Role of Continuous Glucose Monitoring (CGM) in Clinical Trials: Recommendations on Reporting

Short running title: CGM in Trials: reporting recommendations

Oliver Schnell,[1] Katharine Barnard,[2] Richard Bergenstal,[3] Emanuele Bosi,[4] Satish Garg,[5] Bruno Guerci,[6] Thomas Haak,[7] Irl B. Hirsch,[8] Linong Ji,[9] Shashank R. Joshi,[10] Maarten Kamp,[11] Lori Laffel,[12] Chantal Mathieu,[13] William H. Polonsky,[14] Frank Snoek,[15] and Philip Home,[16]

[1]Forschergruppe Diabetes e.V., Munich, Germany

[2]Bournemouth University, Bournemouth, U.K.

[3]International Diabetes Center at Park Nicollet, Minneapolis, MN

[4]Vita-Salute San Raffaele University, Milan, Italy

[5]Barbara Davis Center for Diabetes, University of Colorado at Denver, Denver, CO

[6]Centre Hospitalier Universitaire Nancy, Vandoeuvre-Les-Nancy, France

[7]Diabetes Center Mergentheim, Bad Mergentheim, Germany

[8]University of Washington School of Medicine, Seattle, WA

[9]Department of Endocrinology and Metabolism, Peking University People's Hospital, Peking, China

[10]Indian Academy of Diabetes, Ahmedabad, India

[11]Queensland University of Technology, Brisbane, Australia

[12]Joslin Diabetes Center, Boston, MA

[13]University Hospital Gasthuisberg Leuven, Leuven, Belgium

[14]Behavioral Diabetes Institute, University of California, San Diego, San Diego, CA

[15]Department of Medical Psychology, VU University Medical Center and Academic Medical Center, Amsterdam, the Netherlands

[16]Institute of Cellular Medicine–Diabetes, Newcastle University, Newcastle upon Tyne, U.K.

Corresponding author: Philip Home, philip.home@ncl.ac.uk

Word count: 3680 **Number figures/tables:** 3 tables, 0 figures

Abbreviations: AUC, area under the curve; CGM, continuous glucose monitoring; CV, coefficient of variation; MAGE, mean amplitude of glucose excursion; MARD, mean absolute relative difference; MODD, mean of daily difference; SD, standard deviation; SMPG, self-monitored plasma glucose

Abstract

Thanks to significant improvements in the precision, accuracy, and usability of continuous glucose monitoring (CGM), its relevance in both ambulatory diabetes care and clinical research is increasing. Here we address the latter perspective and derive provisional reporting recommendations. CGM systems have been available since around the year 2000, and used primarily used in people with type 1 diabetes. In contrast to self-measured glucose, CGM can provide continuous real-time measurement of glucose levels, alerts for hypoglycemia and hyperglycemia, and a detailed assessment of glycemic variability. Through a broad spectrum of derived glucose data, CGM should be a useful tool for clinical evaluation of new glucose-lowering medications and strategies. It is the only technology that can measure hyperglycemic and hypoglycemic exposure in ambulatory care, or provide data for comprehensive assessment of glucose variability. Other advantages of current CGM systems include the opportunity for improved self-management of glycemic control, with particular relevance to those at higher risk of or from hypoglycemia. We therefore summarize the current status and limitations of CGM from the perspective of clinical trials, and derive suggested recommendations for how these should facilitate optimal CGM use and reporting of data in clinical research.

[193 words]

Current status of CGM

Technical development

Since CGM was first introduced, the underlying technology has undergone a multi-level improvement, to the extent that it now has significant potential not only for routine ambulatory diabetes management, but also for clinical research. In contrast with early CGM systems (1), overall accuracy of current devices stands around ±10%, reflecting almost a two-fold improvement. Furthermore, accuracy, precision, and specificity continue to improve (2-6), with particular emphasis on the hypoglycemic range. Additionally, the achievement of mean absolute relative difference (MARD) values less than ±10% has made modern CGM a useful basis for insulin dose titration and adjustment (7,8), provided the sensors are deployed for longer periods of time (9). Other continuing technological advances relate to user-friendly software, interface and displays, and to better data management/analysis software, extending to automatic CGM real-time data transfer via internet and smartphones (10).

Continuing technical issues include the need for periodic recalibration (generally every 12 hours), usually by using SMPG measurements (Table 1). Factory calibration would eliminate an important source of human error or omission, and simplify use and clinical trial reporting. For it to be possible, *in vivo* sensitivity differences in sensors as well as sensitivity degradation of the sensor over time (bio-fouling) need to be minimized. As yet, factory calibration is a reality only for the "flash" glucose monitoring system (not US FDA approved) (2), and does not appear to be a priority for many developers, who are more focused on improving accuracy (11). Implantable CGM sensors have the advantage of no repeated sensor replacement in the shorter term (up to 3 months of duration for available sensors and increasing duration under development), mitigating errors arising from sensor insertion (12). However, implantation involves some discomfort and inconvenience and requires a higher level of medical intervention (13,14).

