BMJ - Decision on
Manuscript ID
BMJ.2017.039000.R
1

Body: 02-Feb-2018

Dear Prof. Tsapas:

Manuscript ID BMJ.2017.039000.R1 entitled "Closed-loop insulin therapy for outpatients with type 1 diabetes: a systematic review and meta-analysis" which you submitted to BMJ,

Thank you for sending us your paper. We are pleased to say that we would like to publish it in the BMJ as long you are willing and able to revise your paper as explained below. We are provisionally offering acceptance but will make the final decision when we see the revised version. The comments from editors, the comments from the reviewers and general requirements for submission are available at the end of this letter.

We are looking forward to reading the revised manuscript and, we hope, making a final acceptance decision.

Please note that the BMJ might choose to shorten content or replace or re-size images for the print issue.

Please remember that the author list and order were finalised upon initial submission, and reviewers and editors judged the paper in light of this information, particularly regarding any competing interests. If authors are later added to a paper this process is subverted. In that case, we reserve the right to rescind any previous decision or return the paper to the review process. Please also remember that we reserve the right to require formation of an authorship group when there are a large number of authors.

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Yours sincerely

dr. Wim Weber
European editor, The BMJ
wweber@bmj.com,

Editors' comments:

Might you add a few words on what this adds to the recent SR (Weisman A et al. Effect of artificial pancreas systems on glycaemic control in patients with type 1 diabetes: a systematic review and meta-analysis of outpatient randomised controlled trials. Lancet Diabetes Endocrinol. 2017;5:501-512).

Could you update the search to help differentiate this from the Lancet review?

As it is, the search is one year old now.

Is 'Closed-loop insulin therapy' the best term to use? Others use the term 'artificial pancreas'.

The paper only looks at glucose levels, rather than complications, clinical outcomes and doesn't tell us much about safety.

One could read this entire paper without having any idea of exactly how much time (in hours or minutes) people with these systems spend in the desired glucose range. Table 2 makes it look like this is a very small proportion of time.

All of the included studies seem to compare these systems to another type of pump - are there no studies comparing these systems to daily injections? Wouldn't that be a relevant comparison? Editors would like to know how much value is added (in addition to convenience) with this technology.

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

** Comments from the external peer reviewers**

REFEREE COMMENTS

Reviewer: 1

Recommendation:

Comments:
I am satisfied that my previous comments have now been addressed.

Additional Questions:
Please enter your name: Jennifer Hirst

Job Title: Senior Primary Care Researcher

Institution: University of Oxford

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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If you have any competing interests <A HREF='http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests'target='_new'> (please see BMJ policy) please declare them here:

Reviewer: 2

Recommendation:

Comments:
The authors have responded very well to my comments. I still find the main outcomes about percentage of time in a particular range to be sub-optimal, but this is a limitation of the original studies (I think it should be noted more by the authors though as a limitation in this review, and other approaches in new studies like a repeated measures analysis of the actual value over time would be preferred). So, it difficult to address otherwise without the raw data. I only have minor additional things to say, as the paper is very well written and the methods are well described and chosen:

Minor
1) Move the results about small study effects to the end of the results (currently it comes before the main meta-analysis results, yet discusses how the meta-analysis results would change if 'missing' studies were included)

2) change "Of note, 95% prediction intervals were statistically significant when closed-loop was used overnight (3.97 to 11.62) suggesting that closed-loop will be beneficial in at least 95% of the individual study settings when applied overnight, but not when applied throughout 24h (-6.14 to 27.06)."
To "Of note, 95% prediction intervals were entirely above zero when closed-loop was used overnight (3.97 to 11.62), suggesting that closed-loop will be beneficial in at least 95% of the individual study settings when applied overnight; however, the prediction interval contained negative values when applied throughout 24h (-6.14 to 27.06), and so in some settings may not be beneficial"

3) The numbers in the brackets are often given without any explanation. E.g. "…was decreased by 8.32% (5.10 to 11.53, 84%, 36.43, 17 studies)" – what does 84%, 36.43, etc mean? Please address throughout.

4) Be consistent in using negative values when something is reduced. For example, in the following the sign keeps changing even though the effect is (I think) in the same direction: "Use of closed-loop had a favourable effect on time spent in hyperglycaemia (> 10 mmol/L) during the whole day which was decreased by 8.32% (5.10 to 11.53, 84%, 36.43, 17 studies) compared to control, both in trials where closed-loop was used only overnight (−6.51%, −9.42 to −3.60, 0%, 0.0, two studies), and in trials using closed loop throughout 24h (−8.62%, −12.41 to −4.84, 86%, 45.87, 15 studies)"

5) Appendix 8, the contour enhanced funnel plot's regions (e.g. the white region) looks very odd indeed. Is this actually correct? I think there is an error.

Best wishes, Richard Riley

Additional Questions:
Please enter your name: Richard Riley

Job Title: Professor of Biostatistics

Institution: Keele University

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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