Continuous glucose monitoring and metrics for clinical trials: an international consensus statement

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Randomised controlled trials and other prospective clinical studies for novel medical interventions in people with diabetes have traditionally reported HbA_{1c} as the measure of average blood glucose levels for the 3 months preceding the HbA_{1c} test date. The use of this measure highlights the long-established correlation between HbA_{1c} and relative risk of diabetes complications; the change in the measure, before and after the therapeutic intervention, is used by regulators for the approval of medications for diabetes. However, with the increasing use of continuous glucose monitoring (CGM) in clinical practice, prospective clinical studies are also increasingly using CGM devices to collect data and evaluate glucose profiles among study participants, complementing HbA_{1c} findings, and further assess the effects of therapeutic interventions on HbA_{1c}. Data is collected by CGM devices at 1–5 min intervals, which obtains data on glycaemic excursions and periods of asymptomatic hypoglycaemia or hyperglycaemia (ie, details of glycaemic control that are not provided by HbA_{1c} concentrations alone that are measured continuously and can be analysed in daily, weekly, or monthly timeframes). These CGM-derived metrics are the subject of standardised, internationally agreed reporting formats and should, therefore, be considered for use in all clinical studies in diabetes. The purpose of this consensus statement is to recommend the ways CGM data might be used in prospective clinical studies, either as a specified study endpoint or as supportive complementary glucose metrics, to provide clinical information that can be considered by investigators, regulators, companies, clinicians, and individuals with diabetes who are stakeholders in trial outcomes. In this consensus statement, we provide recommendations on how to optimise CGM-derived glucose data collection in clinical studies, including the specific glucose metrics and specific glucose metrics that should be evaluated. These recommendations have been endorsed by the American Association of Clinical Endocrinologists, the American Diabetes Association, the Association of Diabetes Care and Education Specialists, DiabetesIndia, the European Association for the Study of Diabetes, the International Society for Pediatric and Adolescent Diabetes, the Japanese Diabetes Society, and the Juvenile Diabetes Research Foundation. A standardised approach to CGM data collection and reporting in clinical trials will encourage the use of these metrics and enhance the interpretability of CGM data, which could provide useful information other than HbA_{1c} for informing therapeutic and treatment decisions, particularly related to hypoglycaemia, postprandial hyperglycaemia, and glucose variability.

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Introduction

HbA_{1c} is the gold-standard marker for predicting the relative risk of diabetes complications,[1–3] and has been relied on by regulators to make diabetes medication approvals. However, prospective clinical studies are increasingly using continuous glucose monitoring (CGM) devices to collect data to complement observations of the effects of therapeutic interventions in diabetes. These CGM-derived metrics are the subject of internationally agreed reporting formats.[4–6]

The aim of this consensus statement is to recommend ways CGM data can be used in prospective clinical studies to provide clinical information that can be considered by all stakeholders in clinical trial outcomes. A standardised approach to CGM data collection and reporting will improve the interpretability of CGM data and provide more information than HbA_{1c} alone to inform therapeutic decisions and treatment choices, particularly related to hypoglycemia,[7] postprandial hyperglycemia,[8] and glucose variability.[9]

The use of continuous glucose monitoring (CGM) devices has been associated with reduced HbA_{1c} in children and adults with type 1 diabetes and in adults with type 2 diabetes treated either with insulin or a non-insulin therapy,[10–17] when compared with self-monitored plasma glucose (SMPG).[18–21] Use of CGM is also associated with increased time in the glycaemic target range, reduced time in hyperglycaemia, and reduced time in hypoglycaemia (including nocturnal hypoglycaemia) in people with type 1 diabetes or type 2 diabetes.[22–25] CGM users also have lower glucose variability, better quality of life,[26–28] and fewer hospital admissions for acute diabetes events (eg, diabetic ketoacidosis or severe hypoglycaemia) than people who do not use CGM devices.[29–32]

These benefits of CGM devices show their efficacy and support their use as standard-of-care for people with type 1 diabetes or people with type 2 diabetes who are being treated with insulin therapy.[4–6,33] Therefore, prospective clinical studies are increasingly using CGM devices to evaluate the glucose profiles of study participants. The collection of CGM data in clinical

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***Panel 1:* Consensus recommendations for CGM device selection for use in clinical trials**

