DIABETES TECHNOLOGY & THERAPEUTICS
Volume 19, Number 7, 2017

DOI: 10.1089/dia.2017.0054

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REVIEW

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

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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. In this study, we address the latter perspective and derive provisional reporting recommendations. CGM systems have been available since around the year 2000 and used primarily 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.

Keywords: CGM, Recommendation, Clinical trials.

Introduction and Background

Technical development

Since continuous glucose monitoring (CGM) was first introduced, the underlying technology has undergone a multilevel improvement,[1] 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,[2] the overall accuracy of current devices stands around ±10%, reflecting almost a twofold improvement. Furthermore, accuracy, precision, and specificity continue to improve,[3–7] with particular emphasis on the hypoglycemic

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range. In addition, 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,[8,9] provided the sensors are deployed for longer periods of time[10] and there is good patient adherence (six or more days per week). 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 through Internet and smartphones.[1,11]

Continuing technical issues generally include the need for periodic recalibration (generally every 12 h), usually by using self-monitored plasma glucose (SMPG) measurements (Table 1). Factory calibration can 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 between individual sensors as well as sensitivity degradation of sensitivity of the sensor over time (biofouling) need to be minimized. As yet, factory calibration is a reality only for the ''flash'' glucose monitoring system (US FDA approved),[3,12,13] a system that also allows for masking results, a useful feature for clinical research. 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.[14] However, implantation involves some discomfort and inconvenience, and requires a higher level of medical intervention.[15,16]

Table 1. Some Limitations on the Use of Current Continuous Glucose Monitoring 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

CGM, continuous glucose monitoring; SMPG, self-monitored plasma glucose.

CGM-associated clinical benefits and optimal usage

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.[17] Adequate patient education also implies proper training of medical staff (Table 1).

The properties and roles of CGM have been reviewed by others.[1] Advantage of CGM over conventional self-monitoring has been reported by a number of clinical trials for improved HbA1c levels, decreased time in hypoglycemic /hyperglycemic ranges, and reduction of hypoglycemic events in people with type 1 diabetes.[1,17–25] CGM has been shown to improve HbA1c levels both in people with suboptimal control[19,26,27] and those with ''good'' baseline HbA1c levels.[25,28,29] The analysis of frequency of hypoglycemic events with CGM has shown no increase in hypoglycemia in any trial examining change in HbA1c levels.[17,23–25,28,29] 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.[20,21]

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.[17,20,21,23]

Furthermore, some studies have shown psychosocial benefits and quality of life improvements from CGM use in people with type 1 diabetes.[30,31]

CGM in Clinical Trials of Glucose-Lowering Agents

CGM would appear to have considerable potential in optimizing the performance of clinical trials.[1,32] Moreover, as CGM is increasingly employed in clinical practice, its similar use in clinical trials becomes necessary to ensure their generalizability. More specifically, however, diabetes clinical trials depend on an optimal assessment of relevant outcomes, in essence average glucose levels and hyperglycemic and hypoglycemic excursions. CGM is the only tool that can follow these variables throughout the day in ambulatory care.[33] HbA1c is the only other measure that can provide an integrated measure of glucose exposure over time, but suffers from the consequences of averaging hypoglycemia and hyperglycemia, and in only providing long-term data. In type 1 diabetes, glucose profiles differ markedly in the same individual between days (intraindividual variance), and while SMPG can provide a sense of this variation, CGM is the only approach that can truly measure it. Variance in glucose concentration can also occur over the day as a result of the pharmacodynamic properties of the intervention under test. Accordingly, a proper assessment of the pharmacodynamics of any new glucose-lowering medication would appear to require a series of measures, which only CGM can provide.

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.[34] 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, the study design can compensate for these, either by augmenting patient number or by increasing study duration.[34] 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.[35] The 24-h CGM data analysis showed that both mitiglinide and the combination treatment produced lower glycemic variability (24-h glucose variability reflected by mean amplitude of glucose excursion [MAGE], SD, and coefficient of variation [%]; $P < 0.001$) as well as decreased postprandial glucose excursion (area under the glucose-time curve [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. Another recent study on insulin administration dosages used CGM to assess endpoints such as time-in-range, or hypoglycemia.[36] Clearly, the wealth of data provided by CGM allows a deeper characterization of glucose variability than achievable by 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, in differences between therapies, and in glucose fluctuations and hypoglycemia.[37]

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.[38] The data showed significant effects on postmeal 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 were 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.[39]

CGM may, however, have even more utility in longer duration and more complex studies. Thus, 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 management of people with type 1 diabetes.[40] 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.[40] 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 3 days, repeated thrice (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.

