PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The effect of 6 months hybrid closed-loop insulin delivery in adults with type 1 diabetes: a randomised controlled trial protocol
AUTHORS	McAuley, Sybil; de Bock, Martin; Sundararajan, Vijaya; Lee, Melissa; Paldus, Barbora; Ambler, Geoff; Bach, Leon; Burt, Morton; Cameron, Fergus; Clarke, Philip; Cohen, Neale; Colman, Peter; Davis, Elizabeth; Fairchild, Jan; Hendrieckx, Christel; Holmes-Walker, Deborah; Horsburgh, Jodie; Jenkins, Alicia; Kaye, Joey; Keech, Anthony; King, Bruce; Kumareswaran, Kavita; MacIsaac, Richard J.; McCallum, Roland; Nicholas, Jennifer; Sims, Catriona; Speight, Jane; Stranks, Stephen; Trawley, Steven; Ward, Glenn; Vogrin, Sara; Jones, Timothy; O'Neal, David

VERSION 1 – REVIEW

REVIEWER	Benyamin Grosman Medtronic, USA
REVIEW RETURNED	29-Nov-2017

GENERAL COMMENTS	My only concern is that only 5 weeks of the study period are covered with CGM with the control group. This may bias the outcomes by subjects in the control arm paying more careful attention to their diabetes management at those 5 weeks.

REVIEWER	Satish Garg Barbara Davis Center for Diabetes; University of Colorado Denver, USA
REVIEW RETURNED	25-Jan-2018

GENERAL COMMENTS	The authors plan a 26-week randomized, controlled trial comparing a group of patients using hybrid closed-loop (670G system) vs those using MDI or insulin-pump therapy (current diabetes therapy). I have some concerns regarding their methods and possible conclusions that the authors are expecting from this short-term study. Here are my specific concerns to this study: 1. This is a small sample size of 120 patients who will be randomized to the above two arms. As authors can see, through NCT.gov a much larger study has already been initiated in the US and in Europe involving more than 1,200 patients using the hybrid closed-loop system. Above all, the subjects are truly not being randomized as 1:1 due to the following reasons: a. The control arm may have significant number of patients using insulin-pump therapy as compared to MDI. b. The patients are also allowed to use Libre but not uniformly across all the study population. 2. The inclusion criteria states that A1c <10.5 will be included in this study. I'm concerned about this inclusion criteria as subjects with

	higher A1c might show a drop in A1c in both groups just because they've been enrolled in a study (Hawthorne effect). At the least, the patients need to be stratified at the time of randomization, which might bring the sample size to a much smaller number of patients with different levels of baseline A1cs. 3. I personally think the design is very poor. The ideal design should have been patients randomized to either using 670G system or SAPT or add a third arm of those using MDI with CGM. Heterogeneous group of subjects using CGM in MDI or IPT group will make analysis more difficult in the design proposed. 4. Authors are also proposing to test different biomarkers for vascular health. I don't know what an EKG done at baseline or at the end of the study will show as a vascular health biomarker. At the least, authors should consider either a holter monitor or treadmill test on all subjects. This is too short a study to draw any conclusions on the biomarkers of vascular health that have been proposed. Above and beyond, biomarkers of vascular health may not show anything if patients are <50 years of age, unless authors are planning to enrich their population in the older age group. 5. TIR proposed is too wide as a primary endpoint. As authors know, 670G system tries to bring people to 120mg/dL even though that is not the mean glucose that is achieved in the studies reported so far (JAMA 2016, DTT 2017). I would strongly recommend they change the TIR as a primary endpoint to be between 70-140 mg/dL. 6. Authors also report as a strength of their study paragraph that they will compare their data with a concurrent study examining hybrid closed-loop for 12-25 years of age. Is that an observational study or is it another arm of the current study? And also, are all the analysis and biomarkers, etc being evaluated in the study evaluating younger patients? 7. Authors have repeatedly commented that no long-term data is available. I'm sure many of the authors should know that more than 1 year data in a sizable number of patients have been reported at different leading diabetes meetings (ADA, EASD, ATTD 2017). I understand that much of that data may not have been published yet. 8. How are the subjects going to be guided for carbohydrate ratio? Since the data from the original studies on 670 system have shown that most providers and patients under-calculate the insulin to carb ratio. And in fact, the data clearly highlighted that the boluses taken by patients by the end of three months (or even 1 year) were much higher than the basal insulin delivery. 9. Are the authors planning to pay any attention to protein and fat in the meals? Or are they only concentrating on carb ratios? I think it will be important for authors to consider moving the field forward to design studies where protein and fat are also taken into consideration for meal-time boluses. 10. Are the authors planning to include the catheter occlusions under the microscope or are there specific criteria they're using for specific delivery line failures as quoted? 11. Authors also made a comment that MDI users will use a bolus calculator through a mobile device, but no such calculations were mentioned in the IPT group. 12. As we all know that anemia (especially thalassemia and other hemolytic anemias) may affect glucose measurements and insulin delivery. Authors may consider those subjects to be excluded from the study.

