PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A RANDOMISED CONTROLLED TRIAL OF ADVANCED HYBRID CLOSED-LOOP STUDY IN ADULT POPULATION WITH TYPE 1 DIABETES (ADAPT): STUDY PROTOCOL AND RATIONALE
AUTHORS	de Portu, Simona; Akinola, Titilope; Vorrink, Linda; Re, Roseline; Shin, John; Castaneda, Javier; Habteab, Aklilu; Cohen, Ohad

VERSION 1 – REVIEW

REVIEWER	Beato-Víbora, Pilar Badajoz University Hospital, Endocrinology and Nutrition
REVIEW RETURNED	11-Jul-2021

GENERAL COMMENTS	The paper “ADVANCED HYBRID CLOSED-LOOP STUDY IN ADULT POPULATION WITH TYPE 1 DIABETES (ADAPT): STUDY PROTOCOL AND RATIONALE” describes the protocol for a prospective randomised multicenter evaluation of an advanced hybrid closed-loop system in adults with type 1 diabetes in comparison to MDI with flash glucose monitoring. I would suggest the following changes: Comment 1: The message “Error! Reference source not found” appears 4 times throughout the manuscript. It is not clear if it refers to a missing reference. Comment 2: Cites 1-3 are not referenced in the text. Comment 3: The dates of the study are not included in the manuscript, as required by the Editors. Also, the abstract seems long, please confirm if it meets the journal requirements. Comment 4: Will IS-CGM include alarms? Will they be activated? This aspect can affect outcomes regarding hypoglycaemia events. Comment 5: Will the patients use readers or mobile phones? Will the patients in the AHCL arm be able to link the pump to their mobile phones? This aspect can affect satisfaction. Comment 6: Page 2, Line 18. It should be “an advanced hybrid closed loop system”. Comment 7: Page 3, Line 17: It´s not consistent throughout the manuscript if the comparison is IS-CGM or also RT-CGM. The authors should clarify this aspect. Comment 8: Page 3, Line 38: Hba1c in mmol/mol is missing. Comment 9: Page 5, Line 12: The adjective “difficult-to-manage”, when referring to patients, should be avoided. Comment 10: Page 5, Line 51: which CGM system will be used for blinded CGM? Comment 11: Page 6, Line 33: It should be “closed loop” Comment 12: Page 6, Line 39: is the glucose target of 110 not available for some reason, as in the commercially available 780G system? Comment 13: Page 6, Line 50: My understanding is that it suspends if sensor glucose levels are predicted to go below a pre-defined

	level. Please, clarify this aspect. Comment 14: Page 7, Line 20. Will the patients be willing to switch from RT-CGM to IS-CGM and then to AHCL? Would this mean that some very technological patients will have to be selected, influencing the outcomes? Could the authors comment on this aspect? Comment 15: Page 8, Line 26: The references for the validated questionnaires in French and German should be included. Comment 16: Page 9, Line 45: Will local Ethics Committees from each participant country also approve the protocol? Comment 17: Page 17, Line 44: The end of the parenthesis is missing. Comment 18: Page 19, Line 15: include “respectively”, to clarify the sentence. Comment 19: Page 19, Line 36: Which software will be used to calculate MAGE? Why MAGE and not other glycaemic variability measures? The authors should comment on this aspect. Comment 20: Page 19, Lines 32 and 35: why percent of readings in RT-CGM arm and sensor use in FGM and AHCL? Is there a difference or just a different expression? Comment 21: Page 19, Line 50: The reason for lost days from school or work would also be interesting to know. Comment 22: Other interesting variables to analyse will be the following: number of SMBGs, hypoglycaemia awareness status at baseline, or even changes during follow-up, changes in sleep quality. Also, in the AHCL arm, the number of calibrations, reasons for exits to manual mode, changes in settings during follow-up (active insulin time or glucose target).