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.[42] AUC and the fasting plasma glucose were assessed showing statistically significant changes (uncontrolled) on both dialysis and nondialysis days. More recently, a report from the JDRF Artificial Pancreas Project Consortium included among their consensus recommendations, the inclusion of CGM metrics as outcome measures aside from the glycemic ones in the development of closed-loop systems.[43]

However, CGM does have limitations (Table 1). One such is the lack of regulatory acceptance of CGM data in the United States, except for adjunctive purposes (just one device is approved for nonadjunctive purposes[44]), although this is similar to the situation for SMPG. Appropriate use of the technology requires a high level of education in the practical handling of equipment and data management, for both patients and study personnel.[33] 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.[31] 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.[16] Despite these permanent improvements, there are still issues with data transfer, leading on occasion to missing data and incomplete reports, while processing of sensor output before device output can vary even for subsequent models of the same device.[33] 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 endpoint selection. The huge variability of reported outcomes limits comparability between trials and generalizability of study results.[33] Finally, there are concerns over CGM-driven glycemic outcomes. With few exceptions, none of the studies above, and which do not specifically assess CGM function, report on blinding/masking of participants to CGM results.[37,45] This issue will be further discussed below.

CGM Measurement Parameters and Masking

Metrics

Studies on the use of CGM in clinical settings have often been aimed at determining the accuracy, precision, and reliability of the system. The technology has, however, also been judged mature enough to be used as a tool for the assessment of glycemic variation when using different glucose-lowering interventions in people with type 1 or type 2 diabetes.[46–52]

and continues to improve. 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.[50] Despite suggestions for standardization of endpoints, no consistency has been reached, limiting comparability between CGM systems and publications using them.[51,52] Thus, some studies use historical parameters such as the MAGE, standard deviation (SD) or coefficient of variation about mean plasma glucose level, or the mean of daily difference (MODD).[40] Meanwhile, others use mean glucose level, low/high blood glucose indices, the percentage of time over/under a certain glucose level, the time in target,[32,36] the 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[19,22,46–48,50] (Table 2). This variability of reporting parameters presently makes comparisons of CGM results between studies difficult, thus limiting generalizability and preventing comparisons among trials, including formal meta-analysis and network analysis. A consensus report in the assessment of closed-loop systems considers the basic parameters to be time spent in desired ranges as well as time in hypoglycemia and hyperglycemia, and measures of CGM glucose variability (notably SD) along with other safety measures such as incidence of severe hypoglycemia and diabetic ketoacidosis.[1]

Blood glucose control in diabetes is conventionally measured on the basis of risk of hyperglycemia (risk of vascular

Table 2. Common Metrics Used in the Analysis of Continuous Glucose Monitoring Data

Term/metric	*Detail and caveats*
System performance	
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 predefined 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, for example, postprandial; no weighting is given to more extreme levels
Glucose concentration curve area below a predefined 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, for example, 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 predefined range (time in range)	Usually given as percentage; choice of range open to manipulation to show good/poor results. Is to be reported both in time units and percentage of observed time.
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 predefined 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	
SD or 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 h, 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, prebreakfast, and predosing)
MODD	Similar to previous parameter
MAGE	Direction-independent (absolute) deviation from the mean glucose level (or from some other level, baseline or predetermined), 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 postmeal 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.[59,60]

CV, coefficient of variation; MAGE, mean amplitude of glucose excursion; MARD, mean absolute relative difference; MODD, mean of daily difference; SD, standard deviation.

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 thresholds. A particular issue with such a measurement is that arithmetic averaging does not weight greater excursions more strongly than more minor excursions.

This also touches on the issue of glucose variability, that is, types of deviation of glucose concentrations from mean levels over the chosen period of time. CGM, provided it is performed for a sufficient period of time, can address all of these metrics. Within a study population on a single test medication, the most familiar of these will be between-participant differences in mean individual glucose, akin to the SD of HbA1c. However, within individuals, a series of measures of variably is possible, and some of these will reflect important pharmacodynamic properties of the medication under test.[28,53] For example, comparative within-day variation (over 24 h, or a chosen shorter period) will give information on duration and profile of effectiveness. Between average day variation will give a measure of erratic plasma glucose control, and this can be limited to shorter periods, or even single time slots (e.g., prebreakfast) depending on what property of the medication being studies is under review. This last category of variation is also of importance to people with diabetes using insulin, being essentially a measure of the unpredictability of glucose control they experience.

Rodbard has noted that SD of glucose levels can be as useful a measure of glucose variability as the more complex and derived metrics.[53] SD (or the related coefficient of variation) can be applied to all the measures of variability discussed in the preceding paragraph. However, Rodbard himself also argued that assuming glucose does not follow a Gaussian distribution, the inter-quartile range and median would be more accurate characterizations of glucose distribution at any given time point.[54]

Masking

Use of CGM can be ''real time'' or masked, the latter provides data only for retrospective analysis. Both can provide the same glucose metrics, but with masked CGM, the results cannot bias patient and investigator use of the trial products, such as insulin dose adjustment, a particular problem as many studies of diabetes injectables are necessarily not blind. Both masked and unmasked CGM data can be used after study datalock according to a predetermined statistical analysis plan. However real-time CGM is now increasingly used in clinical practice, notably in the context of insulin dose adjustment, and to deny its availability, it then creates an unnecessarily artificial situation within the clinical trial, and for some individuals may be unethical. Furthermore, the quality of the information provided by CGM may allow for optimal therapy adjustments,[32] which might expose real pharmacological differences between medications, and even possibly increase statistical power.