CGM measurement parameters for assessment of glycemic status

Studies on the use of CGM in clinical settings have often been aimed at determining the accuracy, precision, and reliability of the system (see next section). It has however also been judged mature enough to be used as a tool for assessment of glycemic variation when using different glucose-lowering interventions in people with type 1 or type 2 diabetes (15-19). As the devices provide repeated glucose estimates at very short intervals, a wide variety of derived glycemic status parameters can and have been used for reporting purposes. Despite recommendations for standardization of endpoints, no consistency has been reached, limiting comparability between CGM systems (20, 21). Thus, some studies use historical parameters such as the mean amplitude of glucose excursion (MAGE), standard deviation or coefficient of variation about mean plasma glucose level, or the mean of daily difference (MODD) (22). Meanwhile, others use mean glucose level, low/high blood glucose indices, the percentage of time over/under a certain glucose level, the

area under the glucose-time curve (AUC) at certain time points of defined glucose levels, the mean subsequent sensor glucose nadir, the median time to postprandial peak glucose levels, or the number of excursions above and below some level (15-19, 23-25) (Table 2). This variability of reporting variables presently makes comparisons of CGM results between studies difficult, thus limiting generalizability, and preventing comparisons among trials, including formal meta-analysis and network analysis.

Blood glucose control in diabetes is conventionally measured on the basis of risk of hyperglycemia (risk of vascular damage), risk of hypoglycemia, and associated risk of lifestyle disruption from glucose variability. This suggests that CGM outputs should primarily be directed to measures of hyperglycemic and hypoglycemic exposure, as would be, for instance, the area of the curve above/below some glucose threshold. A particular issue with such a measurement is that arithmetic averaging does not weight greater excursions more strongly than more minor excursions.

A small study comparing basal insulins in people with type 1 diabetes provides useful illustration of some of the data that can be generated to inform clinical research assessments, but also some limitations (22). It includes expected measurements such as times and areas above/below certain blood glucose cut-offs for hyper- and hypo-glycemia, as well as the glucose profiles through the day. Daily profiling of glucose variance was useful in illustrating the pharmacokinetic/pharmacodynamics effect of the different basal insulins studied – indeed this is true clinical pharmacodynamics, since the intent of injected insulin is to control diurnal glucose profile. However, using a diurnal profile, rather than the pre- and post-prandial approach usual for SMPG, means that prandial glucose excursions are smoothed out because of people eating meals at different times. So while the hyperglycemic excursion measurement provides useful data, its visual display is problematic, except where meal times are standardized, something that is unrealistic in ambulatory care.

The article however does provide detailed and useful variability analysis (22). Any glucose data point can be influenced by daily time differences, interpersonal variability, day-to-day variance (or even weeks and years), as by other factors like erratic insulin absorption and lifestyle. However, for CGM the individual, the time unit (day), and the time of day are known, and thus Bergenstal and colleagues could estimate not only overall variability but also day-to-day variance, inter-personal differences, intra-day variability, each independently of the others, as well as the residual variation. This parameter could be estimated for any time of the day just as for SMPG (e.g. pre-breakfast, pre-injection, 03:00 h), but CGM allows extending the time period of interest (e.g. night time). However, since in ambulatory care time standardization of daily events is difficult to achieve, longer periods of data recording may need to be restricted, for example nocturnal hypoglycemia from 24:00-06:00 h, to avoid contamination from late and early meals and injections.

Clinical evidence of CGM-associated benefits

Prerequisites for optimal implementation of CGM as used in the studies below include adequate patient education, training, and support in regard of sensor insertion, calibration, and real-time data interpretation (26). Adequate patient education also implies proper training of medical staff (Table 1).

Advantage of CGM over conventional self-monitoring has been reported by a number of clinical trials for improved HbA1c levels, decreased time in hypo-/hyper-glycemic ranges, and reduction of hypoglycemic events in people with type 1 diabetes (26-35). CGM has been shown to improve HbA1c levels both in poorly controlled people (26) and in those with 'good' baseline HbA1c levels (27-29). The analysis of frequency of hypoglycemic events with CGM has shown no increase in hypoglycemia in any trial examining change in HbA1c levels (23, 29-33). Moreover, two other trials studying the time spent in the low glucose range reported a decrease of time in this range in the CGM group in comparison with self-monitoring alone, despite one study finding no significant difference in hypoglycemic event rate (27,28).

An important factor influencing positive effects on HbA1c levels or time/frequency of hypoglycemia is duration of CGM use. Several studies have shown that only continuous and long-term use of CGM is advantageous for people with type 1 diabetes (23, 27-29).

Furthermore, some studies have shown psychosocial benefits und QoL improvements from CGM use in people with type 1 diabetes (34,35).

CGM in clinical trials of glucose-lowering agents

CGM would appear to have considerable potential in optimizing the performance of clinical trials. As noted above, a key aspect is that, since CGM has been shown to improve HbA1c and hypoglycemia in type 1 diabetes, best outcomes in clinical studies can only be assured by deploying it as a tool to inform insulin dose adjustment and indeed assist appropriate lifestyle adjustments. As CGM is increasingly employed in clinical practice, its similar use in clinical trials becomes necessary to ensure their generalizability.

More specifically, however, clinical trials depend on an optimal assessment of relevant outcomes, which for diabetes, in essence, are hyper- and hypo-glycemic excursions. To date, CGM would be the first and only tool that can follow these variables throughout the day (36). Further, and particularly in type 1 diabetes, glucose profiles differ markedly in the same individual between days (intra-individual variance), and while SMPG can provide a sense of this variation, CGM is the first and only approach that can truly measure it.

