Author's response to reviews

Title: Automated Bolus Advisor Control and Usability Study (ABACUS): Does use of an insulin bolus advisor improve glycaemic control in patients failing multiple daily insulin injection (MDI) therapy?

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Author's response to reviews: see over
Dear Editor,

Thank you for your consideration of our submitted manuscript entitled “Automated Bolus Advisor Control and Usability Study (ABACUS): Does use of an insulin bolus advisor improve glycaemic control in patients failing multiple daily insulin injection (MDI) therapy?” for publication in *BMC Family Practice*.

The reviewers provided great input, and we have attempted to answer their concerns. (Please see attached)

Please let me know if you have any questions or concerns.

My Very Best Regards,

Chris Parkin, MS
RESPONSES TO REVIEWER COMMENTS

Reviewer 1:

Major comments

1. CGM detail: It is unclear how the 50-60% CGM participants will be selected and whether or not they will be representative of the entire cohort. Is CGM available at all UK and German sites or just selected centres? Is CGM not possible for all participants? If not should this be listed as a potential limitation? How will glucose data from the Dexcom sensor be blinded to the study participants? I am not aware of a data blinding feature on that CGM device? Is CGM an optional extra for individual study participants or a requirement?

   RESPONSE: Thank you for your comments. Due to cost constraints, CGM will be used in a randomised cohort within the study population in order to provide additional information towards some of the secondary end-points in the study. Selection will be undertaken by centre (all participants in a centre using CGM would undertake CGM as a core element of their involvement) reflecting an inclusive enrolment policy, not excluding centres who did not have experience of CGM use.

   We believe the characteristics of the cohort studied with CGM will not differ from the characteristics of the group as a whole, we therefore believe that the 100+ subjects studied with CGM are representative of the group as a whole. Thus, we do not consider this to be a limitation. Further Subjects (and investigators) were blinded to the CGM data collected during the study, which will be analysed separately at a centralised laboratory.

   The Dexcom device does indeed have a blinded option, investigators on site will only be able at sensor upload to see if there were gaps in data collection (in order to allow repeat sensor use if necessary). The participants will be able only to see prompts to undertake calibration BG estimation on their handheld device, not any indication of the BG itself or of any trends in control.

2. There is minimal information regarding the randomisation procedures. This should be added. Please also specify whether there are any proposed stratifications for centre, type of diabetes, country etc.

   RESPONSE: Thank you for your comment. We have added more specific information about the randomization procedure to the manuscript. (page 9, first line of first full paragraph). Regarding stratification of centres, we did not stratify by centre.

Minor comments

1. Please comment on whether the very large number of study sites (n=30) and relatively small number of participants (n=6) and therefore 3 control and 3 experimental may limit the investigator experience in utilising and/or optimising the bolus advisor settings.
RESPONSE: Thank you for your comments. All subjects in the study (independent of their device allocation) will be managed identically by the clinicians in term of the insulin adjustment process, based on meter-downloaded data from the previous period and its comparison to the goals of the study. These principles reflect “best-routine care” processes and therefore are well-recognised by investigators (who were all chosen for their familiarity with such principles). The relatively small number of participants for each centre therefore reflects the detail of the involvement required, and the pressures this may put on a clinical team. We do not see this as a limitation of the study; rather, it represents a recognition of the need to incorporate such strategies into routine clinical care. However, we have added some additional information about the sites on page 7, under “METHODS/DESIGN”.

2. The ClinicalTrial.gov register lists “change in magnitude of postprandial glucose excursions” as a secondary trial outcome. For CGM comparisons, this may require more sophisticated statistical analyses such as linear mixed effects modelling (to overcome the issues of multiple highly correlated glucose data measurements)

RESPONSE: Thank you for your comment. We agree that the statistical analysis methodologies that you suggest will be needed to assess changes in the magnitude of postprandial glucose excursions, and we intend to describe our methodologies in our final study report.

3. For readability please keep abbreviations to a minimum – BA (bolus advisor) is not a well recognised abbreviation and likewise there is little to be gained from replacing the control and experimental groups with EXP and CNL.

RESPONSE: Thank you for your response. We agree that the BA abbreviation should be removed, however, we feel that use of EXP and CNL is helpful.

4. There is an unclosed bracket in the 1st line of the 2nd Introductory paragraph – page 5

RESPONSE: Thank you for your comment. This has been corrected.

5. If the study has not yet commenced recruitment (as suggested on the trial register) please review the sentence (page 20) – final data will be available in late 2012

RESPONSE: Thank you for your comment. The study has been initiated, so we will update the clinical trial register accordingly.
Reviewer 2

Major Compulsory Revisions

None

Minor Essential Revisions

1. Background, 2nd paragraph: closed parenthesis is missing.

   RESPONSE: Thank you for your comment. This has been corrected.

Discretionary Revisions

1. Design: Since the stability of bG is different between T1DM and T2DM, each type of DM shoud be equally randomised into EXP and CNL groups.

   RESPONSE: Thank you for your comment. Because we are studying use of the bolus calculator in patients treated with MDI therapy, we anticipate a relatively low number of T2DM subjects, which would not allow for meaningful analysis.

2. Indicices of insulin secretion such as C-peptide levels included in laboratory tests? If not, please include them.

   RESPONSE: Given the likely long duration of diabetes in the population we will be studying, we did not feel that measurement of c-peptide was needed.