Against that, while real-time CGM is increasingly used in clinical practice, its use is rejected by some patients on the grounds of cost, frustration over lack of accuracy, alarm and calibration fatigue, or issues of using a technology.[55] Furthermore, even when trial participants were instructed to continue with their usual exercise and diet routine,[35,37,38,41] it cannot be completely discarded that glycemic improvement is not due to CGM-informed decisions on self-management of diabetes, although for the most part, these should affect the test and control arms. It is also possible that CGM-naive people could misinterpret the data to the detriment of their blood glucose control.

Recommendations

To be useful and valid in clinical trials, the 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

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: inpatient or outpatient setting, description of care team and program, 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
- Given the importance of education programs, they should be an important part of all clinical trials using CGM. Thus, a comprehensive description on the program and the level of training of both patients and medical staff on CGM use and data interpretation is recommended. Ideally, an assessment of efficacy of the training, by capability in managing CGM, should be given.
- Whether CGM was used real time or masked: if real time, were study participants familiar with use of CGM data to modulate insulin doses and lifestyle changes, or newly instructed.
- If masked to the study participants, details of any access and assessment of CGM data by the study medical team before data-lock (frequency, variables considered, therapy adaptations in response to the data).
- 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 readouts.
- 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 h) within longer term CGM data
- Description of application of CGM: when was CGM initiated and for how long it was 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%

Table 3. Summary of Recommendations on Reporting of Continuous Glucose Monitoring Methods and Results When Used in Clinical Trials

Article 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	Inpatient 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
		Duration/timing of implementation
	Classic glucose control data	Including HbA1c, prebreakfast SMPG, hypoglycemia incidence and event rates, and status of these outcomes in results hierarchy
	Data analysis	Use of any averaging function
		Statistical outputs such as time in range and area above and below cutoffs; 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	Methodological	Percent of participants with successful CGM implementation, duration of implementation
		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 cutoffs of 140 and 70 mg/dL
		Similar data using cutoffs 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 prebreakfast) as predetermined 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

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: this might include any averaging technique, cutoffs 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, and descriptive, safety).

Results: 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 last bullet point, previous page).
- Analytical performance of CGM systems (correlation/deviation between CGM and SMPG values).
- Classical clinical trial outcomes not dependent on CGM, including HbA1c, prebreakfast self-measured plasma glucose, hypoglycemia incidence and event rates according to severity and specific definitions, and adverse events.
- CGM output should be reported as interstitial-derived plasma glucose, as glucose levels are measured in interstitial fluid, but the output calibrated to plasma glucose (similar 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 percentage of time) and area above and below glucose thresholds, the area being the best correlate of hyperglycemia and

hypoglycemia exposure; we are not mandated to advise on appropriate cutoffs, 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 cutoffs 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.

- As numbers of events are subject to distortion by fluctuations across a threshold when glucose levels are near a threshold, we suggest that an ''event'' should have a minimum duration of 15 min to be counted as such and events must be separated by at least 30 min. To avoid data being blighted by large numbers of ''events'' on a single day, reporting of numbers of days (and percentage) with at least one event would additionally be useful.
- Hyperglycemia cutoffs other than 140 mg/dL have been described in the literature, notably 8.0 mmol/L and 180 mg/dL.[52,56] Especially these may be more useful in people with type 1 diabetes; so, the use of such cutoffs is additionally recommended, provided they are predefined and >140 mg/dL is also reported, and pending further discussion and consensus in the diabetes community.
- Hypoglycemia cutoffs other than 70 mg/dL (3.9 mmol/L) have been used both for sensitivity analyses and for primary hypoglycemia reporting[57,58]; use of the alternative cutoff of 56 mg/dL (3.1 mmol/L) is therefore also recommended as an addition, pending further discussion; further cutoffs 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/percent 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-h, 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 prebreakfast). Furthermore, we recommend avoiding use of the term ''variability of plasma glucose levels.''

Discussion/conclusion

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, in particular, the effects or otherwise of masking. 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,[56] patient compliance and overall impact of CGM use on trial outcomes, including nonmasking effects, 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 seems likely, offsetting some 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.

Authors' Contribution

The idea to write the article originates solely from the authors. All authors contributed equally to conception, design, and discussion of the article. 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, and referencing). This article contains no original data, and therefore has no data guarantor.

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 article or received any funding for any meeting or expense in connection with the article. O.S., K.B., R.B., E.B., S.G., B.G., T.H., I.B.H., L.J., S.R.J., M.K., L.L., C.M., W.H.P., F.S., and P.H.: 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. K.B. has received unrestricted research funding from T1DX, DRWF, Diabetes UK, and Helmsley Charitable Trust for other work in this area.

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