VERSION 1 – AUTHOR RESPONSE

Editorial Requests:

- **Along with your revised manuscript, please provide a completed copy of the SPIRIT checklist** A completed SPIRIT checklist has been included.

- **Please revise the 'strengths and limitations' section after the abstract. It should include some limitations as well as strengths.**

The 'strengths and limitations' section has been revised to include limitations. These include: 1/ while the standard therapy comparator in the study reflects current practice for most adults in Australia, this does not reflect standard care worldwide, and 2/ while the study visit schedule is identical, CGM information is only available for the CL group at the study visits. With these additions, the bullet points have been re-ordered for clarity.

- **We also received some very brief feedback from one of the unassigned reviewers. The reviewer stated that you do not acknowledge nor include any of the long-term closed loop published studies nor the extensive psychosocial closed loop published research in your introduction or literature overview.**

Please check that your literature review is up to date with the introduction section discussing the most relevant studies on this topic.

Thank you. We have revised the literature review to include long-term CL studies as well as psychosocial CL research, with references reflecting peer-reviewed published literature up to February 2018.

- **We note that you were not able to add all 36 authors to the submission system. If this is still a problem when you submit your revision then please mention this in your cover letter so that our editorial production team are aware of the problem.**

Thank you, we were not able to add all authors in the submission system. Please see the revised manuscript by-line for the full author list and their institutions.

Reviewers' Comments to Author:

Reviewer: 1

Reviewer Name: Benyamin Grosman

My only concern is that only 5 weeks of the study period are covered with CGM with the control group. This may bias the outcomes by subjects in the control arm paying more careful attention to their diabetes management at those 5 weeks.

Thank you. We acknowledge the Reviewer's concern and make the following comments. Firstly, we do not anticipate any differential bias between the study groups in relation to the masked CGM data collection. It is important to collect data independently of the HCL system to measure the primary outcome. Both study groups will wear the same masked CGM for 2 weeks' mid-study and 3 weeks at end-of-study (to collect study end-point data). None of the masked CGM data will be available to any participant during the study. The HCL group will concurrently wear real-time CGM during the masked CGM periods, in the same way they wear real-time CGM for the 26 weeks of study intervention. It would

be unreasonable to expect those in the control group to wear masked CGM for the full 26 weeks post-run-in to collect outcome data. As with all clinical trials, both the intervention and control groups would be anticipated to be impacted by trial participation itself.

Reviewer: 2

Reviewer Name: Satish Garg

1. This is a small sample size of 120 patients who will be randomized to the above two arms. As authors can see, through https://protectau.mimecast.com/s/fj-xC91ZVBS9GzowHPFW2E?domain=nct.gov a much larger study has already been initiated in the US and in Europe involving more than 1,200 patients using the hybrid closed-loop system. The web link provided is not a live link. We presume the reviewer is referring to the trial with ID NCT02748018, a Medtronic-sponsored study which commenced in May 2017. By contrast, study ACTRN12617000520336 described in this manuscript is an investigator-initiated study funded by the Australian Government. This study protocol was finalised in May 2016, and the study visits commenced in April 2017. The delay in commencing the study visits after the protocol was finalised was due to factors external to the study investigators.

