk bolus-beregning eller begge dele?

Erklæring fra forsøgspersonen:

Jeg har fået skriftlig og mundtlig information og jeg ved nok om formål, metode, fordele og ulemper til at sige ja til at deltage.

Jeg ved, at det er frivilligt at deltage, og at jeg altid kan trække mit samtykke tilbage uden at miste mine nuværende eller fremtidige rettigheder til behandling.

Jeg giver samtykke til, at deltage i forskningsprojektet, og har fået en kopi af dette samtykkeark samt en kopi af den skriftlige information om projektet til eget brug.

Forsøgspersonens navn: _____

Dato: _____ Underskrift: _____

Ønsker du at blive informeret om forskningsprojektets resultat samt eventuelle konsekvenser for dig?:

Ja _____ (sæt x) Nej _____ (sæt x)

Erklæring fra den, der afgiver information:

Jeg erklærer, at forsøgspersonen har modtaget mundtlig og skriftlig information om forsøget.

Efter min overbevisning er der givet tilstrækkelig information til, at der kan træffes beslutning om deltagelse i forsøget.

Navnet på den, der har afgivet information:

Dato: _____ Underskrift: _____

Projektidentifikation: (ABC/Flash version 1.0)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym (page 1)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry page (page 1)
	2b	All items from the World Health Organization Trial Registration Data Set (not relevant)
Protocol version	3	Date and version identifier (page 1)
Funding	4	Sources and types of financial, material, and other support (pages 2, 16)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors (pages 1-2)
	5b	Name and contact information for the trial sponsor (not relevant)
	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 (not relevant)
	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) (not relevant)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention (pages 4-5)
	6b	Explanation for choice of comparators (pages 4-5)
Objectives	7	Specific objectives or hypotheses (page 5)

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) (pages 5, 7)

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained (page 5)
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) (page 5)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered (pages 6-8)
	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) (pages 5-8)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) (page 7)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial (pages 6-8)
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 (pages 8-9)
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) (pages 9-10 and Figure 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 (page 11)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size (page 5)

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions (page 7)
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 (page 7)
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions (page 7)
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how (not relevant)
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial (not relevant)
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol (pages 9-11)
	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 (pages 9-11)
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 (pages 10-11)
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 (pages 10-11)
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) (pages 10-11)
	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) (pages 10-11)

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed (not relevant)
	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 (not relevant)
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 (pages 9-10, 11-13)
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor (not relevant)

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval (not relevant, is approved)
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) (pages 11-12)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) (pages 5, 11-12)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable (not relevant)
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 (pages 10-13)
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site (page 16)
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 (not applicable currently)

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 (pages 11-13)
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions (not relevant)
	31b	Authorship eligibility guidelines and any intended use of professional writers (not relevant)
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code (not applicable currently)
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates (attached)
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 (not applicable)

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

BMJ Open

Study protocol for optimising glycaemic control in type 1 diabetes treated with multiple daily insulin injections - intermittently scanned continuous glucose monitoring, carbohydrate counting with automated bolus calculation, or both? A randomised controlled trial

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Title

Original title: Study protocol for optimising glycaemic control in type 1 diabetes treated with multiple daily insulin injections - intermittently scanned continuous glucose monitoring, carbohydrate counting with automated bolus calculation, or both? A randomised controlled trial

Short title: The ABC Flash Study

ADMINSTRATIVE INFORMATION

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Trial registration

The study is carried out in accordance with the Helsinki Declaration after approval by the Regional Scientific Ethics Committee (H-17040573). The data collection and handling are performed in accordance with the General Data Protection Regulation. The trial is registered at www.clinicaltrial.gov (NCT03682237).

Protocol version

Version 4, March 27, 2020.

Funding

The study is investigator initiated and financed by The Capital Region of Denmark. None of the investigators have personal financial interest in the conduct or the outcome of the project.

Roles and responsibilities

KN is the primary investigator of the study. The study concept, trial design and study protocol: ALS, UPB, OLS, BGR, TA, LD and DV.

ABSTRACT

Introduction:

There are beneficial effects of advanced carbohydrate counting with an automatic bolus calculator (ABC) and intermittently scanned continuous glucose monitoring (isCGM) in persons with type 1 diabetes. We aim to compare the effects of isCGM, training in carbohydrate counting with ABC and the combination of the two concepts with standard care.