REVIEWER	Boughton, Charlotte Wellcome Trust-MRC Institute of Metabolic Science, University of Cambridge
REVIEW RETURNED	15-Jul-2021

GENERAL COMMENTS	Thank you for the invitation to review this study protocol. Comments - It appears the initial study was to compare AHCL with MDI plus IS-CGM. The additional comparator of MDI plus RT-CGM perhaps has been added subsequently and this makes the protocol challenging to follow as it is currently. I think it would be clearer if the initial protocol is kept as it was with a separate section for the exploratory comparison with MDI + RT-CGM. The rationale for adding in the MDI + RT-CGM comparator should be more explicit. - The use of ‘confirmatory’ and ‘exploratory’ in study design and analysis are not clear and ideally will be removed by moving the additional comparator (MDI + RT-CGM) into a separate section - The study design e.g. parallel or crossover should be in the title and abstract - How the CGM based outcomes will be collected is not clear – which masked CGM is going to be applied in both arms of the study and over what duration? - Which CGM is being used for Cohort B? - Number of days lost from work or school – how will this be collected? - The authors should be careful with the term ‘advanced hybrid closed loop’ – this is appropriate when describing the current HCL system which indeed is more advanced than the Medtronic first generation system but it should not be inferred that this is more ‘advanced’ than other commercially available closed-loop systems as this has not been demonstrated and is misleading.

	- Patient involvement - would suggest removing the sentence 'but they were actively involved in the recruitment process and intervention implementation' unless this means something other than the patients being recruited into the study as this is not what is meant by patient involvement. - The links to data in appendices need addressing - I was not able to access any supplementary material

REVIEWER	Burckhardt, Marie-Anne University Children's Hospital Basel, Ped. Endocrinology and Diabetology
REVIEW RETURNED	19-Jul-2021

GENERAL COMMENTS	Thank you for asking me to review this protocol paper. It covers the important topic of hybrid closed loop therapy in adults using MDI and isCGM/ RTCGM and will evaluate the impact of an AHCL system compared to MDI and isCGM in adults with suboptimal glycaemic control. Primary outcome is the HbA1c difference from baseline to 6 months between the two groups It is well written and covers an important and interesting topic as most studies to date either compare HCL vs. SAPT or MDI without isCGM/RTCGM. However, I have a few comments. Abstract 1. Methods: Please also state in the methods that two control cohorts (AHCL vs. MDI with isCGM and AHCL vs. MDI and RTCGM). As it stands now it is unclear why participants can be on IS-CGM or RT-CGM prior to screening and the study outcome is AHCL vs. isCGM. Introduction: 2. Consider adding the reference McAuley et al. Diabetes Care. 2020 Dec;43(12):3024-3033. to line 5-9 on page 5. Methods: 3. Can the authors comment on the choice of the primary outcome? In most of the more recent closed-loop trials time spent in a target glucose range is chosen and can take into account the caveats of HbA1c. 4. It is unclear in the text if participants will all be using isCGM during the control arm or if they are allowed to use RTCGM if they were using this prior to the study. I assume, those using RTCGM will continue to do so. If the recruited participant is using RT CGM prior to the study, will they automatically be allocated to cohort B? And vice versa, if on isCGM to cohort A? If this is the case, can you clarify if the recruited participant using RT CGM prior to the study will automatically be allocated to cohort B? And vice versa, if on isCGM to cohort A? Which RTCGM system will participants randomized to the control arm in study B be using? On p. 6, line 58 to 60 it says participants in the comparator arm will use the Abbott Freestyle Libre as a comparator device. This is confusing. 5. The two cohorts in the control arm are almost like two separate studies with two different control treatments: AHCL vs MDI and isCGM and AHCL vs MDI and RTCGM. It might be helpful to provide a reasoning for including both isCGM and RTCGM in the control arm. 6. The study design is well described, however there is no study schedule / protocol (table or graph) with an outline and description of different study visits (content/duration and so on). This should be provided and would strengthen the protocol. 7. Please clarify in the section patient involvement: what will the role be in recruitment and intervention implementation?

	8. PROM: In addition to the PROM's presented, have you considered using the INSPIRE questionnaire specifically designed to evaluate user experiences of closed loop users? Weissberg-Benchell et al. Diabetic Medicine 2019, May 36 (5):644-652 Minor: 1. Abstract (intro): it may read better using regions or countries instead of geographies. 2. Introduction, p.4, line 12: Line 12: should it not read "and/or reduction the risk of hypoglycemic events" 3. Methods: the table and figure referencing does not appear correctly, please revise and insert correct reference/link 4. Methods, P.6 line 33, typo: hybrid closed loop 5. P7 line 37/38 in patient involvement: outcome measures instead of outcomes measures.