This is particularly true for studies in ambulatory care where glycemic variability (glycemic excursions of different kinds) or hypoglycemia reduction (time and extent in the hypoglycemic range) are under investigation. The analysis of data from six CGM studies on people with type 1

diabetes that included a reference blood glucose measurement concluded that CGM is a meaningful primary outcome measure for clinical trials in the appropriate settings (37). In that analysis, CGM-based outcomes had a high concordance with those based on classical reference methods. Even though this study found a certain degree of inaccuracy and underestimation of hypoglycemic/hyperglycemic extremes with CGM measurements, study design can compensate for these, either by augmenting patient number or by increasing study duration (37). Meanwhile, the wealth of information obtained on duration of such excursions cannot be obtained by other methods.

In the last decade, a number of clinical trials have made use of CGM as an outcome evaluation method. For example, a single-day study of 26 type 2 diabetes patients assessed postprandial excursions and glycemic variability with CGM to determine efficacy differences between mitiglinide and sitagliptin, alone or in combination (38). The 24-hour CGM data analysis showed that both mitiglinide and the combination treatment produced lower glycemic variability (24-h glucose variability reflected by MAGE, SD and CV (%); $p < 0.001$) as well as decreased postprandial glucose excursion (AUC, $p<0.001$) and a more statistically significant change from baseline in postprandial hyperglycemia than sitagliptin alone (combination $p=0.044$; mitiglinide $p<0.001$). Moreover, the CGM measured mean 24-h blood glucose level decreased more significantly in the combination group than in the sitagliptin group ($p=0.009$), even when the time spent in the ideal glucose range (70-140 mg/dl) was not significantly improved in any group. Clearly, the wealth of data provided by CGM allows a deeper characterization of glucose variability than achievable by other methodologies.

In short-term studies, CGM has been used to examine changes to postprandial glucose excursions. In a 72-h study (allowing the time of some meals to be standardized and recorded) as many as 260 people with type 2 diabetes used CGM in a study of GLP-1 receptor agonist action (39). The data showed significant effects on post-meal glucose increment as 0-4 h AUC, with confidence intervals suggestive of good statistical performance (95% CI vs degludec –21.1, –4.7 mg/dl; vs liraglutide –10.1, 6.7 mg/dl). Data was presented for all three main meals. Short-term (3-day) CGM has also been use to compare the meal glucose excursions of conventional oral agents (40).

CGM may, however, have even more utility in longer duration and more complex studies. As noted above, it has been used for comparison of measures of hyperglycemic and hypoglycemic excursions and aspects glucose variability, including graphical displays, in a study comparing a new basal insulin analogue to the established analogue in the treatment of people with type 1 diabetes (22). This study is a good example of one of the advantages but also a disadvantage of CGM: the breadth of data it provides, and the large number of derived parameters that can be calculated (22). Another study focused on hypoglycemia outcomes when the timing (or omission) of the last meal of the day is altered in people treated with basal insulin (41). The study took place

over three days, repeated three times (9 days total recording time), in 20 people with type 2 diabetes. CGM allowed the assessment of several aspects of hypoglycemia, and notably revealed that the principal effects of the meal timing changes were observed much later during sleep, 00.00 and 06.00 h, a finding that would have been difficult to replicate with other methodologies.

CGM was also used to characterize two therapeutic combinations in 63 newly diagnosed people with type 2 diabetes, which showed significant decreases from baseline values in derived plasma glucose parameters, differences between therapies, and in glucose fluctuations and hypoglycemia (42).

Studies have also been performed using CGM in special populations. One such was a small study (n=10) of a DPP-4 inhibitor in people having hemodialysis (43). Area under the glucose-time curve (AUC) and the fasting plasma glucose were assessed showing statistically significant changes (uncontrolled) on both dialysis and non-dialysis days.

A SGLT2-blocker study in people with type 1 diabetes used CGM to assess fasting plasma glucose (FPG), postprandial glucose excursion measured as AUC, the percentage of time over/under a certain level, and MAGE, among others (44). Statistically significant effects were shown for mean daily glucose level and time within the target glucose range, and time in gross hyperglycemia (>180 mg/dl) compared with placebo.

Benefits and concerns of CGM

Among the reasons why CGM could potentially be beneficial for clinical trials on glucose-lowering agents are its potential to reduce both duration of studies and number of participants, as suggested by some of the statistically significant results above (36). In ambulatory studies, CGM may come to replace SMPG profiles performed 7-9 times a day, with their problems as to timing and adherence (45, 46). Reasonably, much more data on hypoglycemic excursions should become available, both at night and during the day, though the statistical power of this data has yet to be tested. Moreover, with CGM much more detailed quantification of glycemic variability is possible, and with standardized meal times a more detailed description of postprandial glycemic excursions (47).

