We greatly appreciate the comments provided below and believe the suggestions and issues that were raised have made our manuscript stronger. Below, please find our responses to each item raised.

K. Dovc

Comments- ISPAD Guidelines - Diabetes Technologies Chapter
Dear Authors.

I enjoyed reading the informative chapter on Diabetes Technology.

You have covered such a broad area, as this is one of the fastest developing field. Congratulations for this important work!

I offer the following comments for your consideration:

Page 1, line 6: “Insulin pump therapy can assist with reducing episodes of hypoglycemia (B)”

It would be important to unify labeling (Insulin pump or CSII) throughout the text.

Thank you for this comment. For simplicity, we have used the term insulin pump throughout the document.

Page 1, line 7: “CSII reduces chronic complications of T1D in youth, despite similar hemoglobin A1C (HbA1c) achieved in those on multiple daily injection (MDI) therapy (B)”.

In line with the first bullet point in executive summary, CSII has proven to be more effective, when compared to MDI. Maybe a better expression would be: CSII reduces chronic complications of T1D in youth, even when similar hemoglobin A1C (HbA1c) achieved in those on multiple daily injection (MDI) therapy

Thank you for this suggestion, it does clarify the intent of the sentence and we have altered the text accordingly.

Page 1, line 21: Use of flash glucose monitoring in the pediatric population is safe (also page 10, line 7).

Suggest unifying labeling – as intermittently scanned CGM (isCGM) was suggested in a recent consensus, maybe it a good option (especially because flash glucose monitoring abbreviation (FGM) should be avoided. In the literature also FCGM or FGS are commonly used.

Thank you for this. We have updated the text to use this abbreviation as it more formerly captures the capabilities of this technology.

Page 1, line 22-28:
It would be important to incorporate also time in range in executive summary, as it was suggested as a primary endpoint in a recent consensus and is so well covered in the chapter CGM, page 11 and 12.

A bullet point has been added to the executive summary to highlight the recent guidelines and focus on TIR.

Page 20, line 9:

It would be important to add also a comment on hyperglycemic as few studies reported increased rate of hyperglycemia with PLGs system use.

In the present manuscript, data is provided that following use of the PLGS hyperglycemia can be seen.

Page 23, line 1:

It would be important to mention also CL use with physical activity, as this is one of the major challenges.

A paragraph on physical activity and CL use has been added, which highlights some of the techniques applied to mitigate hypoglycemia during exercise.

Page 26, line 3“**No automated decision support systems are currently available outside of a research setting.**

In the executive summary statement (page 2, line 13) you mentioned, that there is one (The first system for automated dosing adjustment without health-care provider approval has just received regulatory approval), so the text should be amended accordingly. To my knowledge, as least one system is for the HCPs to use.

A sentence regarding the DreaMed Advisor Pro has been added as well as some information on the Sugar.IQ app. Thank you.

Best wishes

Klemen

K. Donaghue
Technical and stylistic suggestions

Thank you for a very broad ranging chapter that examines the evidence (303 references) as well as providing excellent Tables for commencement of Pumps and Sensors. The balance between enough evidence and too much detail is generally well done, but the section on "Sensor augmented pumps" provides far more detail than the other section, and perhaps too much detail of the Device company.

Thank you the section on sensor augmented pump therapy has been edited to remove extraneous details in hopes of closer aligning this topic with others in this section.

The section on bolus calculators could be expanded to include the Paediatric/adolescent publication from the ABACUS trial. Achievement of level "A" evidence needs more detail in the text for this and probably the age group data only deserves a level B.

The ABACUS trial is reference 270. Additionally, we changed to a B level recommendation as per the comments above.

1. Suggest the Bolus calculators section could be cross-referenced to the Nutrition chapter)

   To make each chapter a stand-alone document we will include this section here as well as it is an important component of diabetes technology.

2. Pump is strong: how to access “Diabetes Forecast” for “online reference”, suggest add web address (page 8).
   Thank you this has been added.

3. Reference to ISPAD Guideline recommendations 2017 on preschoolers could be tightened: ISPAD Guideline RECOMMEND rather than current " have been issued and ...states pump therapy is the preferred model...
   Thank you the wording has been updated.

4. CGM starts with SMBG, there could be a better introduction, compare interstitial with capillary glucose variables, Introduction on Page 11 including History may be a better start

   Thank you. Some details on SMBG history have been added to the manuscript.

5. Page 11 long sentence “higher use in younger children .... (could be 2 sentences)
   Thank you this has been changed to 2 sentences.
6. Page 8 long sentence “As the major concern is occlusion..... glargine (small amount of basal insulin

Thank you this has been done.