Each of the recommendations in this consensus have been assigned a level of supporting evidence (ie, A, B, C, or E), that adheres to the evidence-grading system of the American Diabetes Association Standards of Medical Care in Diabetes.[38]

- The same brand and model of continuous glucose monitoring (CGM) device should be used throughout a clinical study to ensure consistent technical characteristics and sensor bias within the study (B)
  - The brand and model and should be identified in study methods
  - The selected CGM device should be used in accordance with the manufacturer product information and regulatory indications for which it is approved[39,40,41,42]
- Clinical trial personnel should be aware that CGM manufacturers update their glucose algorithms periodically, and the system selected for the trial should use a consistent algorithm (B)
  - For multinational trials, ensure that sensors within the same device model do not have separate performance characteristics depending on the region of use[37,39]
- The CGM device used in the clinical trial should be approved by regulatory authorities for clinical use[39,41,43–45] and used in accordance with approved specifications for consistent glucose measurement (B)
  - Specifically with intermittently scanned CGM systems, study participants need to adhere to minimum scanning frequency (3 times per day) and timings (at least once every 8 h)[15]
  - Specifically for CGM sensors that require fingerstick self-monitored plasma glucose (SMPG) calibration, the same model of SMPG meter should be provided to all study participants, who should comply with the CGM manufacturers, calibration schedules, and technique[10,19,41,45]
- Training for the chosen CGM device should be provided for all relevant staff responsible for the clinical study and for all participants or caregivers recruited for the prospective clinical study (E)
  - Training should also be provided for any glucose data collection readers, smartphones, or smartwatch apps
- The accuracy performance characteristics of any CGM device selected for use in a clinical study should be reviewed during study protocol development before the study begins, including ethnic and racial inclusivity, to evaluate whether it meets the needs of the study population and endpoints (E)
- Clinical trial personnel need to be aware of any current medication interference identified by the manufacturer or by independent published research that might compromise sensor accuracy (C)
  - All study participants need to be made aware, before inclusion, to monitor their use of selected medicines during periods when CGM is to be used
  - Study participants should not be recruited if inclusion would prohibit their use of medicines recommended for their short-term or long-term wellbeing[46–48]

studies, however, has not been done or implemented in a standardised manner. In addition, for clinical studies in which CGM devices themselves are not the specified intervention, clinical trial protocols should be designed to incorporate CGM devices in a way that avoids them becoming a confounding factor in the evaluation of the intended intervention. Although the important topics of safety and use of CGM devices in clinical trial settings have received previous scientific recommendations,[34,35] these recommendations have also focused on many of the unmet needs for CGM use in the regulatory process. Some of the identified needs, such as the cost of CGM devices, have not been resolved. However, many of them have, including the requirement to meet accuracy thresholds and the development of standard metrics and targets to apply to CGM data.[5,6] This international consensus statement focuses on the ways CGM and CGM data could be confidently and regularly applied as a standard component of clinical trials in diabetes.

Methods

The diaTribe Foundation, a non-governmental organisation in the USA, invited expert health-care professionals who were experienced with using CGM in clinical trials from academic institutions, the US Food and Drug Administration (FDA), the National Institutes of Health, the American Diabetes Association, and various other associations globally. All the authors of this Review agreed to become members of the consensus writing group. People with diabetes who were not academics were also invited. Participation in the writing group was voluntary and was not remunerated. TB, JH, and MP created a compendium of topic areas for consideration by the rest of the writing group, who provided two rounds of objective feedback. A consolidated draft consensus manuscript and consensus recommendations were developed based on this feedback. The draft manuscript and associated recommendations were then the focus of the International Consensus on CGMs in Clinical Trials, which happened on April 25, 2022, in Barcelona, Spain. All members of the writing group attended the conference either in person or virtually. Each recommendation was separately discussed at the conference until a consensus was agreed. The discussion and outcomes from this conference were used to further refine and revise the consensus recommendations and the consensus manuscript during eight drafts. The final draft was then approved by all members of the writing group.