Methods and analysis:

A multi-centre randomised controlled trial with inclusion criteria; ≥18 years, type 1 diabetes ≥1 year, injection therapy, HbA1c >53 mmol/mol, whereas daily use of carbohydrate counting and/or CGM/isCGM wear are exclusion criteria. Inclusion was initiated in October 2018 and is ongoing. Eligible persons are randomised into 4 groups; standard care, ABC, isCGM, or ABC + isCGM. Devices used are FreeStyle Libre Flash and smart phone diabetes application mySugr. Participants attend group courses according to treatment allocation with different educational contents. Participants are followed for 26 weeks with clinical visits and telephone consultations. At baseline and at study end, participants wear blinded CGM, have blood samples performed and fill in questionnaires on person related outcomes, and at baseline also on personality traits and hypoglycaemia awareness. The primary outcome is the difference in time spent in normoglycaemia (4-10 mmol/l) at study end vs. baseline between the isCGM group and the standard care group. Secondary outcomes will also be analysed. Results are expected in 2020.

Ethics and dissemination:

Regional Scientific Ethics Committee approval (H-17040573). Results will be sought disseminated at conferences and in high impact journals.

Strengths and limitations of this study:

- Despite its relevance for many persons with diabetes and their caregivers, the topic has not yet been rigorously examined to evaluate efficacy on glycaemic control.
- Robustly designed randomised controlled trial.
- Possible limitations may be difficulty with recruiting enough participants in order to reach power estimates, unbalanced withdrawal and basal insulin reductions which may affect the results.

INTRODUCTION

Insulin therapy in type 1 diabetes is generally adjusted according to food intake, physical activity and current blood glucose levels. It typically involves the combination of fast-acting insulin before meals and to correct hyperglycaemia, and long-acting insulin to control blood glucose overnight and in between meals, referred to as multiple daily injections (MDI). In order to obtain optimal glycaemic control it requires dose adjustment based on the amount of carbohydrate ingested at each meal (1) and frequent self-monitoring of blood glucose (SMBG) measurements. Carbohydrate counting is done based on experience or by using either manual or automatic estimates. Several studies have shown improved HbA1c and treatment satisfaction as well as a tendency towards less hypoglycaemia in persons undergoing training in carbohydrate counting and manual bolus calculation compared to insulin dosing based on experience (1–3). In addition, the use of an automatic bolus calculator (ABC) rather than manual bolus calculation has been proved to reduce HbA1c and improve patient satisfaction (2), with unaffected hypoglycaemia rate (4). Even in a routine care setting, group courses of 4 hours in bolus calculation with ABC and follow-up consultations have shown a reduction in HbA1c with maintained effect 12 months post-course (5). Our experience is that many persons with type 1 diabetes have never been trained in carbohydrate counting or the algorithm for insulin dose calculation.

Compared with conventional SMBG, the use of continuous glucose monitoring (CGM) in MDI treated persons reduces HbA1c and the time spent in mild hypoglycaemia and improves treatment satisfaction (6–8). A variation of real-time CGM is the intermittently scanned CGM (isCGM), where the first-generation readers are without glycaemic alerts, and the wearer scans the sensor to transfer glucose data. An early generation of isCGM has been found to decrease time spent in hypoglycaemia and increase treatment satisfaction and other person related outcomes in people with near-optimal HbA1c at baseline (9). A number of observational studies have evaluated isCGM in terms of accuracy and change in HbA1c (10), with positive reports on wearer satisfaction (11). Two recent observational studies including 120 and 900 adults, respectively, mainly on MDI found improved HbA1c levels, however with moderate increase in mild hypoglycaemic events (12,13), but fewer diabetic ketoacidosis admissions (13). The most pronounced reduction in HbA1c was seen in those with higher HbA1c prior to isCGM use (13). To date, however, no randomised controlled trials exist examining the efficacy of isCGM to increase time in range in patients with suboptimal HbA1c.

It also remains unknown which of the two concepts, bolus calculation with ABC or the use of isCGM, is superior and whether there is an additive effect of the two combined. Furthermore, there are no studies on how to structure training and optimise treatment in patients doing bolus calculation with the concomitant use of isCGM.

In the current study, the primary aim is to compare the effect of isCGM with standard care (SMBG) on glycaemic control. The secondary aim is to compare the effect of the combination of training in carbohydrate counting with ABC and the use of isCGM with standard care. We also aim to assess whether isCGM use can outperform training in carbohydrate counting with ABC.