7. CGM use and parental satisfaction, sustained use... page 12

Thank you this has been updated.

8. Unclear how the evidence is Level A from the discussion of CGM

The statement in the executive summary regarding benefit of CGM and impact on mild hypoglycemia and shortening time spent in hypo has been altered to level B.

9. Perhaps too much detail for SAP section 5 compared to CGM

Thank you the section on sensor augmented pump therapy has been edited to remove extraneous details in hopes of closer aligning this topic with others in this section.

10. Page 19 Minimed 640G and 670G plus SmartGuard Technology, very technical

This section has been simplified in the final draft.

11. Recommend reducing the use of acronyms e.g. Telemedicine Acronyms "TREAT"

In the Telemedicine section, some acronyms have been removed.

12. Telemedicine: I recommend omitting references to studies in the Discourage references to the Elderly, the US Army, this section could be shorter Meta-analysis

Given the increasing use of telemedicine in diabetes we have retained, but revised this section.

F. Cameron

Wow what a magnum opus!

Well done on such a comprehensive review. May I suggest though that greater emphasis is given to a more clinically nuanced discussion. Technology is often a great help but not always-this was covered very nicely in Carlo Acerini’s paper ‘The rise of technology in diabetes care. Not all that is new is necessarily better’ (Pediatr Diabetes 2016; 17:168-73).

In particular I would like to highlight the following points
• The process whereby non-adjuvant use of CGM was approved by the FDA was critiqued by Alan Shapiro last year in JAMA (JAMA 2017; September 24). Given the apparent FDA reliance on testimonial evidence (rather than clinical trial evidence), I think we should still be sceptical.

• The oft-cited MARD figures for CGM are those reported under ‘ideal-conditions’ (ie in a normoglycaemic range and non-ambulant). MARD values in a real-world context (ambulant with swinging BG levels) may increase to as high as 30% (Kovatchev et al Diabetes Care 2008; 31:1160-4; Freckmann et al J Diabet Sci Technol 2013; 7:842-53; Andelin et al J Diabet Sci Technol 2016; Bonora et al J Endocrinol Invest 2016)

Thank you for this suggestion. To contextualize the MARD obtained by the CGM devices, we included reference to the recent paper assessing MARD in 17 POC

Please note that the articles suggested above represent assessment of MARD
   1. Kovatchev et al Diabetes Care 2008; 31:1160-4- Medtronic Guardian, Freestyle Navigator, Dexcom STS, and Glucoday

As we have indicated in the introduction to this section, “When interpreting historic data on CGM use, it is critical to take the results in context of the older technology utilized, especially when considering the pediatric age group. Recent advances in these systems have led to improved system performance, accuracy, and user experience; thus, limiting extrapolation of studies conducted with first generation technologies.” Thus, these references were purposefully not included given the systems used.

• One could be forgiven after reading these guidelines that the only complication associated with CSII and CGM were pretty minimal. There is quite a body of literature noting a litany of fairly significant adverse events associated with CSII:
  Wheeler et al Diabet Technol Therap 2014 16:204-7- 45% rate of pump adverse events with 8% rate of hospital attendance- cited in the guidelines but no mention of hospital attendance
  Guenego et al Diabet Technol Therap 2016 18:820-4- 68% pump malfunction rate
  Cope et al, J Diabetes Sci Technol 2012; 6: 1053-9- MAUDE data showing 43% rate of hospitalization in kids when pumps fail (ie not a trivial issue)
  Hommel et al Acta Diabetol 2014; 51:845-51- SWITCH study 44-50% rate of adverse events whilst on CSII. Roughly 1 in 20 hospitalised
  Hanas et al, Pediatr Diabetes 2009; 10:33-7 – risk of DKA doubled amongst pump users
  Brorrson et al, Pediatr Diabetes 2015; 16:546-53- risk of DKA increased 5.6 fold if using CSII
Cox et al Diabetes Care 2009; 32:2177-80 – drivers using CSII 35% more likely to experience a hypoglycaemia-related driving mishap

By no means did we mean to imply that the complications associated with CSII and CGM were minimal. Indeed, the section entitled “complications of pump therapy: infusion sets and hypertrophy” attempted to cover some of this topic. Based on the suggested manuscript above, we have edited the text to cover with more fine detail the risk of pump therapy.

With the MAUDE data detailed by Cope et al, it is critical to note that the vast majority of pump failures are likely not reported to the FDA. As per the limitations section of that article, device manufacturers made most of the reports. It is likely that issues with infusion set failures or issues that could be resolved at home may be under reported in such a database. Therefore, one should likely be cautious in over-interpreting the data on rates of hospitalizations as reporting is likely biased to cases where patients were more likely to be hospitalized.