However, CGM does have limitations (Table 1). One such is the lack of regulatory acceptance of CGM data in the USA except for adjunctive purposes, albeit this is similar to the situation for SMPG. Appropriate use of the technology requires a high level of education in the practical handling of the equipment and data management, for both patients and study personnel (36). Managing patient expectations is important to ensure balancing the additional effort associated with potential intrusiveness, data overload and alarm fatigue with increased confidence over diabetes management, ability to respond quickly to blood glucose information and reduced anxiety associated with diabetes management (34). Calibration still represents a clear complication to data analysis/interpretation, and is dependent on another patient-performed technology (SMPG).

Calibration of CGM at manufacture should solve this problem in time. Data management tools are still in evolution, being constantly improved by the development of new software, as well techniques for data transmission and sharing (14). Issues of accuracy and precision do still arise with CGM, at least by comparison with SMPG, and this may be more problematic at the extremes of glucose excursions (MARDs of most devices are above 10% at the extremes), an issue more for safety considerations rather than efficacy outcomes. It is therefore important that performance of systems used in clinical trials should be properly documented and in the public domain.

To date, however, the greatest issue for CGM in clinical trials is that of end-point selection. The huge variability of reported outcomes limits comparability between trials and generalizability of study results (36).

Lastly, there are concerns over CGM-driven glycemic outcomes. With one exception, none of the studies mentioned above report on blinding/masking of participants to CGM results (42). Therefore, even when patients were often instructed to continue with their usual exercise and diet routine (38, 39, 42, 44), it cannot be completely discarded that glycemic improvement is not due to CGM informed decisions on self-management of diabetes. It is also possible that CGM naïve people would misinterpret the data to the detriment of their blood glucose control. For an accurate evaluation of the impact of glucose control agents on glycemic variation when using CGM, adequate patient education and blinding to the data are of great importance.

Recommendations

To be useful and valid in clinical trials use of CGM needs to be better standardized. To that end, we propose some suggestions on how CGM should be used in clinical studies, and how data should be reported (Table 3).

Study protocol, Methods section

To ensure high quality CGM data from clinical trials, the study protocol should detail different aspects of the estimation of plasma glucose through measurement of interstitial glucose levels:

- The CGM system used needs to be described in detail, including device and manufacturer, and version number
- Information on the setting and patient population: in-patient or out-patient setting, description of care team and program, whether a CGM education program is provided, characterization of participants and any specific indications for CGM; and whether CGM was used to modulate continuous subcutaneous insulin infusion (‘‘sensor-augmented pump’’), or as a component of a closed-loop system
- Whether CGM was used real-time or blind: if real-time, were study participants familiar with use of CGM data to modulate insulin doses and lifestyle changes, or newly instructed

- Quality and characteristics of education/training of study participants in performing and interpreting CGM (if real-time)
- Input of CGM outputs into any therapy dosing schedule or algorithm, both by the study participant and in telephone and clinic visits; which actions are to be taken in response to low (or high) CGM read-outs
- If relevant, details of any special meal or physical activity studies, type of time standardization and exclusion/handling parameters for data from subsequent time periods (e.g. overnight or for 24 hours) within longer-term CGM data
- Description of application of CGM: When was CGM initiated, and for how long performed
- Methods of calibration and the devices employed to that aim
- Definition of CGM adequate performance, namely protocol-determined criteria for data inclusion for analysis; for example, data might have to be 70 % complete in any time period analyzed over the projected duration of CGM use
- The statistical tools used in preparing CGM data for reporting in the Results section (see below): this might include any averaging technique, cut-offs used to assess high and low glucose excursions, definitions of hypoglycemia, analyses of glucose variation and the terminology used to describe its different parameters, as well as methods of handling missing data
- The status of any outcomes from CGM (primary, secondary, descriptive, safety).

Results section: methodological and outcome measures

The following topics should be addressed in the Results section:

- Percentage of participants in each study arm having valid CGM data according to protocol-determined criteria, and thus used in further statistical analysis (see above)
- Analytical performance of CGM systems (correlation/deviation between CGM and SMPG values)
- Classical clinical trial outcomes not dependent on CGM, including HbA1c, pre-breakfast self-measured plasma glucose, hypoglycemia incidence and event rates according to severity and specific definitions, and adverse events
- CGM output should be reported as plasma glucose, since even though glucose levels are measured in interstitial fluid, the output of CGM is calibrated to plasma glucose; similarly to SMPG where plasma glucose is reported from a whole blood specimen
- Measures of glucose excursions: for standardization, we suggest the measurement of time and area above and below glucose thresholds, the latter being the best correlate of hyperglycemia and hypoglycemia exposure; we are not mandated to advise on appropriate cut-offs, but >140

mg/dl and <70 mg/dl approximately define the upper and lower limits of physiological glucose levels in healthy people; so for standardization purposes these should be reported even if other cut-offs are judged more relevant to study aims and are also included; hyperglycemic and hypoglycemic excursions have different clinical meaning and should be reported separately, even if also described as an aggregate 'outside the normal range'; other parameters such as mean of glucose excursions or number of dips into hypoglycemia may be considered at investigator (protocol-defined) discretion