VERSION 1 – AUTHOR RESPONSE

Comments from Reviewer 1:

I would suggest the following changes:

Comment 1: The message "Error! Reference source not found" appears 4 times throughout the manuscript. It is not clear if it refers to a missing reference.

The authors have corrected the references to tables and figures, where the "Error! Reference source not found" was being shown.

Comment 2: Cites 1-3 are not referenced in the text.

Citations are included in the strengths and limitations, and have been separated from the main text.

Comment 3: The dates of the study are not included in the manuscript, as required by the Editors. Also, the abstract seems long, please confirm if it meets the journal requirements.

The authors have included the study start date and estimated primary completion and study closure dates in the study design section of the methods. Text has been amended to:

The study will be conducted at multiple sites with experience in CSII use in adults with T1D in France, Germany, and the UK, with a study start date of July 13, 2020. The estimated primary completion date is December 15, 2021 and estimated study closure is July 30, 2022.

The abstract has been edited due to peer review comments, and has been kept below the 300 word threshold.

Comment 4: Will IS-CGM include alarms? Will they be activated? This aspect can affect outcomes regarding hypoglycaemia events.

The IS-CGM use was according to the specific model and to the current best clinical practice. This will be added in the methods as per reviewer comment:

Participants will use the IS-CGM device according to the specific model and to the current best clinical practice.

Comment 5: Will the patients use readers or mobile phones? Will the patients in the AHCL arm be able to link the pump to their mobile phones? This aspect can affect satisfaction.

Subjects using IS-CGM or RT-CGM can use readers or mobile phones, according to their routine practice, and continue to do so throughout the study.

The AHCL pump used in this study does not connect with a mobile phone, which is currently a feature of the MiniMed 780G system. This may negatively affect patient satisfaction, and will be addressed in the study results.

Comment 6: Page 2, Line 18. It should be “an advanced hybrid closed loop system”.

This error has been corrected.

Comment 7: Page 3, Line 17: It´s not consistent throughout the manuscript if the comparison is IS-CGM or also RT-CGM. The authors should clarify this aspect.

The main objective of the study is the comparison of AHCL versus MDI+IS-CGM, in the primary cohort A. Comparison with RT-CGM will also be done in cohort B in an exploratory manner Additional clarification has been added to the study design section:

There will also be an additional exploratory part of the study, with a separate cohort, comparing the same AHCL system with MDI plus RT-CGM,

Comment 8: Page 3, Line 38: Hba1c in mmol/mol is missing.

The unit was on the subsequent line so a non-breaking space has been included to avoid confusion.

Comment 9: Page 5, Line 12: The adjective “difficult-to-manage”, when referring to patients, should be avoided.

This phrase has been replaced with:

Patients with sub-optimally controlled T1D

Comment 10: Page 5, Line 51: which CGM system will be used for blinded CGM?

The authors have included the description of the CGM system to the study design, Guardian™ Link 3 attached to the Guardian™ Sensor 3.

Comment 11: Page 6, Line 33: It should be “closed loop”

Typo has been corrected

Comment 12: Page 6, Line 39: is the glucose target of 110 not available for some reason, as in the commercially available 780G system?

The glucose target 110mg/dL is not available in this investigational MiniMed 670G version 4.0 pump model.

Comment 13: Page 6, Line 50: My understanding is that it suspends if sensor glucose levels are predicted to go below a pre-defined level. Please, clarify this aspect.

The authors have clarified this point, as the reviewer is correct that suspension of basal insulin delivery also occurs when sensor glucose levels are predicted to go below the pre-defined level, and text now reads:

When used in open loop, SmartGuard™ features such as suspend before low (which temporarily suspends basal insulin delivery if sensor glucose levels go below, or are predicted to go below, a pre-defined threshold level) can be used.

Comment 14: Page 7, Line 20. Will the patients be willing to switch from RT-CGM to IS-CGM and then to AHCL? Would this mean that some very technological patients will have to be selected, influencing the outcomes? Could the authors comment on this aspect?

The study protocol does not include switching from RT-CGM to IS-CGM.