This ACTRN12617000520336 study is sufficiently powered to detect a clinically significant primary outcome. Notably, this study also has many novel secondary outcomes beyond glucose control, which are not being measured in NCT02748018. These secondary outcomes include psychosocial well-being, sleep, cognitive functioning, driving and electrocardiograph profile. ACTRN12617000520336 is planned to be completed in 2019, whereas NCT02748018 is planned for completion late 2021.

Above all, the subjects are truly not being randomized as 1:1 due to the following reasons: a. The control arm may have significant number of patients using insulin-pump therapy as compared to MDI.

As outlined in the manuscript study design and randomisation sections, approximately half the participants recruited will be using MDI and the other half will be using IPT at enrolment. For the 1:1 randomisation, the baseline insulin delivery modality (MDI or IPT) will be one of three minimisation variables. We therefore we expect the MDI participants will be equally randomised to control and intervention, and that the IPT participants will be equally randomised to control and intervention.

b. The patients are also allowed to use Libre but not uniformly across all the study population. All participants are permitted to use Libre uniformly across the study if they choose to do so and can afford it. This reflects standard diabetes care in Australia, which is the purpose of the control arm. In practice, few patients in Australia can afford to pay for this technology in the long-term (no subsidies are available for adults >21 years of age). For this study, we anticipate that those in the control arm would be more likely to avail themselves of the Libre device than those in the intervention arm (who will be provided with real-time CGM). Of note, participants in the intervention arm have not been specifically precluded from using the Libre device.

2. The inclusion criteria states that A1c <10.5 will be included in this study. I'm concerned about this inclusion criteria as subjects with higher A1c might show a drop in A1c in both groups just

because they've been enrolled in a study (Hawthorne effect). At the least, the patients need to be stratified at the time of randomization, which might bring the sample size to a much smaller number of patients with different levels of baseline A1cs.

We intend the study findings to be applicable to the broad type 1 diabetes population. We did not want to restrict our study findings to people living with type 1 diabetes who have either well-controlled or moderately-controlled glucose levels. By including a control group in the study design, we will be accounting for the Hawthorne effect when interpreting the study results.

As explained in the manuscript, to account for potential differential responses to intervention depending on baseline glucose levels, baseline time-in-range (TIR) 3.9–10 mmol/L (dichotomised to ≤50% and >50%) will be one of the three minimisation variables used for randomisation. Groups will therefore be balanced for baseline TIR in the final analysis.

3. I personally think the design is very poor. The ideal design should have been patients randomized to either using 670G system or SAPT or add a third arm of those using MDI with CGM. Heterogeneous group of subjects using CGM in MDI or IPT group will make analysis more difficult in the design proposed.

This study is the result of a competitive grant process and the design was scrutinised by a panel of international experts. We have given careful consideration to SAP as a comparator. Ideally, the study would have four randomised arms: MDI, MDI plus CGM, pump without CGM, and SAP. However, this was beyond the available resources. For a four-arm study to be adequately powered to differentiate between all four groups, much larger participant numbers would be required, and this is beyond the amount of government funding available.

Current standard of care for adults with type 1 diabetes in Australia does not include CGM, due to the fact that there is no funding for CGM for adults (age 21+ years). Therefore, <5% of adults with T1D in Australia use (self-funded) real-time CGM or Libre on a regular basis.

As described in the manuscript, the data analysis will account for the participants' baseline insulin delivery modality.

4. Authors are also proposing to test different biomarkers for vascular health. I don't know what an EKG done at baseline or at the end of the study will show as a vascular health biomarker. At the least, authors should consider either a holter monitor or treadmill test on all subjects.

This is too short a study to draw any conclusions on the biomarkers of vascular health that have been proposed. Above and beyond, biomarkers of vascular health may not show anything if patients are <50 years of age, unless authors are planning to enrich their population in the older age group.

Thank you. We understand this concern but believe that including the assessment of levels of biomarkers known to modulate vascular risk that can change in the short-term (hours–days or weeks) is relevant, timely and a time- and cost-effective study. The results of the Swedish Diabetes Registry study (Steineck, et al. BMJ 2015) showing substantial CVD death reduction in type 1 diabetes using CSII vs MDI, with comparable HbA1c levels, is supportive evidence of the need for such a study. We would not

expect structural measures (such as IMT) which are not included in this study, nor vascular event rates to change.