METHODS AND ANALYSIS

Methods: Participants, interventions and outcomes

Participants

The ABC Flash Study is a randomised controlled, open-label, four-arm parallel trial carried out at five sites in The Capital Region of Denmark; Steno Diabetes Center Copenhagen, Rigshospitalet, Amager and Hvidovre Hospital, Nordsjællands Hospital Hillerød, and Bispebjerg and Frederiksberg Hospital. Inclusion criteria are age ≥ 18 years, type 1 diabetes duration ≥ 1 year, HbA1c > 53 mmol/mol, and the use of MDI therapy with basal insulin accounting for ≥ 30 % of the total daily insulin dose. Exclusion criteria are daily use of carbohydrate counting or CGM, use of NPH insulin, pregnancy, breastfeeding, gastroparesis, severe diabetes complications (i.e. proliferative retinopathy, myocardial infarction within the last six months), other medical or psychological conditions judged unsuitable for study participation, participation in other diabetes-related clinical research, the use of other drugs than insulin affecting glucose metabolism, or the inability to understand the individual information and to give informed consent. All persons screened for participation fill out the ABC Flash Study patient consent form (supplementary file). Hence, participants are adults with type 1 diabetes and suboptimal glycaemic control, treated with basal and bolus insulin and attending an outpatient diabetes clinic in the Capital Region of Denmark. Screening for inclusion was initiated October 1, 2018 and is planned to continue until March 31, 2020.

Intervention

Devices

The automatic bolus calculator

The ABC system used for this trial is the CE-marked mobile telephone diabetes application mySugr available for Android and iPhone. It is a digital logbook designed to support persons with diabetes in their self-management. It consists of an insulin bolus calculator based on the following settings that can be individually adjusted for every half an hour lap though the 24-hours: carbohydrate ratio, insulin sensitivity, target glucose value and insulin duration time. For every meal, the user enters current glucose value and estimated carbohydrate intake and receives a suggestion on insulin bolus dosage. In case of correction of hyperglycaemia, the user enters current glucose value and receives a suggestion on corrective insulin dosage. Data are stored for 3 months.

The intermittently scanned CGM

The isCGM device used in this trial is the FreeStyle Libre Flash CGM system (Abbott Diabetes Care, Alameda, CA, USA). It consists of a 14-day disc sensor to be worn on the upper arm, a reader and/or a mobile phone application to scan and display data. The sensor measures and continuously stores interstitial glucose concentrations every 15 minutes (800 glucose readings / 24 hours). The sensor is inserted into the upper arm skin and placed by a thin needle, which is immediately retracted, leaving a thin 6 mm long plastic glucose recorder in the skin. To obtain a current glucose value, the wearer scans the sensor with either the reader device or a mobile phone application (FreeStyle Libre Link available for Android and iPhone, Abbott Diabetes Care) producing real-time data. The reader devices used for this study were updated mid-2019 (14). The application was available in Denmark for Android and iPhone from mid-2019 (15). The system is CE-marked and accurate enough for insulin dosing except during fluctuant and low glucose levels. Wearers do not need to calibrate the system but to avoid loss of data, the sensor must be scanned every 8 hours. Scanned glucose data are presented to the wearer on the display as numerical values including glucose trends based on automatically stored data. Both intermittently scanned as well as continuously stored glucose data are displayed as graphs and logbooks and are available as numerical values after download from the reader device/mobile phone to a computer by the software program Diasend (Glooko, USA).

Assignment of interventions

Persons eligible for inclusion are randomised 1:1:1:1 by drawing a sealed and opaque randomisation envelope at the screening visit. The envelopes were centrally prepared by a person without relation to the specific trial. The main site was assigned to screen 72 participants, while the four remaining sites were each assigned to screen 32 participants. There is equal distribution of group assignments at each site (18 at the main site; 8 at each of the other four sites). The envelope is left unopened until after the initial blinded CGM period, where the given intervention is revealed; A (standard care), B (ABC), C (isCGM) or D (ABC and isCGM). In case of drop-out, the participant´s allocation is not to be replaced in the remaining randomisation envelopes.