CGM devices and sensors

All commercially available CGM devices provide a quantification of glucose levels in the interstitial fluid in the subcutaneous space,[36,37] either using a thin sensor filament that is inserted into the subcutaneous space (ie, transcutaneous) or by insertion of the sensor itself into the subcutaneous tissue in the upper arm (ie, implantable). Glucose readings are transmitted wirelessly at 1 min and 5 min intervals to a reader, an app, or an automated insulin delivery device. CGM devices that transmit glucose data only when the user scans their sensor with a reader or smartphone app are referred to as intermittently scanned CGM (isCGM). Transcutaneous systems have sensors that currently have wear times from 6 days to 14 days, after which a new sensor should be applied. Implantable systems currently transmit glucose data for up to 180 days before replacement.

For this consensus statement, the term CGM is used for any of these systems. Only if a functional difference is of importance to the application of a CGM device in a clinical trial do we differentiate between device types. Considering the heterogeneity of the systems available, choosing the same system throughout a study, with appropriate training for staff and users, is recommended (panel 1).

Sensor calibration

CGM sensors can be factory calibrated[39] or calibrated with a code provided with each sensor.[40] Alternatively, CGM sensors might require daily calibration with SMPG.[49,50] The need for SMPG calibration is a consideration when selecting the CGM device for use in a clinical trial. Because SMPG testing can be uncomfortable, user compliance can be affected[51] and poor SMPG technique could affect accuracy.[52] If SMPG calibration is required during a clinical trial, the same model of SMPG meter should be provided to all participants and the calibration process should comply with the instructions of the CGM manufacturer (panel 1).

Sensor accuracy

The ability of CGM devices to accurately collect and document glucose levels is accepted by the clinical community.[39,41,43,44] Several CGM devices are authorised by regulators to replace SMPG testing for diabetes treatment decisions, which is the so-called non-adjunctive use of these devices. In addition, a specific category of FDA class 2 device type, known as an integrated CGM (iCGM) device,[53,54] is used by the FDA to refer to CGM devices that are suitable for use with digitally connected medical devices, including automated insulin delivery systems.[55]

Quantifying CGM sensor accuracy

Mean absolute relative difference (MARD) is an established statistic that can be used to assess the accuracy of CGM devices by averaging the absolute values of the relative differences between a CGM measurement and the corresponding simultaneous value obtained by the reference system. Ideally, MARD should be calculated in a racially diverse population, including individuals with type 1 diabetes or type 2 diabetes, and be based on a large set of paired readings with an adequate number of samples to assess accuracy in hypoglycaemic, hyperglycaemic, and euglycaemic ranges.[56] Because the precision of sensor measurements is reduced at low glucose concentrations, relative differences, and thus MARD, tend to be increased at low reference glucose values. Therefore, the mean absolute difference (MAD) is the preferred accuracy statistic[39,43] for glucose levels less than 80 mg/dL (<4·4 mmol/L). Currently available CGM devices have MARD values between 8% and 14%.[39,43,44,56] However, no prospective clinical studies have evaluated the possible added clinical benefit of low MARD values.

A further test of system accuracy and precision used alongside MARD is the consensus error grid (cEG),[57] which evaluates the distribution of inaccuracies in sensor-glucose readings and whether these inaccuracies have an effect on clinical decision making.

Panel 2: **Consensus recommendations for reporting time in ranges and other CGM-derived glycaemic metrics**

Each of the recommendations in this consensus have been assigned a level of supporting evidence (ie, A, B, C, or E), that adheres to the evidence-grading system of the American Diabetes Association Standards of Medical Care in Diabetes.[38]

- Prospective clinical studies using continuous glucose monitoring (CGM) devices should report endpoints for all core metrics for time in ranges
  - This recommendation is important for time below <70 mg/dL (3·9 mmol/L) and time below range 54 mg/dL (3·0 mmol/L; E)
  - Time below <70 mg/dL (3·9 mmol/L) includes time below <54 mg/dL (<3·0 mmol/L)
  - Both <70 mg/dL (3·9 mmol/L) and time below <54 mg/dL (<3·0 mmol/L) should be reported separately (E)
- Time in range, time below range, and time above range metrics should be reported both as a percentage of time per day and as estimated hours and minutes per day in clinical study outcomes (E)
- In prospective clinical studies that evaluate the safety, efficacy, and clinical effects of an intervention, CGM sensor glucose data should also be reported separately for nocturnal (0000 h to 0559 h) and daytime periods (0600 h to 2359 h; B)[65,66]
- Study investigators should be aware of any discordance between mean glucose exposure as evaluated by the glucose management indicator and a concurrent laboratory-tested HbA_{1c}
- This discordance can be expected and does not indicate lack of sensor accuracy (C)[67,68]