As noted in the manuscript, there is a nocturnal Holter monitor worn for one week at each of baseline, mid-study and end-of study. Secondary outcomes relating to the Holter monitor data are: QT interval, heart rate and cardiac arrhythmias (see Table 1). It is well-recognised that hypoglycaemia can induce cardiac arrythmais, and also induce vascular endothelial dysfunction, and inflammatory and prothrombotic responses (in type 1 diabetes and even non-diabetic individuals), and that hypoglycaemia is associated with increased cardiovascular risk and death. Implicated markers such as related to inflammation, thrombosis and vascular reactivity can change in the very short term (within hours to days) and this study is over months. Inflammatory markers which are associated with, and predictive of, vascular events in type 1 diabetes that can change acutely include CRP, vascular cell adhesions molecules (e.g. sVCAM-1, sICAM, sE-Selectin), interleukins, TNF-alpha and haptoglobin (Joy, et al. 2015 Diabetes; Zoungas, et al. 2010 N Engl J Med; Lopes-Virella, et al. 2013 Diabetes Care; Hunt, et al. 2015 Diabetes Care; Rajab, et al. 2015 Diabetes Complications; Lopes-Virella, et al. 2008 Diabetes Care). Similarly, microRNA profiles have a half-life of days to weeks and are emerging as vascular risk factors in diabetes (Joglekar, et al. 2016 Diabetes).

Blood and urine collection for biochemical and molecular biomarkers related to glycaemia and to vascular health has been approved and are being stored in a bio-bank. Funding has been secured for some of these measures, and additional funding is being sought for additional biomarkers that may impact vascular health.

5. TIR proposed is too wide as a primary endpoint. As authors know, 670G system tries to bring people to 120mg/dL even though that is not the mean glucose that is achieved in the studies reported so far (JAMA 2016, DTT 2017). I would strongly recommend they change the TIR as a primary endpoint to be between 70-140 mg/dL.

The Investigators' opinion is that the glucose target of 3.9–10.0 mmol/L is the most appropriate primary outcome for this study. A target of 3.9–10.0 mmol/L is consistent with the international consensus in the CL and CGM field (Danne et al, Diabetes Care 2017;40:1631–1640). Moreover, the

670G system's target of 6.7 mmol/L is near the mid-point of this target.

The clinical target during 24 hr/day wear of a hybrid closed-loop system, which depends on insulin boluses to control post-prandial excursions (in turn depending on CHO-counting estimation) is 3.9– 10.0 mmol/L (which includes acceptable post-prandial rise). A target of 3.9–7.8 mmol/L is unrealistic for daytime when post-prandial excursions in part relate to bolus dosing; such a tight target would be appropriate as a secondary study outcome (Danne et al, 2017), and this is currently listed in the secondary outcomes in Table 1. By contrast, when measuring only nocturnal CGM (when meals are not a factor), a tighter target could be suitable.

6. Authors also report as a strength of their study paragraph that they will compare their data with a concurrent study examining hybrid closed-loop for 12-25 years of age. Is that an observational study or is it another arm of the current study? And also, are all the analysis and biomarkers, etc being evaluated in the study evaluating younger patients?

The concurrent study (trial ID ACTRN12616000753459) is also a randomised controlled trial, intervention 670G and with aligned core protocol. As stated in the manuscript's "strengths and

limitations" bullet points, the two trials have aligned glucose end-points which will facilitate comparison of results. The same biomarker analysis is not being undertaken in the study evaluating individuals aged 12–<25 years.

Authors have repeatedly commented that no long-term data is available. I'm sure many of the authors should know that more than 1 year data in a sizable number of patients have been reported at different leading diabetes meetings (ADA, EASD, ATTD 2017). I understand that much of that data may not have been published yet.

Although long-term studies CL safety studies have been undertaken, we are not aware of any peer-reviewed publications from randomised controlled CL studies with intervention periods longer than 3 months. We are aware that longer term studies are currently underway (e.g. NCT02748018), though we are not aware of even interim data from these studies being reported.