- Hyperglycemia cut-offs other than 140 mg/dl have been described in the literature, notably 8.0 mmol/l and 180 mg/dl (21, 45). Especially these may be more useful in people with type 1 diabetes, so use of such cut-offs is additionally recommended, provided they are pre-defined and >140 mg/dl is also reported, and pending further discussion and consensus in the diabetes community
- Hypoglycemia cut-offs other than 70 mg/dl (3.9 mmol/l) have been used both for sensitivity analyses and for primary hypoglycemia reporting (46, 47); use of the alternative cut-off of 56 mg/dl (3.1 mmol/l) is therefore also recommended as an addition, pending further discussion; further cut-offs can be included if judged relevant to study aims, and according to study-protocol
- At present there is no standard for reporting hypoglycemia unawareness, where excursions to low glucose levels or different duration and extent are found on CGM without symptoms of hypoglycemia being reported; we suggest that pending such standards, the number of days or nights at least one such episode occurs is reported and analyzed
- Variability of glucose levels should only be employed for the precise analysis conducted; most useful are within-day, within-person daily variability (fluctuations across 24-hours, although sometimes a shorter part of the day may be analyzed), and within-person inter-day variability (erratic control) which can be reported for daily means or for particular time periods (e.g. nocturnal or pre-breakfast). Furthermore, we recommend avoiding use of the term 'variability of plasma glucose levels'.

Discussion/Conclusion section

An essential point in the discussion of a trial involving CGM use should be the potential impact of CGM on the study results, and hence their generalizability. Such areas might include lifestyle behaviors, dose and therapy changes, and hypoglycemia detection. This might include comparisons to previous research performed without CGM, or under different conditions of use. Furthermore, in line with recommendations for reporting of SMPG use in clinical research (45), patient compliance and overall impact of CGM use on trial outcomes should be discussed.

Conclusion

In the appropriate setting, CGM may be a very useful tool for providing relevant information on hyperglycemia, hypoglycemia and glucose variability in clinical trials of glucose-lowering agents. This is particularly true to studies performed in ambulatory care and for those answering research questions related to variability and hypoglycemia reduction, both for people with type 1 and 2 diabetes. However, the nature and extent of the data generated mean that the technology is presently ahead of our ability to establish which output parameters are relevant and most useful. In time, reduction of trial duration and participant numbers seem likely, offsetting some of the cost of the technology itself. We suggest that, pending broader and more formal consensus, the recommendations above should improve on the potential of CGM to advance our understandings of new and established therapies in quality clinical trials.

Guarantor statement

This paper contains no original data, and has therefore no data guarantor.

Contribution statement

The idea to write the paper originates solely from the authors. All authors contributed equally to conception, design and discussion of the manuscript. The first draft was prepared by the lead author. We thank Dr. Rosa Garcia-Verdugo and Dr. Michael Erbach of Sciarc GmbH for writing support (language, style, bibliographic review, referencing).

Duality of interest

The medical writing of the publication was supported by an unrestricted research grant from Roche Diagnostics Germany GmbH to Sciarc GmbH, a medical communication entity allied to the first author. None of the authors was compensated for writing the paper, or received any funding for any meeting or expense in connection with the paper.

OS, KB, RB, EB, SG, BG, TH, IH, LJ, SJ, MK, LL, CM WP, FS, PH: The authors or institutions with which they are associated all receive funding from manufacturers of glucose monitoring systems including Roche Diagnostics for their advisory, lecturing and/or research activities. The authors also take part as investigators in clinical trials together including all the major pharmaceutical manufacturers in diabetes.

KB has received unrestricted research funding from T1DX, DRWF, Diabetes UK, and Helmsley Charitable Trust for other work in this area.