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	Systems affected	Effect
Hydroxycarbamide	Dexcom G4 platinum, G5, G6; Medtronic Guardian 3	Sensor readings will be higher than actual glucose
Paracetamol	Dexcom G4 platinum, G5, G6, G7;* Medtronic Guardian 4	Sensor readings will be higher than actual glucose
Ascorbic Acid	FreeStyle Libre 2	Sensor readings will be higher than actual glucose at >500 mg per day
Alcohol	Dexcom G4 platinum; Medtronic Guardian 3	Sensor readings might be higher than actual glucose
Tetracycline	Eversense	Sensor bias at therapeutic doses
Mannitol	Eversense	Sensor bias at therapeutic doses

*As specified in the Dexcom G7 user manual.

Table 1: **Interference with CGM accuracy**[46–48,62,63]

Accuracy and device selection in clinical trials

As these accuracy measures, which are the most prominent and most often quoted, are derived from analytical studies that aggregate sensor glucose values across all glucose ranges and days of wear,[58] researchers should review accuracy performance in the context of the clinical trial and the specified endpoints. For example, if hypoglycaemia is a study outcome, CGM accuracy (as measured by MAD) and the direction of bias at low glucose levels will be more important than overall MARD. Once a CGM device has been selected for the study, this device should be used for data collection at all timepoints to ensure consistent accuracy throughout the study. Further minimisation of potential variations in CGM accuracy could be done with production batches of glucose sensors with comparable accuracy profiles within the selected model of CGM device.

It is a limitation of accuracy studies that the study population is usually not documented in the study protocol[41,42] and is not racially diverse, with a predominance of White participants and few Black or Asian participants recruited.[39,40,43] This limitation should be considered when selecting a device as many diabetes clinical trials recruit diverse study populations[18,59] or exclusively non-White participants.[60,61]

Data collection and sharing

An important consideration in study design is the choice to configure CGM devices to operate either in unblinded or blinded modes. Unblinded systems allow the wearer to see their glucose values in real time and to act based on these values, for example to avoid hypoglycaemia or hyperglycaemia. Blinded systems collect, store, and transmit glucose data for use in the clinical trial setting for unbiased review by health-care professionals without being revealed to the user, and can therefore minimise the confounding effect of CGM in a clinical trial.

Some CGM sensors can store glucose data autonomously, independent from a connection to a reading device. However, the isCGM sensor can only store up to 8 h of data, meaning that if they are not scanned at least once every 8 h, glucose data are lost, creating data gaps. This limitation should be a consideration in a trial context as manual scanning introduces a potential compliance issue when isCGM is used in unblinded clinical studies.

Concomitant medication that can affect CGM accuracy

Some medications can affect CGM sensor accuracy[46] depending on the glucose-sensing electrochemistry or fluorescence detection[46] used by the system. Paracetamol, for example, can cause biases large enough for the sensors to potentially miss clinically significant hypoglycaemia (table 1).[47,63] This effect could be of importance for study participant selection and inclusion criteria, as well as for advice given to participants.

Time in glucose ranges in clinical trials

Several metrics have been used for interpreting glucose data provided by CGM devices and have been agreed upon by international consensus groups for use in people with type 1 or type 2 diabetes,[4–6] including separate targets for people who are pregnant with pregestational type 1 diabetes and for people who are at high risk of hypoglycaemia because of their increased age, duration of diabetes, duration of insulin therapy, or impaired awareness of hypoglycaemia (table 2). Consensus targets for children, adolescents, and young adults aged 25 years or younger with type 1 diabetes are similar to the overall recommendations for adults but acknowledge the recommendation of the International Society for Pediatric and Adolescent Diabetes that people aged 25 years or younger should aim for the lowest HbA_{1c} without unnecessary exposure to severe hypoglycaemia (panel 2).[69]