8. How are the subjects going to be guided for carbohydrate ratio? Since the data from the original studies on 670 system have shown that most providers and patients under-calculate the insulin to carb ratio. And in fact, the data clearly highlighted that the boluses taken by patients by the end of three months (or even 1 year) were much higher than the basal insulin delivery. During run-in, all participants will have the same detailed clinical reviews and education undertaken by endocrinologists, diabetes nurse educators and dieticians who are experienced in pump therapy; this aims to optimise carbohydrate-counting for all participants (pre-randomisation).

The Investigators are aware of data relating to 670G systems suggesting that strengthening the ICR may be required when using auto mode. The ICR will be reviewed and addressed in the education for participants randomised to intervention when they start a 670G, and also during the study's scheduled reviews by endocrinologists, diabetes nurse educators and dieticians when reviewing the participants and their 670G system uploaded data (as now outlined in the strengths and limitations bullet points section).

9. Are the authors planning to pay any attention to protein and fat in the meals? Or are they only concentrating on carb ratios? I think it will be important for authors to consider moving the field forward to design studies where protein and fat are also taken into consideration for mealtime boluses.

The design of this study does not intend to control for or to change the dietary composition of the meals. For both the intervention and control groups, meal-time bolus doses will be based upon the user's estimation of planned carbohydrate consumption.

10. Are the authors planning to include the catheter occlusions under the microscope or are there specific criteria they're using for specific delivery line failures as quoted?

Line failures will be self-reported, and recorded in real-time by participants in the study diaries provided. All participants using insulin pumps (both in the control group and those on 670G) will receive education about detecting and managing line failures.

11. Authors also made a comment that MDI users will use a bolus calculator through a mobile device, but no such calculations were mentioned in the IPT group.

The IPT group will use the in-built bolus calculators in their insulin pumps, with estimated carbohydrate consumption to be entered by the user. We acknowledge that the bolus calculator used by the MDI control group (Roche Aviva Expert), the pump control group (pump's bolus calculator) and the intervention group are not identical. However, these bolus calculators are integral to the mode of therapy, and reflect the reality of clinical care. Therefore, the study design and the subsequent findings remain valid. Considering this reviewer feedback, the manuscript has been revised for clarity regarding use of bolus calculators with the added text of "with bolus calculator in the glucose meter or pump, respectively" added to the control group's standard therapy description.

12. As we all know that anemia (especially thalassemia and other hemolytic anemias) may affect glucose measurements and insulin delivery. Authors may consider those subjects to be excluded from the study.

The automated and manual insulin dosing relates to CGM and glucose meter values. Potential participants with severe or unstable anaemia will be excluded (as per the final exclusion criterion).

We have chosen not to exclude people with mild, stable anaemia for the following reasons:

1/ The insulin dosing is not determined by HbA1c. Rather, HbA1c provides a metric for glycaemic exposure. Therefore, we would not expect the system's algorithm to be significantly influenced by a mild and stable anaemia.

2/ We are unaware of any data relating to the effects of anaemia on interstitial fluid CGM measures; therefore, do not anticipate anaemia to affect CL insulin delivery.

3/ The Roche Aviva Expert glucose meter being used in the study is reported to be accurate for haematocrit levels between 10% to 65%, which includes levels well outside the normal haematocrit range. We therefore do not consider that glucose meter readings will be inaccurate in the cases of mild and stable anaemia.

4/ We have not specified a lower cut-off for HbA1c inclusion, and the medically-qualified investigators will judge as to whether they expect an individual to have equivalent glucose control to an HbA1c ≤10.5% (for inclusion) though in the presence of anaemia. Individuals with stable mild chronic anaemia, and falsely-lowered HbA1c results, will not be excluded from the study; however, the HbA1c results of these individuals will not be used towards calculation of the secondary HbA1c outcome.

We trust that the above information and modifications to the manuscript provide the editors and reviewers with sufficient information to make a positive recommendation regarding the suitability of our work for publication. Should there be further information required please do not hesitate to contact us.