Author’s response to reviews

Title: Rationale and protocol for the Assessment of Impact of Real-time Continuous Glucose Monitoring on People Presenting with Severe Hypoglycaemia (AIR-CGM) Study

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Author’s response to reviews:

We thank the reviewers and the editorial team for their helpful comments and suggestions to improve our manuscript. Please find below our responses to the comments highlighted in bold. The new changes in the manuscript have been highlighted in bold blue.

We have also addressed the corresponding author, included the statement “all authors have read and approved the manuscript”, added statement in ‘Consent to participate’ in the declaration section, and removed funding information in acknowledgements.

1. The inclusion criteria are very broad. This may result in inclusion of a very heterogenous cohort, which may challenge the premises for the power calculation. E.g. there may be well-controlled participants experiencing their only severe hypo, people running at very low glucose levels, who will contribute massively to the primary endpoint, and people with excessive use of alcohol or other substances, who may benefit less from the intervention. I would recommend to seek for a more homogenous population or increase the number of participants.

Thank you for your suggestion. We agree that people with a history of alcohol or substance use may differ from other participants and are able to exclude these on an individual basis in line with the “Unable to participate due to other factors, as assessed by the Chief Investigators” criteria. We accept that the participants may otherwise be heterogeneous in their history of severe hypoglycaemia but, as with all clinical studies, we have selected a pragmatic inclusion criteria to ensure recruitment is feasible, and will ensure that the data are analysed with HbA1c, previous severe hypoglycaemia, and awareness of hypoglycaemia given due consideration.
2. Intervention: It is a little unclear whether the intervention is limited to improving glucose control or if behavioural issues are dealt with as well. To release the full potential of the CGM, this is important to include. In the same line: are the study personnel familiar with the patients aforesaid? 

The study personnel are not familiar with the participants beforehand as participants are primarily recruited by their interaction with the London Ambulance Service. This only means that they are in London at the time of their event but they may live anywhere in the country, they may receive care in any specialist unit, or may not be under the care of a diabetes specialist multidisciplinary team. The intervention is primarily assessing glucose control. Simple insulin management education is provided in line with DAFNE principles and CGM education and support is provided. We recognise that people with severe hypoglycaemia may have co-existing diabetes psychology needs and that a complex intervention may be more impactful but that requires a larger study and we are aiming to demonstrate the impact of a clinical intervention. We are, however, collecting validated questionnaire data that can be used in developing future studies.

3. Endpoints: The hypoglycaemic endpoint are only defined according to CGM data. It would be important to know the clinical consequence: asymptomatic, symptomatic or even severe?

Thank you, we have included secondary outcome measures to address the clinical consequence- “Number of episodes of severe hypoglycaemia requiring third party assistance”.

4. First 2 sentences - suggest rework for clarity. Eg "Severe hypoglycaemia carries a significant risk of morbidity and mortality for people with type 1 diabetes. Economic costs are also high, estimated at £13 million annually in England."

Thank you– we have amended as per suggestion.

5. Suggest replace "glycaemic control" with "glycaemia", (also in other places through the manuscript - "Language Matters statement suggests avoiding using the word "control").

Amended.

6. Suggest "and is cost effective" rather than "as well as being cost effective".

Amended.

7. Why use the phrase "Continuous glucose sensing technology" rather than "Continuous glucose monitoring"? Amended.
8. "Changing service demands" sentence would benefit from clarification. Perhaps something like "Changing demand means that novel approaches need to be taken to healthcare provision. This study has the potential to shape future national standards."

Thank you– we have amended as per suggestion.

9. P16 L1 - delete comma after "severe hypoglycaemia".

Amended.

10. Keywords: Not 3-10 words.

Amended.

11. Background: P5L32 Suggest say people with T1D "report" this number of hypos rather than "have", especially as the authors then quite rightly point out this may be an underestimate.

Amended.

12. P5L37 "However, it is likely this may well be under-reported by individuals" might read better as "This may be an underestimate."

Amended.

13. P5L54 delete comma after "both".

Amended.

14. P7L53-58 suggest replace "early follow-up" with "early review".

Amended.

15. Suggest "there are low levels of follow-up, therapy change and specialist input following an episode of hypoglycaemia"

Amended.

16. Sentence beginning "This corroborates the delay..." adds little. If to include something, would suggest something along the lines of "This is in line with the clinical experience of the authors."

Thank you– we have amended as per suggestion.

17. P8L17: "and is therefore used" needs fleshing out - perhaps "and therefore this is used as the basis for the primary study outcome"

Amended
18. Eligibility criteria: General point - may be better as bullet point lists –

Updated.

19. Inclusion: P8L56 suggest "through ambulance call-out…" be replaced with "with potential participants identified following ambulance call-out or ED attendance"

Amended

20. Exclusion: "Participants" not "subjects"

Amended.

21. Sample size and feasibility: Not clear of the relevance of the Greater London LAS figures here, except to say that conveyance rates are comparable.

As a collaborative project with LAS, figures have been included here to provide background and context for feasibility, as well as provide the reader with greater overview and understanding of clinical burden to individuals with T1D.

22. Recruitment: Delete comma after "eligibility checks of individuals"

Amended.

23. "who will make a welfare ring back to the patient within 2 hours" is not clear. I think I know what is meant, but perhaps "will contact the person within 2 hours by telephone to check on their welfare. If the person has capacity and is well…."

Amended.

24. "Potential participants will be identified"

Amended

25. Screening visit and enrolment: There is a mixture of future and present tense. Would use one (future?) for consistency.

Updated

26. Bloods will need to be taken at 9am, this should be made explicit (otherwise a 9am cortisol will not be obtained). TFT, 9am cortisol and TTG are to be checked. Will potential participants be excluded eg if 9am cortisol is low, thyroid function is abnormal or untreated coeliac disease is identified? These are not currently in the exclusion criteria.
Potential participants are excluded if adrenal insufficiency is identified and will undergo appropriate investigation and treatment to address this. Additionally, if thyroid function is overtly abnormal or untreated coeliac disease is identified, as this may contribute to their ongoing potential for hypoglycaemia and will be managed as a precipitant of hypoglycaemia and the participant will be withdrawn. We have included a sentence for this and for bloods to be taken at 9am.

27. Are there any limitations on access to education? Is education/educational material available in languages other than English? If not, then perhaps have lack of English as an explicit exclusion criterion.

Participants who are unable to take part in the study due to language, education, or other reasons will be excluded on an individual basis. We aim to be inclusive but will prioritise the safety of participants and the feasibility of delivering the study.

28. Could the "desirable range" be defined for sensor glucose? This should be consistent across participants. 3.9-10 mmol/l (as per secondary outcomes)?

Desired sensor glucose for (instructing participants to test capillary blood glucose) - 3.9 mmol/L – 13.3mmol/L; 70mg/dL – 240mg/dL included in paper.

29. Secondary outcomes: Would consider also adding "Number of episodes of severe hypoglycaemia requiring third party assistance" as a secondary outcome. Ambulance call-out rates is included (this will have an impact on cost-effectiveness assessments) but not all episodes will necessarily require third party assistance.

Included, thank you

30. Statistics and data analysis: Please define what is mean by "nocturnally" (e.g. midnight to 6am).

Included (22.00 – 06.00hrs)

31. References: References 1 & 8 are identical papers although given different names. Should delete one.

Done – thank you