## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | 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 |
| **AUTHORS** | Secher, Anna; Pedersen-Bjergaard, Ulrik; Svendsen, Ole; Gade-Rasmussen, Birthe; Almdal, Thomas; Dørflinger, Liv; Vistisen, Dorte; Nørgaard, Kirsten |

## VERSION 1 - REVIEW

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| **REVIEWER** | Denice Feig<br>Department of Medicine, University of Toronto<br>Lunenfeld-Tanenbaum Research Institute<br>Mount Sinai Hospital<br>Canada<br>Medtronic: Speaker<br>NovoNordisc: Advisory Board for Randomized Trial |
| **REVIEW RETURNED** | 17-Jan-2020 |

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| **GENERAL COMMENTS** | Review of Protocol<br><br>This study protocol describes a randomized trial of patients with type 1 diabetes. The aim is to see if iCGM improves time in glucose target over standard care, and secondly if carbohydrate counting with automatic bolusing improves time in target. In this RCT, patients with type 1 diabetes are randomized to one of 4 groups: 1) Carbohydrate counting with automatic bolusing + SMBG 2) intermittently seen CGM and Experience-based bolusing 3) Both Carb counting and IsCGM and 4) Standard care (with SMBG and Experience-based bolusing). The primary outcome is time in range between the isCGM group and the standard care group.<br><br>The design is scientifically sound and well thought out. I have just a few suggestions/clarifications;<br>1. On page 10, “The primary outcome is stated as the difference in change from baseline to end of study between groups C and A in time spent in normoglycemia in minutes/24 hours and percentage of time”. The sample size is calculated based on minutes/24 hours, so would it not be more appropriate to have the primary outcome as ‘minutes/24 hours’ and % of time as a secondary outcome?<br>2. Page 10: “Blood and urine sampling are performed at screening and last study visit for analysis of HbA1c (mmol/mol) and general/health safety”. ‘General health/safety’ is quite vague.<br>3. Page 9: It says ”Persons eligible for inclusion draw a centrally |

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| | prepared, sealed randomization envelope". There should be more detail on the randomization. Are they to draw them in any order or just choose any envelope? How was the randomization schedule made? Did they use random block sizes? Was the ratio 1:1? Are the envelopes opaque?<br>4. Page 7, line 8: It says "The envelope is left unopened until after the initial blinded CGM period, where the given intervention is revealed". What if the patient can't complete the blinded CGM, are they still considered randomized and withdrawn? What happens to their envelope?<br><br>Minor comments:<br>1. Page 1: the site is: clinicaltrials.gov instead of "clinical trial.gov"<br>2. Page 6 line 22: it says "application and receive'. I suggest 'and receives'<br>3. Page 6 line 25 It says "receive a suggestion on corrective insulin dosage". I suggest" receives a suggestion on a corrective insulin dose".<br>4. Page 6 line 33. It says "scan and data display". I suggest "scan and display data"<br>5. Page 6 line 38 it says "thin and 6 mm". I suggest they take out the word 'and'<br>6. Page 11 line 28 it says "sought involved". I suggest "sought to be involved"<br>7. Page 12, line 40 it says "be presented via". I suggest "be presented".<br>8. Figure 1 under Exclusion it says "Severe diabetes complications' twice. Also under Exclusions, it says "Use of drugs than insulin". I suggest "Use of drugs other than insulin.." |

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| **REVIEWER** | Nick Oliver<br>Imperial College, UK |
| **REVIEW RETURNED** | 23-Jan-2020 |

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| **GENERAL COMMENTS** | Many thanks for asking me to review this protocol, I have the following questions:<br>1. Will the study recruit people with impaired awareness of hypoglycaemia or a history of severe hypoglycaemia? If so, what is the ethical justification for not providing rtCGM?<br>2. How will the investigators exclude gastoparesis?<br>3. isCGM readers include a bolus calculator, how will investigators prevent this being used?<br>4. Is there a structured approach to adaptation of the ICR/ ISF/ target settings?<br>5. How will changes to basal insulin dose impact on the assessment of effectiveness of the ABC? Should basal insulin be optimised during the run-in, then fixed?<br>6. A discussion of the limitations of the study design would be a useful addition |

**VERSION 1 – AUTHOR RESPONSE**

Reviewer(s)'

Comments to Author:

Reviewer: 1

Please leave your comments for the authors below Review of Protocol.