Subjects in cohort A on IS-CGM will continue using the same system used prior to study start as well as Cohort B on RT-CGM, therefore removing selection bias the reviewer was concerned with. Additional clarification has been added to the study design section:

Participants using IS-CGM will be randomized in cohort A, and those using RT-CGM will be randomized in cohort B.

Comment 15: Page 8, Line 26: The references for the validated questionnaires in French and German should be included.

DTSQ has been developed and validated by HPR (https://www.healthpsychologyresearch.com/). (Reference has been added to manuscript)

The University of Virginia has provided licenses for linguistic validation of the HFS questionnaires. For simplicity, the reference is added only for the initial publication.

DQoL has been validated in UK and France. French reference has been added.

Comment 16: Page 9, Line 45: Will local Ethics Committees from each participant country also approve the protocol?

Ethics committees in France, UK and Germany have reviewed and approved the protocol prior study start (details of the ECs are added to the manuscript, in Ethics section).

Comment 17: Page 17, Line 44: The end of the parenthesis is missing.

Missing parenthesis has been added.

Comment 18: Page 19, Line 15: include “respectively”, to clarify the sentence.

Respectively has been added to sentence.

Comment 19: Page 19, Line 36: Which software will be used to calculate MAGE? Why MAGE and not other glycaemic variability measures? The authors should comment on this aspect.

An in-house algorithm was used to calculate MAGE following the definition in the literature.

Other glycaemic variability measures have been included. The coefficient of variation of SG values is also part of the ancillary endpoints (Table 3), and the times in the different ranges (in hypoglycemic and hyperglycemic ranges) also are provided for the assessment of glycemic variability. These factors were chosen as they are the most commonly used and familiar in clinical practice and market access.

Comment 20: Page 19, Lines 32 and 35: why percent of readings in RT-CGM arm and sensor use in FGM and AHCL? Is there a difference or just a different expression?

In line 32, the number of scans and percentage of sensor readings is indeed for the MDI plus IS-CGM control arm. While in line 33, only the percentage of sensor readings for MDI plus RT-CGM control arm as there is no scan with RT-CGM systems.

The percentage of sensor use, line 35 is intended for AHCL group.

Comment 21: Page 19, Line 50: The reason for lost days from school or work would also be interesting to know.

The reason for absenteeism from school or work collected is not collected. Thank you for this comment, we will consider collecting this data for future protocol development.

A comparison of the number of days lost in the 2 groups will be performed.

Comment 22: Other interesting variables to analyse will be the following: number of SMBGs, hypoglycaemia awareness status at baseline, or even changes during follow-up, changes in sleep quality. Also, in the AHCL arm, the number of calibrations, reasons for exits to manual mode, changes in settings during follow-up (active insulin time or glucose target).

The number of SMBG tests in the AHCL arm is collected (Table 3 Ancillary endpoints). Hypoglycemia awareness and sleep quality were not collected as these were not the focus of the study. All other AHCL parameters are collected.

Comments from Reviewer 2:

Comments

It appears the initial study was to compare AHCL with MDI plus IS-CGM. The additional comparator of MDI plus RT-CGM perhaps has been added subsequently and this makes the protocol challenging to follow as it is currently. I think it would be clearer if the initial protocol is kept as it was with a separate section for the exploratory comparison with MDI + RT-CGM. The rationale for adding in the MDI + RT-CGM comparator should be more explicit.

For clarification, no protocol change was done during the study. The primary study Cohort is based on people with T1D on IS-CGM. The secondary pre-defined cohort on RT-CGM is exploratory only.

Based on a comment from reviewer 1, additional clarification has been added to the study design section:

There will also be an additional exploratory part of the study, with a separate cohort, comparing the same AHCL system with MDI plus RT-CGM,

The use of 'confirmatory' and 'exploratory' in study design and analysis are not clear and ideally will be removed by moving the additional comparator (MDI + RT-CGM) into a separate section

We would like to explain the two different cohorts:

The confirmatory part of the trial corresponds to Cohort A (670G version 4.0 AHCL versus MDI plus IS-CGM) where power analysis was conducted, and the sample size will allow performing powered statistical tests. To allow observation of a minority of patients who are using MDI + RT-CGM, a separate second cohort, which is not powered for significant endpoints, was considered for exploratory analysis to seek for potential trends. We find the reviewer comment useful and to further clarify this, we will separate the results of the two cohorts.