When it comes to CGM, Alan Shapiro noted that in the US. “As of October 1, 2016, more than 25 000 medical device reports indicating large inaccuracies with blood glucose levels measured with the CGM device had been filed with the FDA since the start of 2015… By June 30, 2017, the number of reports of inaccuracy had increased to more than 40 000. ….there have been detailed reports of unexplained inaccurate readings associated with loss of consciousness, seizures, car crashes, hospitalizations, intensive care unit stays, and deaths.”

These are not trivial issues methinks

Fergus Cameron

C. Acerini

Thanks for the opportunity to comment on this important new chapter to the ISPAD guidelines ‘stable’

I note the previous comments / suggestions already posted on this chapter.

I’d like to highlight the following for consideration / clarification:

1. Conflict of interest statement
This is always a rather tricky / sensitive issue - but one that is nevertheless very relevant to this this chapter given its subject matter. I believe that all of the authors listed are significantly involved in either supporting or leading diabetes technology research programmes. The authors may therefore be perceived as having a ‘vested interest’ and therefore potentially ‘conflicted’.

I suggest that for the sake of transparency and openness that a conflict of interest statement for each contributing author should be included at the beginning of this chapter. This should
clarify the grant funding / support received for their research in this area - from both charitable and industry sources. Also the usual relationships with industry partners should be clarified (honoraria; lectures etc...), including whether they hold shares in any of these companies; hold intellectual property (IP) rights or patents in the area of diabetes technologies.

In an attempt to post the new chapter as quickly as possible this was errantly left out. This has been added for each author as we concur transparency is important.

2. Executive summary.
   a. “CSII reduces chronic complications of T1D in youth, despite similar hemoglobin A1C (HbA1c) achieved in those on multiple daily injection (MDI) therapy (B)”

   As far I can ascertain, this statement is based on observations made by one study. I am therefore not convinced that this merits inclusion in the executive summary, certainly not as currently written.

   Whilst the evidence rating assigned to this statement - B - may be correct, it is only based on the results from a single study. The statement should be either removed or, at least, rephrased. If the latter I suggest - “CSII has been shown in one study to be associated with a reduction in chronic complications of T1D in youth, despite similar hemoglobin A1C (HbA1c) achieved in those on multiple daily injection (MDI) therapy (B)”

   Thank you. We agree that the statement that this level B evidence is correct. We have reworded the statement as per another reviewer’s comments.

   b. “Sensor augmented pump (SAP) therapy is superior in children and adolescents over MDI with self-monitoring of blood glucose (SMBG) in reduction of HbA1c without an increase in hypoglycemia or severe hypoglycemia (A)” -

   This statement seems a bit overstated given the body of evidence presented (mainly extrapolated from the STAR3 trial), the fact that SAP ‘success’ is heavily dependent on the amount of sensor usage, and that it is not supported so far by ‘real world’ observations. Suggest rephrase / moderate - appropriately

   A line has been added to clarify that sensor adherence is required, likely with a minimum threshold of 60% use to achieve the benefits noted.

3. Section 3 - Page 4 & 5
   a. “Furthermore, data from meta-analyses conducted by various groups have depicted similar findings with pump therapy”.

   I am not sure this is entirely true /correct. The authors appears to have overlooked other - perhaps more robust / rigorous - meta-analyses undertaken to those cited that have different conclusions. For example Yeh , et al. Ann Intern Med. 2012;157(5):336-47
Data on the Yeh paper has been added for balance. Thank you for calling this to our attention.

b. The discussion regarding the pooled analyses from the DPV / T1DX and NPDA paper (Sherr et al, Diabetologia 2016) - should address / acknowledge the limitations of this study - i.e. its cross-sectional nature, etc... HbA1c values in the NPDA cohort were significantly higher than those observed in the DPV / T1Dx cohorts. Differences between CSII and MDI in the better controlled DPV and T1DX cohorts were small and perhaps of debatable ‘clinical’ significance?

Acknowledgement that this paper used cross-sectional data for the pooled analysis has been added.

While it may be difficult to glean from the graphs in the paper cited, the following table provides the raw data on differences between pump vs. injection users in each cohort:

<table>
<thead>
<tr>
<th></th>
<th>Pump</th>
<th>Injection</th>
<th>Difference between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPV</td>
<td>7.9±0.3</td>
<td>8.1±0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>T1DX</td>
<td>8.1±0.3</td>
<td>8.5±0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>NPDA</td>
<td>8.5±0.3</td>
<td>9.0±0.4</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Thus, while the DPV had a smaller difference, the 0.4 and 0.5 differences are likely clinically significant, especially as reductions in A1c are more difficult to achieve the closer to targeted control one gets.

d. Discussion / mention regarding the DPV “database analysis of almost 10,000 participants” (Karges et al, JAMA 2017) merits further explanation and clarification. Why are the key data from this study not shown / highlighted here - particularly regarding HbA1c? Whilst the differences in HbA1c between CSII vs MDI in this analysis may have been statistically significant (p= <0.001) their clinical significance (8.04% vs 8.22%; difference = - 0.18%) is debatable, and are unlikely to be of any significant benefit over the long-term in terms of chronic complications reductions or from a health economic perspective.