Courses for participants

Four types of group courses for participants are included in the trial (Table 1). Each course includes one to three educational elements according to group allocation. Course length (4-4.5 hours) and group size (4-6 participants) are rather similar between the groups. The educational elements are:

1. General diabetes: Training in general diabetes health issues, how to do experience-based dosing, how to handle sick days, exercise etc. in general terms.
2. ABC: Theoretic and practical training in carbohydrate counting and bolus calculation (5).
3. mySugr diabetes application: The application is downloaded on the participants personal smartphone. The insulin to carbohydrate ratio (the amount of carbohydrates needed to match the glucose lowering effect of 1 unit of subcutaneously injected rapid-acting insulin) and the insulin sensitivity (the decrease in blood glucose in mmol/l caused by 1 unit of subcutaneously injected rapid-acting insulin) are empirically estimated for each participant using the 500- and the 100- rule, respectively (16). The insulin duration time is set at 4 hours. The target glucose value is in general set at 6 mmol/l during daytime and 7 mmol/l during night time.
4. FreeStyle Libre Flash CGM: Participants are instructed to use the system according to our local guideline and those in group D are also instructed in how to incorporate isCGM trend arrows to adjust the mySugr application settings.

All the above-mentioned educational concepts are also practiced during individual consultations throughout the 26-week trial period.

Training of study personnel

The healthcare professionals at the different study sites have been educated in the protocol and different course content and treatment modalities, how to conduct courses and study visits on two separate days before inclusion was initiated. Teachers on these study personnel training sessions were an endocrinologist (KN), a diabetes nurse and a dietitian from the investigator group with substantial experience in the field.

Diabetes care

In line with national guidelines (17), the overall aim in term of diabetes management is to obtain fasting and pre-prandial glucose values of 4-6 mmol/l, post-prandial glucose values lower than 10 mmol/l, to avoid any glucose values lower than 3 mmol/l and keep the number of glucose values below 4 mmol/l at an absolute minimum. At baseline and up to the last study visit, all participants fill in work sheets for daily reporting of basal insulin units, insulin boluses and SMBG values during the two weeks of blinded CGM wear to adjust insulin therapy. Moreover, participants receive a hypoglycaemia diary to fill in symptoms of hypoglycaemia and/or glucose values below 3.9 mmol/l, throughout the trial which is also used for insulin adjustments.

Participants in groups A (standard care) and B (ABC) are encouraged to measure SMBG at least four times daily with their personally preferred glucose meter. Participants in group C (isCGM) and D (isCGM and ABC) are instructed to use the isCGM system according to a local guideline based on manufacturer's guideline (18) and in line with recent publications on the topic (19–21). During both study visits and telephone consultations (see below) study personnel titrate insulin doses based on the different types of glucose values provided and other clinical information i.e. hypoglycaemic events, planned physical activity etc. For participants in group B and D, both the basal insulin dose and the ABC settings (primarily carbohydrate ratio and insulin sensitivity) are evaluated and, if needed, adjusted according to a local guideline based on previous publications and clinical experience (2,22).

Outcomes

The primary outcome is the difference in change from baseline to end of study between groups C (isCGM) and A (standard care) in time spent in normoglycaemia (defined as glucose of 4-10 mmol/l, minutes/24 hours, obtained by blinded CGM (23)).

Secondary outcomes are; difference in change from baseline to end of study between groups in HbA1c (mmol/mol), difference between groups in severe hypoglycaemia occurrence during the study period (defined as an event requiring assistance of another person, plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal, number of events during study period), difference between groups in symptomatic and confirmed hypoglycaemia occurrence during the study period (defined as glucose (SMBG or isCGM) < 3 mmol/l, number of events per week), difference in change between baseline and end of study between groups in diabetes distress, diabetes treatment satisfaction, diabetes empowerment, diabetes quality of life, time spent in hypo- (blinded CGM glucose <3 mmol/l, <4 mmol/l, minutes/day) and hyperglycaemia (>10 mmol/l, minutes/day), glycaemic variability (standard deviation), total insulin dose (recorded as a mean of 2 weeks during blinded CGM (insulin units (IU)/day/kg), total basal insulin dose (IU/day/kg), insulin boluses (number/24 hours), body weight (kg) and urinary albumin/excretion rate (mg/24 hours), and last the association between personality traits evaluated by questionnaire at baseline with any other outcome measures in the different groups.