References

1. Gross TM, Bode BW, Einhorn D, Kayne DM, Reed JH, White NH, et al. Performance evaluation of the MiniMed continuous glucose monitoring system during patient home use. Diabetes Technol Ther 2000;2:49-56
2. Bailey T, Bode BW, Christiansen MP, Klaff LJ, Alva S. The performance and usability of a factory-calibrated flash glucose monitoring system. Diabetes Technol Ther 2015;17:787-794
3. Damiano ER, McKeon K, El-Khatib FH, Zheng H, Nathan DM, Russell SJ. A comparative effectiveness analysis of three continuous glucose monitors: the Navigator, G4 Platinum, and Enlite. J Diabetes Sci Technol 2014;8:699-708
4. Laffel L. Improved accuracy of continuous glucose monitoring systems in pediatric patients with diabetes mellitus: results from two studies. Diabetes Technol Ther 2016;18(Suppl 2):23-33
5. Nakamura K, Balo A. The accuracy and efficacy of the Dexcom G4 Platinum continuous glucose monitoring system. J Diabetes Sci Technol 2015;9:1021-1026
6. Pleus S, Schoemaker M, Morgenstern K, Schmelzeisen-Redeker G, Haug C, Link M, et al. Rate-of-change dependence of the performance of two CGM systems during induced glucose swings. J Diabetes Sci Technol 2015;9:801-807
7. Kovatchev BP. Hypoglycemia reduction and accuracy of continuous glucose monitoring. Diabetes Technol Ther 2015;17:530-533
8. Kovatchev BP, Patek SD, Ortiz EA, Breton MD. Assessing sensor accuracy for non-adjunct use of continuous glucose monitoring. Diabetes Technol Ther 2015;17:177-186
9. Pickup JC, Freeman SC, Sutton AJ. Glycaemic control in type 1 diabetes during real time continuous glucose monitoring compared with self monitoring of blood glucose: meta-analysis of randomised controlled trials using individual patient data. BMJ 2011;343:d3805
10. Rodbard D. Continuous glucose monitoring: a review of successes, challenges, and opportunities. Diabetes Technol Ther 2016;18(Suppl 2):3-13
11. Hoss U, Budiman ES, Liu H, Christiansen MP. Feasibility of factory calibration for subcutaneous glucose sensors in subjects with diabetes. J Diabetes Sci Technol. 2014;8:89-94
12. Heinemann L, Freckmann G. CGM versus FGM; or, continuous glucose monitoring is not flash glucose monitoring. J Diabetes Sci Technol 2015;9:947-950
13. De Vries JH. Kropff J, Pratik C, et al. Accuracy and longevity of an implantable continuous glucose sensor in the Precise study: a prospective multi-center pivotal trial; 90 day interim results. (Abstract) Diabetes Tech Ther 2016:18(S1): A-1-A-140. doi:10.1089/dia.2016.2525
14. Whitehurst TK, Colvin AE, DeHennis AD, et al. Fluorescence-based implantable glucose sensor with smartphone interface. EASD Annual Meeting 2012. Available from: http://www.easdvirtualmeeting.org/resources/fluorescence-based-implantable-glucose-sensor-with-smartphone-interface--2 (Last accessed 11 November 2016)
15. Ando K, Nishimura R, Tsujino D, Seo C, Utsunomiya K. 24-hour glycemic variations in drug-naive patients with type 2 diabetes: a continuous glucose monitoring (CGM)-based study. PLoS One 2013;8:e71102
16. Derosa G, Franzetti I, Querci F, D'Angelo A, Maffioli P. Effect of acarbose on glycemic variability in patients with poorly controlled type 2 diabetes mellitus receiving stable background therapy: a placebo-controlled trial. Pharmacotherapy 2015;35:983-990
17. Kusunoki Y, Katsuno T, Nakae R, Watanabe K, Ochi F, Tokuda M, et al. Insulin resistance and beta-cell function influence postprandial blood glucose levels in Japanese patients with gestational diabetes mellitus. Gynecol Endocrinol 2015;31:929-933.
18. Nielsen JB, Abild CB, Pedersen AM, Pedersen SB, Richelsen B. Continuous glucose monitoring after gastric bypass to evaluate the glucose variability after a low-carbohydrate diet and to determine hypoglycemia. Obes Surg 2016;26:2111-2118
19. Zhou J, Li H, Ran X, Yang W, Li Q, Peng Y, et al. Reference values for continuous glucose monitoring in Chinese subjects. Diabetes Care 2009;32:1188-1193

20. Bergenstal RM, Ahmann AJ, Bailey T, Beck RW, Bissen J, Buckingham B, et al. Recommendations for standardizing glucose reporting and analysis to optimize clinical decision making in diabetes: the Ambulatory Glucose Profile (AGP). Diabetes Technol Ther 2013;15:198-211
21. Fonseca VA, Grunberger G, Anhalt H, Bailey TS, Blevins T, Garg SK, et al. Continuous glucose monitoring: a consensus conference of the American Association of Clinical Endocrinologists and American College of Endocrinology. Endocr Pract 2016;22:1008-1021.
22. Bergenstal RM, Rosenstock J, Bastyr EJ, 3rd, Prince MJ, Qu Y, Jacober SJ. Lower glucose variability and hypoglycemia measured by continuous glucose monitoring with novel long-acting insulin LY2605541 versus insulin glargine. Diabetes Care 2014;37:659-665
23. Deiss D, Bolinder J, Riveline JP, Battelino T, Bosi E, Tubiana-Rufi N, et al. Improved glycemic control in poorly controlled patients with type 1 diabetes using real-time continuous glucose monitoring. Diabetes Care 2006;29:2730-2732
24. Barone MT, Wey D, Schorr F, Franco DR, Carra MK, Lorenzi Filho G, et al. Sleep and glycemic control in type 1 diabetes. Arch Endocrinol Metab 2015;59:71-78.
25. Choudhary P, Olsen BS, Conget I, Welsh JB, Vorrink L, Shin JJ. Hypoglycemia prevention and user acceptance of an insulin pump system with predictive low glucose management. Diabetes Technol Ther 2016;18:288-291
26. American Diabetes Association. Standards of medical care in diabetes - 2016. Diabetes Care 2016;39 (Suppl. 1):1-112
27. Battelino T, Phillip M, Bratina N, Nimri R, Oskarsson P, Bolinder J. Effect of continuous glucose monitoring on hypoglycemia in type 1 diabetes. Diabetes Care 2011;34:795-800
28. Beck RW, Hirsch IB, Laffel L, Tamborlane WV, Bode BW, Buckingham B, et al. The effect of continuous glucose monitoring in well-controlled type 1 diabetes. Diabetes Care 2009;32:1378-1383
29. Tamborlane WV, Beck RW, Bode BW, Buckingham B, Chase HP, Clemons R, et al. Continuous glucose monitoring and intensive treatment of type 1 diabetes. N Engl J Med 2008;359:1464-1476
30. Hermanides J, Norgaard K, Bruttomesso D, Mathieu C, Frid A, Dayan CM, et al. Sensor-augmented pump therapy lowers HbA(1c) in suboptimally controlled Type 1 diabetes; a randomized controlled trial. Diabet Med 2011;28:1158-1167
31. Hirsch IB, Abelseth J, Bode BW, Fischer JS, Kaufman FR, Mastrototaro J, et al. Sensor-augmented insulin pump therapy: results of the first randomized treat-to-target study. Diabetes Technol Ther 2008;10:377-383
32. O'Connell MA, Donath S, O'Neal DN, Colman PG, Ambler GR, Jones TW, et al. Glycaemic impact of patient-led use of sensor-guided pump therapy in type 1 diabetes: a randomised controlled trial. Diabetologia 2009;52:1250-1257
33. Raccah D, Sulmont V, Reznik Y, Guerci B, Renard E, Hanaire H, et al. Incremental value of continuous glucose monitoring when starting pump therapy in patients with poorly controlled type 1 diabetes: the RealTrend study. Diabetes Care 2009;32:2245-2250
34. Kubiak T, Mann CG, Barnard KC, Heinemann L. Psychosocial aspects of continuous glucose monitoring: connecting to the patients' experience. J Diabetes Sci Technol 2016;10:859-863
35. Barnard K, Crabtree V, Adolfsson P, Davies M, Kerr D, Kraus A, et al. Impact of type 1 diabetes technology on family members/significant others of people with diabetes. J Diabetes Sci Technol 2016;10:824-830
36. Heinemann L. Continuous glucose monitoring and clinical trials. J Diabetes Sci Technol 2009;3:981-985.
37. Beck RW, Calhoun P, Kollman C. Use of continuous glucose monitoring as an outcome measure in clinical trials. Diabetes Technol Ther 2012;14:877-882
38. Baek JH, Jin SM, Kaku K, Jung JA, Kim JR, Ko JW, et al. Efficacy of mitiglinide and sitagliptin, alone or in combination, on postprandial excursion and glycemic variability assessed by continuous glucose monitoring: a post hoc analysis with single-day treatment. Expert Opin Pharmacother 2015;16:1127-1136
39. Holst JJ, Buse JB, Rodbard HW, Linjawi S, Woo VC, Boesgaard TW, et al. IDegLira improves both fasting and postprandial glucose control as demonstrated using continuous glucose monitoring and a standardized meal test. J Diabetes Sci Technol 2015;10:389-397