The study design e.g. parallel or crossover should be in the title and abstract

The study is a randomized controlled study for the first six months, and this is the primary design.

The one-arm crossover at 6 months from the control arm to the ACHL will be analyzed separately as a continuation phase. Therefore, the title reflects the main objective of the study.

How the CGM based outcomes will be collected is not clear – which masked CGM is going to be applied in both arms of the study and over what duration?

For scientific validity, the same CGM system is used to assess glycemia in both arms.

Therefore, the blinded CGM in control arm uses the same sensor and same algorithm as the treatment arm, over 2 weeks at baseline, 3 and 6 months. These measurements will be used for the comparisons of CGM data. This is now explained in the study ~~deisgn~~design sections:

The same CGM system will be used in both arms to allow for comparisons of CGM data.

Which CGM is being used for Cohort B?

All RT-CGM models available at the sites can be used in the study, per standard of care. This has been added to study design section:

Subjects in the MDI plus RT-CGM will use any RT-CGM model available at the study site, in line with standard of care.

Number of days lost from work or school – how will this be collected?

Number of days lost from work or school are asked at each follow up visit in the database.

The authors should be careful with the term 'advanced hybrid closed loop' – this is appropriate when describing the current HCL system which indeed is more advanced than the Medtronic first generation system but it should not be inferred that this is more 'advanced' than other commercially available closed-loop systems as this has not been demonstrated and is misleading.

The study device uses the same algorithm to the commercially available MiniMed 780G, which is an advanced version compared to the MiniMed 670G (as mentioned in the Methods "MiniMed 670G version 4.0 AHCL system (with an equivalent algorithm and commercialized as the MiniMed 780G system, referred to throughout the manuscript as AHCL)")

The authors understand the distinction between hybrid closed loop and advanced hybrid closed loop, and believe that throughout the manuscript they have used the term AHCL as a method of easily identifying the device used in the treatment arm and not as a way to imply superiority over other closed loop systems.

Patient involvement - would suggest removing the sentence 'but they were actively involved in the recruitment process and intervention implementation' unless this means something other than the patients being recruited into the study as this is not what is meant by patient involvement.

Sentence has been deleted.

The links to data in appendices need addressing

No appendices were included together with this manuscript at submission.

I was not able to access any supplementary material

No supplementary materials were included together with this manuscript at submission.

Comments from Reviewer 3:

Abstract

1. Methods: Please also state in the methods that two control cohorts (AHCL vs. MDI with isCGM and AHCL vs. MDI and RTCGM). As it stands now it is unclear why participants can be on IS-CGM or RT-CGM prior to screening and the study outcome is AHCL vs. isCGM.

To add clarity, additional text has been added to the abstract:

An exploratory part of the study will compare the MiniMed 780G system with MDI plus RT-CGM.

Introduction:

2. Consider adding the reference McAuley et al. Diabetes Care. 2020 Dec;43(12):3024-3033. to line 5-9 on page 5.

Reference has been added to this sentence.

Methods:

3. Can the authors comment on the choice of the primary outcome? In most of the more recent closed-loop trials time spent in a target glucose range is chosen and can take into account the caveats of HbA1c.

HbA1c remains a major predictor of long-term glycemic complications and costs, as well as a major input in the health-economic models. The aim of study is to provide evidence, beyond the clinical benefit, of the economic impact of the AHCL. Therefore, HbA1c was chosen as the primary outcome. Nevertheless, other important clinical related endpoints (Time in ranges, hypoglycemia) are collected and analyses as secondary endpoints (refer to Table 2)

4. It is unclear in the text if participants will all be using isCGM during the control arm or if they are allowed to use RTCGM if they were using this prior to the study. I assume, those using RTCGM will continue to do so. If the recruited participant is using RT CGM prior to the study, will they automatically be allocated to cohort B? And vice versa, if on isCGM to cohort A?

If this is the case, can you clarify if the recruited participant using RT CGM prior to the study will automatically be allocated to cohort B? And vice versa, if on isCGM to cohort A? Which RTCGM system will participants randomized to the control arm in study B be using? On p. 6, line 58 to 60 it says participants in the comparator arm will use the Abbott Freestyle Libre as a comparator device. This is confusing.