Time in glucose ranges indicate the proportion of each day that a person with diabetes spends with glucose readings in each of three ranges that have been defined by the International Consensus on Time in Range group (table 3).[6] Time in range indicates the amount of time that glucose readings are within a defined target glucose range of 70–180 mg/dL (3·9–10·0 mmol/L; 63–140 mg/dL [3·5–7·8 mmol/L] during pregnancy). A secondary consensus time in range metric,[5] also known as time in tight range, is emerging as a reported measure of time in range, particularly for people with type 1 diabetes using automated insulin delivery systems or in people with type 2 diabetes using glucose-lowering agents. Time in tight range is defined as the percentage of time that glucose readings are within 70–140 mg/dL (3·9–7·8 mmol/L).[5,70] For participants in whom time in tight range is proposed as a metric, the suggested target

	Measures	Aim
Percentage of sensor data obtained	The proportion of possible obtained readings by the CGM device; provides a measure of confidence in the all data-derived metrics	≥70% of data during the collection period
Frequency of scanning (eg, scans per day)	For FreeStyle Libre and FreeStyle Libre 2 systems, the sensor should be scanned periodically with a reader or the smartphone app; the frequency of scanning is associated with changes in glucose metrics[64]	Frequency of minimum once every 8 h to ensure no gaps in data
Time in ranges		
Time in range	Measures the percentage of time spent in consensus target glucose range 70–180 mg/dL (3·9–10·0 mmol/L); during pregnancy, this range is 63–140 mg/dL (3·5–7·8 mmol/L).	>70% of time per day (ie, 16 h 48 min) in type 1 and type 2 diabetes; >50% of time per day (12 h) in people older than 60 years or patients at high risk
Time in tight range	A secondary measure of time in range, measures the percentage of time spent in target glucose range 70–140 mg/dL (3·9–7·8 mmol/L)	Suggested time in tight range aim is >70% of each day[47]
Time below range (<70 mg/dL [<3·9 mmol/L])	Measures the percentage of time spent with glucose <70 mg/dL (<3·9 mmol/L), including readings <54 mg/dL (<3·0 mmol/L)	<4% of time per day (1 h) in type 1 and type 2 diabetes; <1% of time per day (15 min) in people older than 60 years or patients at high risk
Time below range (low glucose or Level 1 hypoglycaemia)	Measures the percentage of time spent with glucose 54–69 mg/dL (3·0–3·9 mmol/L); Level 1 hypoglycaemia is an alert threshold	No international consensus recommendations
Time below range (very low glucose or Level 2 hypoglycaemia)	Measures the percentage of time spent with glucose <54 mg/dL (<3·0 mmol/L); Level 2 hypoglycaemia is considered clinically significant and requiring immediate attention	<1% of time per day (15 min) in type 1 and type 2 diabetes
Time above range (>180 mg/dL [>10·0 mmol/L])	Measures the percentage of time spent with >180 mg/dL (>10·0 mmol/L), including readings >250 mg/dL (>13·9 mmol/L)	<25% of time per day (6 h) in type 1 and type 2 diabetes; <10% of time per day (2 h 24 min) in people older than 60 years or patients at high risk
Time above range (high glucose or Level 1 hyperglycaemia)	Measures the percentage of time spent with glucose 181–250 mg/dL (10·1–13·9 mmol/L)	No international consensus recommendations
Time above range (very high glucose or Level 2 hyperglycaemia)	Measures the percentage of time spent with glucose >250 mg/dL (>13·9 mmol/L)	<5% of time per day (1 h 12 min) in type 1 and type 2 diabetes
Mean sensor glucose	A measure of the mean 24 h glucose concentration calculated across all recorded glucose readings	No international consensus recommendations
Glucose Management Indicator	A measure of short-term glucose levels that can be used to predict long-term glucose exposure; the Glucose Management Indicator is expressed in the same units as HbA_{1c} (eg, as a percentage or mmol/mol) for comparative purposes, but they are usually not identical	No international consensus recommendations
Glycemia Risk Index	A single-number summary of the quality of glycaemia; ranks the quality of glucose control, allocating increased weight to very low and very high glucose; the Glycemia Risk Index can also be displayed graphically on a Glycaemia Risk Index grid	No international consensus recommendations
Coefficient of variation	A measure of dynamic glucose variability expressed as percentage coefficient of variation and calculated as 100 × (SD divided by mean glucose); coefficient of variation is correlated with time below range	≤36% of glucose variability in type 1 diabetes
SD of mean glucose	The SD of mean glucose values is a measure of dynamic glucose variability; SD is strongly correlated with mean glucose	No international consensus recommendations