40. Wang JS, Lin SD, Lee WJ, Su SL, Lee IT, Tu ST, et al. Effects of acarbose versus glibenclamide on glycemic excursion and oxidative stress in type 2 diabetic patients inadequately controlled by metformin: a 24-week, randomized, open-label, parallel-group comparison. Clin Ther 2011;33:1932-1942
41. King AB, Clark D. Omitting late-night eating may cause hypoglycemia in "well controlled" basal insulin-treated type 2 diabetes. Endocr Pract 2015;21:280-285
42. Ma Z, Chen R, Liu Y, Yu P, Chen L. Effect of liraglutide vs. NPH in combination with metformin on blood glucose fluctuations assessed using continuous glucose monitoring in patients with newly diagnosed type 2 diabetes. Int J Clin Pharmacol Ther 2015;53:933-939
43. Wada N, Mori K, Nakagawa C, Sawa J, Kumeda Y, Shoji T, et al. Improved glycemic control with teneligliptin in patients with type 2 diabetes mellitus on hemodialysis: Evaluation by continuous glucose monitoring. J Diabetes Complications 2015;29:1310-1313
44. Sands AT, Zambrowicz BP, Rosenstock J, Lapuerta P, Bode BW, Garg SK, et al. Sotagliflozin, a dual SGLT1 and SGLT2 inhibitor, as adjunct therapy to insulin in type 1 diabetes. Diabetes Care 2015;38:1181-1188.
45. Schnell O, Barnard K, Bergenstal R, Bosi E, Garg S, Guerci B, et al. Clinical Utility of SMBG: recommendations on the use and reporting of SMBG in clinical research. Diabetes Care 2015;38:1627-1633
46. American Diabetes Association Workgroup on Hypoglycemia. Defining and reporting hypoglycemia in diabetes. Diabetes Care 2005;28:1245-1249
47. Hovorka R, Kumareswaran K, Harris J, Allen JM, Elleri D, Xing D, et al. Overnight closed loop insulin delivery (artificial pancreas) in adults with type 1 diabetes: crossover randomised controlled studies. BMJ 2011;342:d1855
48. Service FJ. Glucose variability. Diabetes 2013;62:1398-1404
49. Cameron FJ, Donath SM, Baghurst PA. Measuring glycaemic variation. Curr Diabetes Rev 2010;6:17-26

Table 1. Some limitations on the use of current CGM systems in clinical trials

Domain	***Limitations of CGM***
Technical	Need for regular recalibration by SMPG
	Lack of long-term stability
	Require user insertion – potential for error
	Not implantable
	Lower accuracy/precision at extremes of glycemia
	Evolving data communication systems
Necessary process	Extended period (continuous/long-term) of use
	Adequate professional (trial staff) training needed
	Adequate patient education, training, and support
	Management of patient expectations
	Limited available patient reported outcomes presently
	Blinding/masking of patients to CGM results
Reporting	Diverse reporting variables for glucose excursions
	Lack of agreement on thresholds
	Diverse glucose variability reporting parameters
	Lack of system comparability
	Averaging with time hides glycemic excursions
	Visual display of glycemic excursions
	Diverse statistical tools including data averaging

