Reviewer's report

Title: Closed-loop insulin delivery for treatment of type 1 diabetes

Version: 1 Date: 1 September 2011

Reviewer: Garry Steil

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Major Compulsory Revisions

1. The authors report that they review the current status of closed-loop insulin delivery systems extending previous work [9,10,11,12], with reference 9 being a review article published by their group on the same topic in February 2011 (Closed-loop insulin delivery: from bench to clinical practice, R. Nat. Rev. Endocrinol. 7, 385–395 (2011)). (references 10-12 refer to a 2006 review by this group, a 2005 review by Steil, and a 2006 review by Renard focused on implantable pumps and sensors). Given the Feb. 2011 review by this group, the authors need to focus on what has changed since then, and avoid repeating arguments and Figures.

2. In addition to not repeating text or having the same Figures, the authors should be consistent in how algorithms are classified. Having "Suspended Insulin Delivery" and "Nighttime closed-loop" categories in both reviews, followed by "Day and Night closed-loop", and "Dual-hormone closed-loop" and "Other approaches" in the earlier review (R. Nat. Rev. Endocrinol. 7, 385–395, 2011) and "Fully closed-loop versus Closed-loop with meal announcement" as a single category in this review creates confusion. The reviewer would recommend following a progression of increasing automation:

- Suspended insulin delivery 25, 26-29, 31-35, 36, and 37
- Overnight closed-loop22 38,39, 40,41,42, 43 44
- Closed-loop with meal announcement 10 24 41 44
- Fully closed-loop

where numbers indicate references discussed by the authors in each of the section as written. More important is that each section identify the clinical studies that have been conducted for each of these approaches with all the existing studies being identified and correctly categorized.

For this, a clear definition of what constitutes a “Suspend Insulin Delivery Study” from an “Overnight Closed-loop study” versus “Closed-loop with meal announcement” and “Fully closed-loop”. Clearly, a 30 hour closed loop study includes a “nighttime”, and during the night the pump may be “suspended”, making it possible to discuss the study under multiple headings. This should be avoided. What the reviewer would suggest is classifying each study according to the highest level of control achieved – thus a closed-loop study that includes day
and nighttime control with no meal announcements would be classified as “Fully closed-loop”; a study controlling meals with announcement would be classified “Fully closed-loop with meal announcement”, a study of nighttime control without meals but with the control allowed to increase insulin would be classified as “Nighttime control”, and a study that was limited to a pump suspend was be classified as “Suspend”. Studies should appear one category only with reference to primary (first) manuscript published on that study (manuscripts generated from secondary analysis should be identified). Using this approach, clinical studies could be grouped as:

- Suspended insulin delivery [36, 37, (38)]
- Overnight closed-loop [40, 42, (84)]
- Closed-loop with meal announcement [44, {23, 55}, (25, 60)]
- Fully closed-loop [22, 41, 43, {51}]

where the reviewer has indicated studies referenced in the present manuscript at some point, but not discussed under the existing headings by {}, and reconciled the list with closed-loop clinical studies previously identified by this group in their Feb 2011 review (reference 9 of this report), identifying in (). It is unclear why these studies were reported in the earlier review and not included here. One addition study by Bruttomesso D (J Diabetes Sci Technol. 2009 Sep 1;3(5):1014-21) should also be referenced and discussed if it includes closed-loop data. In total, the list only includes 16 studies which even if included in the prior review should still be mentioned in this review.

3. There are far fewer clinical closed-loop studies than a casual reader might infer from reading the present manuscript. This is primarily due to the large number of simulation studies that have been conducted. When reading a tile such as "An improved PID switching control strategy for type 1 diabetes" [14] it may not be clear to many readers whether the manuscript reports clinical data or simulation data (in this case simulation). There are numerous examples of this: "Nonlinear model predictive control of glucose concentration in subjects with type 1 diabetes", "A model-based algorithm for blood glucose control in type I diabetic patients", "A closed-loop artificial pancreas using model predictive control and a sliding meal size estimator", "Closed-loop control of artificial pancreatic Beta-cell in type 1 diabetes mellitus using model predictive iterative learning control" where it is not clear from the title or text if the reference is to a simulation, animal, or clinical study. Although simulation studies are unquestionable useful, they carry substantially less weight than clinical or animal studies.