This study protocol describes a randomized trial of patients with type 1 diabetes. The aim is to see if iCGM improves time in glucose target over standard care, and secondly if carbohydrate counting with automatic bolusing improves time in target. In this RCT, patients with type 1 diabetes are randomized to one of 4 groups: 1) Carbohydrate counting with automatic bolusing + SMBG 2) intermittently seen CGM and Experience-based bolusing 3) Both Carb counting and IsCGM and 4) Standard care (with SMBG and Experience-based bolusing). The primary outcome is time in range between the isCGM group and the standard care group. The design is scientifically sound and well thought out.

Thank you.

I have just a few suggestions/clarifications;

1. On page 10, “The primary outcome is stated as the difference in change from baseline to end of study between groups C and A in time spent in normoglycemia in minutes/24 hours and percentage of time”. The sample size is calculated based on minutes/24 hours, so would it not be more appropriate to have the primary outcome as ‘minutes/24 hours’ and % of time as a secondary outcome?

Thank you for this comment. To assure complete consistency between trial registration and this manuscript we have chosen to remove % as unit in the manuscript. Please see changes in the manuscript. We do not believe that it would be appropriate to apply to units (min/day and % of time) for the same measurement (time in range) as separate outcomes but will probably present data in both units when we have the results.

Pages 8-9:

“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 (22)).“

Page 10: “Blood and urine sampling are performed at screening and last study visit for analysis of HbA1c (mmol/mol) and general/health safety”. ‘General health/safety’ is quite vague.

Thank you for this relevant comment. Screening for participation includes a full objective examination which has been added on page 10:

“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.”

2. Page 9: It says “Persons eligible for inclusion draw a centrally prepared, sealed randomization envelope”. There should be more detail on the randomization. Are they to draw them in any order or just choose any envelope? How was the randomization schedule made? Did they use random block sizes? Was the ratio 1:1? Are the envelopes opaque?

Thank you for this comment. We have added detailed information on the randomisation procedure on page 7:

“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.”

3. Page 7, line 8: It says “The envelope is left unopened until after the initial blinded CGM period, where the given intervention is revealed”. What if the patient can’t complete the blinded CGM, are they still considered randomized and withdrawn? What happens to their envelope?

Thank you for this comment. There have been a few cases where the blinded CGM sensor fell off before completion of the 14-day period, or insufficient glucose data after download. To secure data we ask the participants to contact us if the sensor falls off, so that we can make a new appointment to insert a new sensor. In the very few cases with insufficient data after download, we have also inserted a new sensor, and if relevant postponed course participation a few weeks.

Minor comments:

- Page 1: the site is: clinicaltrials.gov instead of “clinical trial.gov”
- Page 6 line 22: it says “application and receive’. I suggest ‘and receives’
- Page 6 line 25 It says “receive a suggestion on corrective insulin dosage”. I suggest” receives a suggestion on a corrective insulin dose”.
- Page 6 line 33. It says “scan and data display”. I suggest “scan and display data”
- Page 6 line 38 it says “thin and 6 mm”. I suggest they take out the word ‘and’
- Page 11 line 28 it says “sought involved”. I suggest “sought to be involved”
- Page 12, line 40 it says “be presented via”. I suggest “be presented”.
- Figure 1 under Exclusion it says “Severe diabetes complications’ twice. Also under Exclusions, it says “Use of drugs than insulin”. I suggest “Use of drugs other than insulin.”

Thank you, it has all been corrected accordingly.

Reviewer: 2

Please leave your comments for the authors below.