Methods: data collection, management, and analysis

Data collection

Blinded CGM

After screening for inclusion (before opening the randomisation envelope), and at study end, all participants are asked to wear a blinded (non-real-time) CGM (The FreeStyle Libre Professional CGM system, Abbott Diabetes Care, Oxon, UK) to obtain glucose data. The sensor is inserted by a health care professional (see above for details on the isCGM). While wearing the sensor, users do not need to enter any fingerstick data or carry around a receiver, since the device collects all glucose data automatically. Following two weeks of sensor wear, data are downloaded in office by a reader device and a manufacturer-provided computer software program (LibreLink, Abbott Diabetes Care). These data are collected between screening visit and course participation (baseline data) and the two last study visits (final data), respectively.

Glucose and automatic bolus calculator data

Glucose (SMBG or isCGM) are downloaded to a computer (software Diasend, Glooko, USA) and data from the ABC are sent by e-mail from the user to the project health care professional at study visit 2, 4 and 6. The average number of symptomatic mild hypoglycaemic episodes per week and any severe hypoglycaemic episode are consecutively recorded throughout the trial.

Questionnaires

At screening and last study visit, all participants fill in the following validated questionnaires; Problem Areas in Diabetes Questionnaire (PAID), Diabetes Treatment Satisfaction Questionnaire (DTSQs at baseline and DTSQs and DTSQc at last visit) (24), Diabetes empowerment test (DES short form) and Diabetes quality of life (ADDQoL-19). At screening, they also fill in the questionnaire Neuroticism Extraversion Openness Agreeableness Conscientiousness Five-Factor Invertory-3 (NEO-FFI-3) and hypo-awareness assessment (25–28).

General health, blood and urine sampling and body weight

A general health/safety assessment, including full objective examination (cardiac and pulmonal auscultation, blood pressure measurement, inspection of insulin injection sites etc.) and information on history of severe hypoglycaemia is performed at screening. At both screening and last visit, all participants have blood and urine samples taken, as well as body weight measured (kg), which is done using the same scale every time. HbA1c (mmol/mol) is measured at screening, midway through the study, and again at last visit.

Study visits and telephone consultations

There are in total five clinical follow-up study visits (visit 2-6) at 2, 4, 12, 24 and 26 weeks planned during the 26 weeks trial participation (see Figure 1). Participants in group A (standard care) and C (isCGM) have appointments with the project nurse, whereas participants in group B (ABC) and D (isCGM and ABC) have joint appointments with both the project nurse and the project dietician. All participants have appointments with the project physician at first visit (screening) and midways throughout participation (visit 4). Visit 3 is not mandatory but proposed to participants in need of extra support or renewed teaching in the allocated intervention. In between the clinical study visits, there are three telephone consultations (1-3) at 0, 8 and 17 weeks where the project nurse contact the participants.

Data management

The data management is performed in accordance with the General Data Protection Regulation. Data are consecutively collected and stored in a browser-based software and workflow database (REDCap). The database is password protected and only the local and primary investigators have access to the data.

Data analysis

A sample size of 160 (40 per group) was calculated to have 80% power to detect a difference in mean time in target glycaemic range (4-10 mmol/l) between treatment group A and C of 75 minutes per day with a standard deviation of 120 minutes, and a 2-sided α-level of 0.05. Sample size is increased to 180 (45 per group) to account for a potential drop out of approximately 10%.

Changes in primary and secondary outcomes over the intervention period and effects of the treatments will be modelled by linear mixed-effects models with a patient-specific random intercept to account for the correlation of repeated measurements within patients and a random intercept for centre to account for the clustering effect of study centre. The exact times of measurements will be used. All analyses will be performed as an intention to treat analysis. Statistical significance will be inferred at a two-tailed $P < 0.05$. The p-values for secondary outcomes will be corrected by the Benjamini-Hochberg method for multiple comparisons (29).

Public and patient involvement

Persons with type 1 diabetes were not involved in the initial phases of the study. Already recruited participants, however, are asked to assess the burden of the intervention and time required to participate in the research. This has resulted in a supplementary document that is presented to possible participants to give a realistic picture of time spent on participation over time. Persons with type 1 diabetes will be sought to be involved in the dissemination plan of the results by for example commenting on written information with regards to language and form.

ETHICS AND DISSEMINATION

The study is carried out in accordance with the Helsinki Declaration after approval by the Regional Scientific Ethics Committee (H-17040573) and is registered at clinical trial.gov (NCT03682237).