Each of these measures of glucose control can be derived and reported by CGM devices. They are all endorsed by international consensus guidance on the use of CGM devices in the management of diabetes.[4–6]

Table 2: **Objective measures of glycaemic control derived from CGM devices**

for time in tight range is more than 70%,[71] as for time in range 70–180 mg/dL (3·9–10·0 mmol/L).[6]

Time below range refers to the amount of time that glucose readings are below the target glucose range of less than 70 mg/dl (3·9 mmol/L; <63 mg/dL [3·5 mmol/L] during pregnancy), and time above range refers to the amount of time that glucose readings are above the target range of more than 180 mg/dL (10·0 mmol/L; >140 mg/dL [7·8 mmol/L] during pregnancy). As a clinical study endpoint, time below range of less than 70 mg/dL (<3·9 mmol/L) also includes clinically significant hypoglycaemic readings of less than 54 mg/dL (<3·0 mmol/L); both measures of time below range should be reported separately.

Many of the CGM-defined time in range measures identified in this consensus statement can be categorised into temporal subgroups (eg, within a 24 h period, diurnal, or nocturnal). These subgroups should be considered when specifying endpoints (panel 2). For example, change in nocturnal hypoglycaemia (0000 h to 0559 h) can be a separate outcome from hypoglycaemia in the daytime (0600 h to 2359 h) or within a 24 h period. In paediatric trials and other trials (eg, in participants older than 60 years, in participants with cystic fibrosis, or of diabetes and exercise), additional definitions

	Units and quantity
Core endpoints	
Time in range 70–180 mg/dL (3·9–10·0 mmol/L)	Percentage of time in range; amount of time (hours and minutes)
Time below range <70 mg/dL (<3·9 mmol/L), including readings of <54 mg/dL (<3·9 mmol/L)	Percentage of time below range; amount of time (hours and minutes)
Time below range <54 mg/dL (<3·0 mmol/L)	Percentage of time below range; amount of time (hours and minutes)
Time above range >180 mg/dL (>10·0 mmol/L), including readings of >250 mg/dL (<13·9 mmol/L)	Percentage of time above range; amount of time (hours and minutes)
Time above range >250 mg/dL (>13·9 mmol/L)	Percentage of time above range; amount of time (hours and minutes)
Coefficient of variation	Percentage coefficient of variation intraday (ie, within 24 h) and interday (ie, over multiple days)
SD of mean glucose	SD
Mean sensor glucose	mg/dL (mmol/L)
Secondary endpoints (continuous outcomes)	
Time in tight range 70–140 mg/dL (3·9–7·8 mmol/L)	Percentage of time in tight range; amount of time (hours and minutes)
Change in Glucose Management Indicator	Absolute mean change in mmol/mol or percentage
Extended hypoglycaemic event rate <70 mg/dL (<3·9 mmol/L)	Number of events with sensor glucose <70 mg/dL (<3·9 mmol/L) lasting at least 120 min; event ends when glucose returns to ≥70 mg/dL (≥3·9 mmol/L) for ≥15 min
Extended hyperglycaemic event rate >250 mg/dL (>13·9 mmol/L)	Number of events with sensor glucose >250 mg/dL (>13·9 mmol/L) lasting at least 120 min; event ends when glucose returns to ≤180 mg/dL (≤10·0 mmol/L) for ≥15 min
Secondary endpoints (binary outcomes)	
Proportion of participants with time in range 70–180 mg/dL (3·9–10·0 mmol/L) for >70% of each day	Percentage of participants
Proportion of participants with time in range 70–180 mg/dL (3·9–10·0 mmol/L) with ≥5% points improvement from baseline	Percentage of participants
Proportion of participants with time in range 70–180 mg/dL (3·9–10·0 mmol/L) with ≥10% points improvement from baseline	Percentage of participants
Proportion of participants with time below range <70 mg/dL (<3·9 mmol/L) for <4% of each day	Percentage of participants
Proportion of participants with time below range <54 mg/dL (<3·0 mmol/L) for <1% of each day	Percentage of participants
Proportion of participants with time above range >180 mg/dL (>10·0 mmol/L) for <25% of each day	Percentage of participants
Proportion of participants with time above range <250 mg/dL (>13·9 mmol/L) for <5% of each day	Percentage of participants
Composite endpoints	
Proportion with improvement in HbA1c >0·5% points without an in increase in TBR <54 mg/dL (<3·0 mmol/L) of >0·5%	Percentage of participants
Proportion of participants with >10% points improvement in percentage of time in range 70–180 mg/dL (3·0–10·0 mmol/L) without an increase in time below range <54 mg/dL (<3·0 mmol/L) of >0·5%	Percentage of participants
Proportion of participants with mean glucose <154 mg/dL (<8·6 mmol/L) and <1% time below range <54 mg/dL (<3·0 mmol/)	Percentage of participants
Proportion of participants with >70% time in range 70–180 mg/dL (3·0–10·0 mmol/L) and <4% time below range <70 mg/dL (<3·9 mmol/)	Percentage of participants
Proportion of participants with >70% time in range 70–180 mg/dL (3·0–10·0 mmol/L) and <1% time below range <54 mg/dL (<3·0 mmol/)	Percentage of participants