What is needed in the present manuscript is a clear indication to the reader as to which studies/manuscripts are reporting clinical data and which are reporting simulation data.

4. The authors have provided some discussion of simulation studies (in silico studies). Simulation studies do play an increasingly important role in advancing closed-loop research; however, the authors have referenced on two of the many models used to perform these simulations (a model the authors developed at
Cambridge [45] and a model developed at the University of Virginia (UVA) [46]). Of these two it unclear what is different. They report their model to include inter- and intra-subject variability but do not comment on whether the UVA model also has these features, leaving the reader to infer that it does not.

What is needed is a clear statement about what differentiates their model [45] from the UVA model [46]. It should also be pointed out, with some expanded discussion, that the UVA [46] model has been accepted in the US as a replacement for animal studies (the authors should confirm the exact FDA status) and acknowledge other models that have been used. At a minimum, the model used by Medtronic Diabetes (J Diabetes Sci Technol. 2009 Sep 1;3(5):1047-57, Diabetes Technol Ther. 2005 Feb;7(1):94-108.) should be discussed as that model was used in developing the Medtronic PID controller which accounts for 1/3 of the referenced studies describing closed-loop insulin delivery with meals (references 23, 41, and 43).

Minor Essential Revisions

1. "In silico studies play a crucial role to complement clinical testing and address scenarios which cannot be practically or ethically tested in clinical studies [45,46]" - should read “in clinical” with a space between in and clinic.

2. Glucose control around meals has been shown challenging in laboratory studies both in adults and young people [43,41] – should read either “has been” or “was”. The author might also consider using “inpatient” to describe these studies rather than “laboratory” (people are studied in clinics; animals are studied in laboratories).

Discretionary Revisions

1. The authors should consider shortening the sections relating to HOME STUDIES AND BEYOND, EXPECTATIONS FOR CLINICAL PRACTICE, THE FUTURE: PERFECTING CLOSED-LOOP as much of the material in presented in these sections seems rather obvious. For example:

   a. When moving towards home studies, the emphasis should be on recognising real-life conditions whilst providing appropriate support from the research team.

   b. Pilot studies may evaluate efficacy, safety and utility over a short period of time, whereas longer studies are needed to demonstrate effectiveness on glycaemic control and rates of hypoglycaemia.

   c. The main goal of closed-loop therapy is to achieve good glycaemic control whilst reducing the risk of hypoglycaemia in people with type 1 diabetes.

   d. Alongside the benefits of closed-loop therapy, it is essential to set realistic goals to keep up with reasonable clinical expectations.

   e. Etc

The reviewer does not intend to minimize the importance of any of these points; however, virtually no one would argue that: a) we should not be support subjects
in home studies, b) short term inpatient pilot studies should not precede long-term home studies, c) the main goal of closed-loop therapy is to achieve good glycaemic control whilst reducing the risk of hypoglycaemia in people with type 1 diabetes, the main goal, or d) that unrealistic goals and expectations should be set. The reviewer would recommend removing anything for which there is already wide scale agreement and focusing the discussion on the more difficult questions on which there is not agreement. These could include questions as to what will the regulatory agencies require before allowing home studies (the FDA has guidance on this but this may differ in Europe), how good does the sensor need to be, what type of safety constraints need to be implemented, and others.

2. A number of studies of items are brought up for the first time rather late in the manuscript (sections analogous to discussion). The closed-loop studies by El-Kathib [ref 51], the use of amylin [52], faster acting insulin [53,54], and intraperitoneal insulin [55, 56].

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

The reviewer is a former employee of Medtronic Diabetes. The reviewer no longer has any financial interest in Medtronic but has patents that are assigned to the company that cover the PID controller reference in this manuscript 23, 41, 43, and the simulation model used to develop the controller. The reviewer has also received funds (MicroChips, BD) and device support (Abbott, Animus, HemoCue) from companies working in this field.