Until now, an early generation isCGM has been found to improve time spent in hypoglycaemia, treatment satisfaction and other person related outcomes in people with near-optimal HbA1c (9). A number of observational studies have evaluated isCGM in broader populations with regards to change in HbA1c and accuracy and satisfaction among wearers (10–13). To date, however, no randomised controlled trials have been performed to examine the efficacy of isCGM to increase time in range in patients with suboptimal HbA1c. In addition, carbohydrate counting with ABC has been proved to improve HbA1c and patient satisfaction (2) and nutritional therapy has an integral role in diabetes management (30). Which one of the two treatment concepts that is superior to the other, and whether there is an additive effect of the two combined, has to our knowledge not previously been evaluated. Most important, however, no randomised controlled trials have been performed to examine the efficacy of isCGM to increase time in range in patients with suboptimal HbA1c. A possible limitation may be difficulty with recruiting enough participants in order to reach power estimates. Unbalanced withdrawal may be a risk, as we believe that the demands are higher on participants allocated to one of the two carbohydrate counting groups. Furthermore, as isCGM us not fully reimbursed in Denmark, some participants may sign up for the study with the hope of being randomised to isCGM. Basal insulin reductions may also play a role in achieving glycaemic aims.

The investigators expect that the current study results will help guiding persons with type 1 diabetes treated with MDI and their health care professionals in choosing evidence-based methods for optimal glycaemic control. We believe that the possible risks and side effects among participants are outweighed by the potential benefits from the conduct of this study. The overall individual risk of side effects is expected to be modest and is mainly related to the time spent on learning how to count carbohydrates and use the mySugr application and/or using the isCGM system. With regards to all other planned study procedures, the risk of complications or adverse events is negligible and outweighed by the possible beneficial effects of conducting the study. The occurrence of any adverse events will be assessed at every visit and telephone contact during the study period. All participants are covered by the mandatory individual insurance at each local hospital in The Capital Region of Denmark. Blood samples are analysed directly after sampling without the establishment

of a biobank. If the study is prematurely terminated, the investigators will promptly inform the Regional Scientific Ethics Committee and the participants to assure appropriate therapy and follow-up.

The study results are expected to be disseminated at international and national diabetes conferences and meetings and published in international journals with considerable impact. All participants who at first study visit expressed an interest in the results will receive a short version of the main findings expressed in lay terms and will be invited to a short oral presentation at the main study site. The results will also be sought presented to the Danish Diabetes Association and communicated to the public by a press release.

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AUTHOR´S CONTRIBUTION

ALS wrote the first draft of the manuscript. Critical revision of the manuscript: UPB, OLS, BGR, TA, LD, DV and KN.

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The study is investigator-initiated and -driven, financed by The Capital Region of Denmark. None of the investigators have personal financial interest in the conduct or the outcome of the project.

COMPETING INTEREST STATEMENTS

KN is a shareholder of Novo Nordisk; has received research support from Novo Nordisk, Roche Diagnostics, Dexcom and Zealand Pharma; has received lecture fees from Medtronic, Roche Diagnostics, Rubin Medical, Sanofi, Zealand Pharma, Novo Nordisk, and Dexcom; and has served on advisory panels for Medtronic, Abbott, and Novo Nordisk. UPB has served on advisory boards for AstraZeneca, Bristol-Myers Squibb, Sanofi-Aventis, Novo Nordisk and Zealand Pharma and has received lecture fees from AstraZeneca, Bristol-Myers Squibb, Sanofi-Aventis and Novo Nordisk. TA holds stocks in Novo Nordisk. ALS, OLS, BGR, LD and DV do not have any competing interests.