Thank you for this comment. Additional information regarding A1c levels and rates of the events of DKA and SH has been added to the manuscript. Additionally, we highlighted that the difference in A1c may be of limited clinical significance.

Thus the statement “Thus, the benefits of pump use have now been echoed in various registry assessments.” therefore seems, again, rather overstated and presumptive.
Although registry data reflects real world experience, it may include bias. We respectfully feel that the registry data does demonstrate the benefits of pump therapy.

General comments

I wonder if the following topics / themes need specific inclusion, or in some areas, more in depth consideration and clarification:

a. Statistically significant vs clinical significant observations. Some statistically significant results may not necessarily be of clinical significance and should accordingly be interpreted with this in mind.

While it is important to delineate the difference between statistically vs. clinically significant, in these guidelines our goal was to summarize the literature. Thus, we have strived to provide justification for our recommendations while not including the same level of detail that may be seen in a review article. By accessing the primary literature cited, readers can make their own determinations on clinical vs. statistical significance.

b. Health-economic considerations / implications. This topic is not really mentioned. What are the future challenges we face regarding the costs of diabetes technology. Does the current evidence base justify the drive to make the use of diabetes technologies the new ‘standard of care’ from a health economic perspective?

While the topic of health economics is an important area and one of great interest, we believe for this first consensus guidelines it may be beyond what we are able to cover. To recognize the importance of this topic we have added a sentence to the conclusion and hope to expand this in future iterations of the manuscript.

c. Access to technology - I wonder if more explicit, practical, recommendations should be made regarding who should be strongly considered / prioritised for access to diabetes technologies? This is particularly relevant given that in many health care systems access to technologies may be significantly restricted or rationed through limited funding. For example:

1. What specific clinical situations / scenarios should diabetes technologies be strongly considered / recommended or prioritised?
   ‘Table 1 - partially addresses this issue - but only for CSII and not for CGM / SAP. Also the indications highlighted on Table 1 are very broad / vague to say the least, and are based on recommendations made in 2007. Given the evidence base has moved on since then - could these recommendations be better defined or refined and made more specific?

As the authors believe pump therapy is suitable to almost any youth living with T1D, we have kept the indications for pump therapy as noted in table 1. Importantly, the areas included in the pump section entitled “barriers to adoption of pump therapy and predictors of success” and “frequency and causes of discontinuation of pump therapy” highlight which patients may be
more successful with the transition. Indeed, we highlight that those with “suboptimal control and/or exhibiting alterations in psychological well-being” would warrant additional support and education during the transition as they may be at higher risk for discontinuation.

2. Identifying the ‘type’ of patients / families - who are likely to represent a “good fit for the device”.

Are there any specific factors / characteristics - psychological; behavioural, social etc… - that would support or preclude consideration for using a specific diabetes technology? What factors are likely to determine success / failure? Can these be listed? Are there any ‘tools’ / resources that could help ‘screen’ to identify patients / families who may (or may not) do well with technology.

For pump therapy, we have highlighted some of this information based on published data in the sections entitled “barriers to adoption of pump therapy and predictors of success” and “frequency and causes of discontinuation of pump therapy.” Indeed, we highlight that those with “suboptimal control and/or exhibiting alterations in psychological well-being” would warrant additional support and education during the transition as they may be at higher risk for discontinuation.

3. There is an appropriate focus on “barriers to [technology] uptake” and recommendations to “conduct a brief assessment of barriers” and to “problem-solve”, yet no practical advice is provided as to how this should be done, other than perhaps to refer to a psychologist. However - not all (many) health care systems will have ready access to a clinical psychologist or to psychological services.

To our knowledge, no evidence exists on an approach to utilize in such situations; however, interventions to reduce barriers to technology use are actively being investigated (Tanenbaum ML, Hanes SJ, Miller KM, Naranjo D, Bensen R, Hood K. Diabetes Device Use in Adults With Type 1 Diabetes: Barriers to Uptake and Potential Intervention Targets. Diabetes Care 2017; 40: 181-187). Importantly, this data was collected in adult participants, highlighting the need to further these findings in the pediatric population.