Many thanks for asking me to review this protocol, I have the following questions:

1. Will the study recruit people with impaired awareness of hypoglycaemia or a history of severe hypoglycaemia? If so, what is the ethical justification for not providing rtCGM?

Thank you for this relevant comment.

Hypoglycemia unawareness was not an exclusion criterion. However, we systematically ask into a history of severe hypoglycaemia at screening visit and evaluate whether the person can be included in the trial or should be referred to the clinic to have another type of sensor with alarms. Until now we have had one participant who after screening was withdrawn from the trial due to hypoglycaemia unawareness. We also ask all participants into episodes of mild and severe hypoglycemia at each study visit. This has been clarified in the manuscript on page 10:

“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.”

On page 9 we describe the procedure on consecutive assessment of hypoglycaemia risk:

“The average number of symptomatic mild hypoglycaemic episodes per week and any severe hypoglycaemic episode are consecutively recorded throughout the trial.”

2. How will the investigators exclude gastoparesis?

The participants are systematically asked into a history of diabetes complications including gastroparesis at screening and the medical records are thoroughly evaluated before inclusion.

3. isCGM readers include a bolus calculator, how will investigators prevent this being used?

Thank you for this relevant comment. The reason for not choosing the built-in bolus calculator as the ABC tool in this trial was that the user must type in SMBG values rather than sensor glucose values. To access the bolus calculator part of the Flash Libre reader one must type in a code that was not handed out to the participants.

4. Is there a structured approach to adaptation of the ICR/ ISF/ target settings?

Thank you for this relevant comment. There is a structured approach and a local guideline to secure the same approach on insulin treatment at all five sites. This has now been added on page 8 with an extra reference (Schmidt, Nørgaard, J Diabetes Sci Technol, 2014):

“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).”

5. How will changes to basal insulin dose impact on the assessment of effectiveness of the ABC? Should basal insulin be optimised during the run-in, then fixed?

Thank you for this comment. As mentioned above, information on how to tackle basal insulin dosing in this study has been clarified as described above. The basal insulin dose is not fixed during the study.

6. A discussion of the limitations of the study design would be a useful addition.

Thank you. We have added a sentence on study limitations to the discussion section on page 12:

“A possible limitation may be difficulty with recruiting enough participants in order to reach power estimates.”

## VERSION 2 – REVIEW

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| **REVIEWER** | Denice Feig<br>Mt Sinai Hospital,<br>Toronto, Canada |
| **REVIEW RETURNED** | 14-Mar-2020 |

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| **GENERAL COMMENTS** | Changes made in response to reviewers are satisfactory. |

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| **REVIEWER** | Nick Oliver<br>Imperial College, London |
| **REVIEW RETURNED** | 18-Feb-2020 |

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| **GENERAL COMMENTS** | Many thanks, all of my comments except one have been addressed. There is really no discussion of the limitations of the study design - failure to recruit to a powered study is a universal challenge. What in the study might compromise the data and how might the study design fail to meet the aims? For example, large changes in basal insulin, large variance in the accuracy of isCGM, unbalanced withdrawal, and others should be discussed. |

## VERSION 2 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 2, Reviewer Name: Nick Oliver, Institution and Country: Imperial College, London. Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below: Many thanks, all my comments except one have been addressed. There is really no discussion of the limitations of the study design - failure to recruit to a powered study is a universal challenge. What in the study might compromise the data and how might the study design fail to meet the aims? For example, large changes in basal insulin, large variance in the accuracy of isCGM, unbalanced withdrawal, and others should be discussed.

Thank you for this valuable comment. We have revised the manuscript with supplemental information as presented below:

Page 3:

“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. Unbalanced withdrawal and basal insulin reductions may affect the results.”

Page 12:

“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.”

Reviewer: 1, Reviewer Name: Denice Feig, Institution and Country: Mt Sinai Hospital, Toronto, Canada. Please state any competing interests or state ‘None declared’: None

Please leave your comments for the authors below: Changes made in response to reviewers are satisfactory.