Table 2. Common metrics used in the analysis of CGM data

Term/metric	*Detail and caveats*
System performance	
Mean absolute relative difference (MARD)	Absolute deviation of CGM glucose measurement from a reference system. May be calculated for different ranges of plasma glucose (e.g. low);
Glucose control measures	
Mean blood (plasma) glucose (MBG, MPG); Total area under glucose concentration curve	Mean of data over a defined period. Concatenates hyperglycemic and hypoglycemic excursions (*cf* HbA1c). CGM, like self-measured glucose, is reported as plasma glucose, but the term 'blood' is often casually and incorrectly used
Glucose concentration curve area above a pre-defined threshold for a defined time period	Hyperglycemic deviation of glucose concentration multiplied by time; if the time base is the same as the time units, is the same as the average excursion; can be limited to a particular time of day, e.g. post-prandial; no weighting is given to more extreme levels
Glucose concentration curve area below a pre-defined threshold for a defined time period	Hypoglycemic deviation of glucose concentration multiplied by time; if the time base is the same as the time units, is equivalent to the average excursion; can be limited to a particular time of day, e.g. nocturnal; no weighting is given to more extreme levels;
Time above or below some pre-defined threshold	Usually given as percentage of some defined time period; takes no account at all of the magnitude of the excursion
Time within some pre-defined range	Usually given as percentage; choice of range open to manipulation to show good/poor results
Time to peak (nadir) and peak (trough) level	Conventional pharmacodynamic measures used in clinical laboratory challenge studies (e.g. meal challenges)
Number of excursions above or below some pre-defined level	A single excursion is time since crossing a threshold till return to that same threshold; fails to account for extended excursions
Low/high blood (plasma) glucose indices	Attempts to weight measurements for more extreme excursions; quantitative pathophysiological basis is uncertain
Glucose variability measures	
Standard deviation (SD) or coefficient of variation (CV) of blood (plasma) glucose (SDBG, SDPG, CVBG, CVPG)	SD from mean level, and CV as percentage of mean level; can be restricted to a time of day; independent of direction of glucose excursions
Within-day, within person glucose variability	A measure of mean changes usually over 24-hours, but can be restricted to other periods
Between day, within person glucose variability (erratic glucose control)	May use variability between the average for each day in one person, but can be restricted to other time intervals (e.g. nocturnal, pre-breakfast, pre-dosing);
Mean of the daily differences (MODD)	Similar to previous parameter
Mean amplitude of the glucose excursion (MAGE)	Direction-independent (absolute) deviation from the mean glucose level (or from some other level, baseline or pre-determined) ignoring levels within 1SD
Graphical displays	Combined display by time of glucose control (mean of time) and between person, between day variability (study SD) at all time points; likely to create certain average basal and post-meal values due to between and within person variation in times of eating, thus flattening glucose excursions

Other parameters have been proposed such as M-value, J-index, CONGA, ADRR, Lability/HYPO score, and GRADE, but have not been widely adopted. See references (48, 49)

Table 3. Summary of recommendations on reporting of CGM methods and results when used in clinical trials

Manuscript Section	Information domain	Example of detail
Introduction	Purpose of CGM in study	Secondary endpoints, hypoglycemia detail
Methods	Make and version of CGM technology	Manufacturer; read-out system
		Calibration methodology
		Criteria for successful use in the individual
	Setting of CGM utilization	In-patient or ambulatory care
		Education to participants and investigators
		Injection therapy and dose algorithms; meal-time dose calculator; open-loop pump; closed loop functions
		Real-time or blinded
	Classic glucose control data	Duration/timing of implementation Including HbA1c, pre-breakfast SMPG, hypoglycemia incidence and event rates, and status of these outcomes in results hierarchy
		Use of any averaging function
	Data analysis	Statistical outputs such as time in range and area above and below cut-offs; other outputs
		Parameters of glucose variability and how they are calculated
		Whether outputs are primary, secondary, or observational/safety
		Definitions and standards of hypoglycemia used
Results		Percent of participants with successful CGM implementation, duration of implementation
	Methodological	Deviation between CGM and SMPG calibration measurements
		Use of CGM in dose or therapy changes
	Classic glucose control outcomes	See Methods above
	CGM outcomes	Time in/out of range, and area/average glucose out of range high and low separately using default cut-offs of 140 mg/dl and 70 mg/dl
		Similar data using cut-offs of investigator choice appropriate to study question and technology under investigation
		CGM-based hypoglycemia data by time of day as appropriate to study, and to include glucose nadirs and presence or absence of symptoms during low excursions
		Within-patient, within-day glucose variability, and between day (average day) within-patient variability. Such other within-patient variability for defined time periods (e.g. night or pre-breakfast) as pre-determined and appropriate to study.
Discussion		Impact of CGM findings on study findings using conventional measures
		Generalizability of findings to people not using CGM (if real-time and dose/therapy adjustment utilized)
		Limitations of CGM: extent of usable data, calibration findings, extreme glucose excursions