Subjects using the IS-CGM will continue using it throughout the study. Per exclusion criteria, subjects are not allowed to switch from IS-CGM to RT-CGM during the study. Subjects using IS-CGM will be randomized in Cohort A, and those using RT-CGM in Cohort B respectively, as shown in Figure 1. The 2 cohorts have separate randomizations. For both cohorts, subjects will continue using the same system used prior to randomization, following standard of care. Additional clarification in the study design section:

Participants using IS-CGM will be randomized in cohort A, and those using RT-CGM will be randomized in cohort B.

The use of the Abbott Freestyle Libre only occurs in cohort A. Clarification has been added:

Subjects in the MDI plus IS-CGM arm ~~of~~ (cohort A) will use an Abbott FreeStyle Libre IS-CGM device.

5. The two cohorts in the control arm are almost like two separate studies with two different control treatments: AHCL vs MDI and isCGM and AHCL vs MDI and RTCGM. It might be helpful to provide a reasoning for including both isCGM and RTCGM in the control arm.

The real-world use of both IS-CGM and RT-CGM are outlined in the introduction, and the authors believe this provides context for the use of both devices as control arms. The primary cohort (Cohort A) is indeed the primary study design related to the group using IS-CGM being the most commonly used system, in standard of care. However, since a minority of patients are using MDI + RT-CGM, a

second cohort, which is not powered for significant endpoints, was considered for exploratory endpoints to seek for potential similarity in trends. The results will be presented separately. Clarification has been added to the study design:

There will also be an additional exploratory part of the study, with a separate cohort, comparing the same AHCL system with MDI plus RT-CGM to look for potential similarities in trends.

6. The study design is well described, however there is no study schedule / protocol (table or graph) with an outline and description of different study visits (content/duration and so on). This should be provided and would strengthen the protocol.

A table of the study visits has been added to the manuscript. We recommend to add this to the supplemental data.

Figure 1: Visit schedule overview

▫ *Visits allowed to be conducted remotely in pandemic period.*

7. Please clarify in the section patient involvement: what will the role be in recruitment and intervention implementation?

This sentence has been deleted

8. PROM: In addition to the PROM's presented, have you considered using the INSPIRE questionnaire specifically designed to evaluate user experiences of closed loop users? Weissberg-Benchell et al. Diabetic Medicine 2019, May 36 (5):644-652

We thank the reviewer for the suggestion, and we agree that the aim of the questionnaires is to collect the most relevant and useful data about the use of the AHCL system. Whilst the INSPIRE questionnaire would provide data that fits this description, the protocol has included questionnaires that have been used across previous MDT studies to have consistency, and more broadly recognized by the European Health authorities across the region.

Minor:

1. Abstract (intro): it may read better using regions or countries instead of geographies.

In line with the reviewers comment 'geographies' has been replaced with 'regions'.

2. Introduction, p.4, line 12: Line 12: should it not read "and/or reduction the risk of hypoglycemic events"

Sentence has been corrected to:

The standard of care for people with T1D has evolved greatly over time, with each advance offering stepwise incremental improvements in glycemic control and/or reduce the risk of hypoglycemic events.

3. Methods: the table and figure referencing does not appear correctly, please revise and insert correct reference/link

The authors have corrected the references to tables and figures, where the "Error! Reference source not found" was being shown.

4. Methods, P.6 line 33, typo: hybrid closed loop

Typo has been corrected.

5. P7 line 37/38 in patient involvement: outcome measures instead of outcomes measures.

Typo has been corrected.

VERSION 2 – REVIEW

REVIEWER	Beato-Víbora, Pilar Badajoz University Hospital, Endocrinology and Nutrition
REVIEW RETURNED	06-Oct-2021

GENERAL COMMENTS	The authors have satisfactorily responded to all the questions and made the necessary changes to the manuscript

REVIEWER	Burckhardt, Marie-Anne University Children's Hospital Basel, Ped. Endocrinology and Diabetology
REVIEW RETURNED	22-Oct-2021

GENERAL COMMENTS	The authors addressed all my comments.