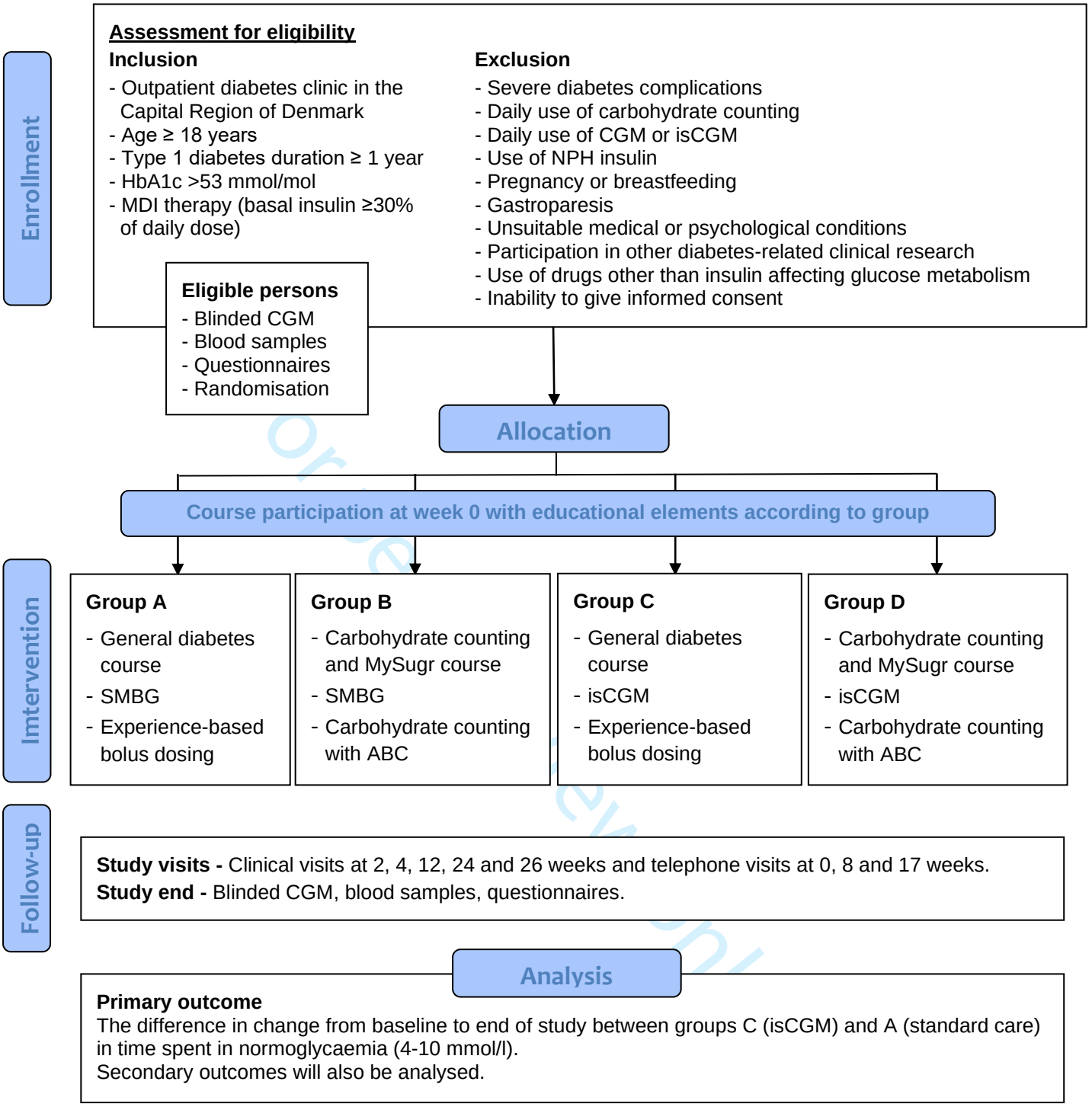
WORD COUNT

Abstract 300 words, full text 3,411 of 4,000 allowed words.

Table 1. Overview of glucose measurement methods, decision on insulin bolus and educational element in course according to group allocation. Abbreviations: SMBG (self-monitored blood glucose), isCGM (intermittently scanned glucose monitoring).

Intervention group	Glucose measurement method	Decision on insulin bolus	Educational element in course
A	SMBG	Experience-based	• General diabetes
B	SMBG	Carbohydrate counting with automatic bolus calculator	• Training in carbohydrate counting • Training in the use of the application mySugr
C	isCGM	Experience-based	• General diabetes • Training in FreeStyle Libre Flash use
D	isCGM	Carbohydrate counting with automatic bolus calculator	• Training in carbohydrate counting • Training in the use of the application mySugr • Training in FreeStyle Libre Flash use and how to incorporate glucose trend arrows to adjust the mySugr application settings

Figure legend, figure 1. Flow chart of participants throughout the trial.


Enrollment
Assessment for eligibility
Inclusion
- Outpatient diabetes clinic in the Capital Region of Denmark
- Age ≥ 18 years
- Type 1 diabetes duration ≥ 1 year
- HbA1c >53 mmol/mol
- MDI therapy (basal insulin ≥30% of daily dose)
Exclusion
- Severe diabetes complications
- Daily use of carbohydrate counting
- Daily use of CGM or isCGM
- Use of NPH insulin
- Pregnancy or breastfeeding
- Gastroparesis
- Unsuitable medical or psychological conditions
- Participation in other diabetes-related clinical research
- Use of drugs other than insulin affecting glucose metabolism
- Inability to give informed consent
Eligible persons
- Blinded CGM
- Blood samples
- Questionnaires
- Randomisation
Allocation
Course participation at week 0 with educational elements according to group
Imtervention
Group A
- General diabetes course
- SMBG
- Experience-based bolus dosing
Group B
- Carbohydrate counting and MySugr course
- SMBG
- Carbohydrate counting with ABC
Group C
- General diabetes course
- isCGM
- Experience-based bolus dosing
Group D
- Carbohydrate counting and MySugr course
- isCGM
- Carbohydrate counting with ABC
Follow-up
Study visits - Clinical visits at 2, 4, 12, 24 and 26 weeks and telephone visits at 0, 8 and 17 weeks.
Study end - Blinded CGM, blood samples, questionnaires.
Analysis
Primary outcome
The difference in change from baseline to end of study between groups C (isCGM) and A (standard care) in time spent in normoglycaemia (4-10 mmol/l).
Secondary outcomes will also be analysed.

(S1)

Informeret samtykke til deltagelse i et sundhedsvidenskabeligt forskningsprojekt.

Forskningsprojektets titel:

Optimizing metabolic control in type 1 diabetes treated with multiple daily insulin injections - flash glucose monitoring, carbohydrate counting with automated bolus calculation, or both?

Dansk:

Forbedring af diabeteskontrollen hos Type 1 diabetes patienter - Flash glukose måling, kulhydrattælling med automatisk bolus-beregning eller begge dele?

Erklæring fra forsøgspersonen:

Jeg har fået skriftlig og mundtlig information og jeg ved nok om formål, metode, fordele og ulemper til at sige ja til at deltage.

Jeg ved, at det er frivilligt at deltage, og at jeg altid kan trække mit samtykke tilbage uden at miste mine nuværende eller fremtidige rettigheder til behandling.

Jeg giver samtykke til, at deltage i forskningsprojektet, og har fået en kopi af dette samtykkeark samt en kopi af den skriftlige information om projektet til eget brug.

Forsøgspersonens navn: _____

Dato: _____ Underskrift: _____

Ønsker du at blive informeret om forskningsprojektets resultat samt eventuelle konsekvenser for dig?:

Ja _____ (sæt x) Nej _____ (sæt x)

Erklæring fra den, der afgiver information:

Jeg erklærer, at forsøgspersonen har modtaget mundtlig og skriftlig information om forsøget.

Efter min overbevisning er der givet tilstrækkelig information til, at der kan træffes beslutning om deltagelse i forsøget.

Navnet på den, der har afgivet information:

Dato: _____ Underskrift: _____

Projektidentifikation: (ABC/Flash version 1.0)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym (page 1)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry page (page 1)
	2b	All items from the World Health Organization Trial Registration Data Set (not relevant)
Protocol version	3	Date and version identifier (page 1)
Funding	4	Sources and types of financial, material, and other support (pages 2, 16)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors (pages 1-2)
	5b	Name and contact information for the trial sponsor (not relevant)
	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 (not relevant)
	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) (not relevant)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention (pages 4-5)
	6b	Explanation for choice of comparators (pages 4-5)
Objectives	7	Specific objectives or hypotheses (page 5)

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) (pages 5, 7)

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained (page 5)
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) (page 5)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered (pages 6-8)
	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) (pages 5-8)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) (page 7)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial (pages 6-8)
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 (pages 8-9)
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) (pages 9-10 and Figure 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 (page 11)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size (page 5)

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions (page 7)
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 (page 7)
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions (page 7)
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how (not relevant)
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial (not relevant)
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol (pages 9-11)
	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 (pages 9-11)
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 (pages 10-11)
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 (pages 10-11)
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) (pages 10-11)
	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) (pages 10-11)

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed (not relevant)
	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 (not relevant)
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 (pages 9-10, 11-13)
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor (not relevant)

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval (not relevant, is approved)
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) (pages 11-12)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) (pages 5, 11-12)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable (not relevant)
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 (pages 10-13)
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site (page 16)
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 (not applicable currently)

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 (pages 11-13)
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions (not relevant)
	31b	Authorship eligibility guidelines and any intended use of professional writers (not relevant)
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code (not applicable currently)
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates (attached)
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 (not applicable)

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