Table 3: **Recommended CGM-derived endpoints for clinical trials**

appropriate to sleep periods and active periods might need to be specified in the study protocol.

Based on current evidence, confident interpretation of CGM metrics requires 14 consecutive days of CGM data with at least 70% of data collected during that time period, which is predictive of glycaemia for 3 months (panel 3).[72,77] For the assessment of mean glucose, time in range, and measures of hyperglycaemia, additional days of data do not substantially increase this correlation. This assessment assumes that any data that is not collected should be representative of random data gaps that are balanced across the treatment and control groups. If participants included in the study population are expected to have more hypoglycaemia or higher glycaemic variability than is typical, long periods of sensor use might be indicated.[78] A long review period

might also be needed for people with higher baseline glucose variability than expected.[72–74] An alternative to the recommendation to obtain at least 70% of data in 14 consecutive days is a data collection period of 10 consecutive days with 80–100% data obtainment, accepting any loss of accuracy that might be associated with a short review period.[74]

Time in glucose ranges as outcome measures

From a clinical perspective, CGM can detect unrecognised hypoglycaemia, which is an important benefit for use in clinical trials. Whether a person with hypoglycaemia is symptomatic or not, time below range can also be divided into Level 1 and Level 2, which indicate different amounts of urgency for clinical action.[5,6] Level 1, with a glucose level of 54–69 mg/dL (3·0–3·9 mmol/L), is an alert threshold[79] independent of any acute symptoms. Health-care professionals and people with diabetes should monitor time spent in Level 1 hypoglycaemia. Level 2, with a glucose level of less than 54 mg/dL (<3·0 mmol/L), with or without symptoms, is considered clinically significant and requires immediate attention. In Level 1 or Level 2 hypoglycaemia, the episode is considered clinically relevant to CGM data-obtainment if it is 15 min or more in duration before it returns to more than 70 mg/dL (3·9 mmol/L).[79] Level 1 or Level 2 time below range does not indicate symptomatic hypoglycaemia or provide direct information of episodes of severe hypoglycaemia requiring assistance—this requires patient-reported information in a clinical trial context. However, time below range and other CGM-derived measures of hypoglycaemia risk in clinical trials have been shown to be predictive of future severe hypoglycaemia,[80] validating CGM in this context (table 4).

Time above range is either 181–250 mg/dL (10·1–13·9 mmol/L), known as Level 1 hyperglycaemia, or more than 250 mg/dl (>13·9 mmol/L), known as Level 2 hyperglycaemia. Blood glucose values exceeding 250 mg/dL (13·9 mmol/L) might increase the risk of diabetic ketoacidosis,[83] and Level 1 and Level 2 hyperglycaemia should be reported in study outcomes. Extended hyperglycaemia, particularly after eating, can be defined as sensor glucose more than 250 mg/dL (>13·9 mmol/L) for 120 min or more (table 4).

As a measure for assessing glucose control, time in range 70–180 mg/dL (3·9 mmol/L) is immediately responsive to changes in medication, diet, and lifestyle that can be visualised in a clinical trial setting. Percentage of time in range is an outcome measure that can be associated with complications of diabetes, as indicated by retrospective analysis of the effect of percentage of time in range on retinopathy, nephropathy,[84,85] neuropathy,[86,87] and cardiovascular disease.[88,89] However, no long-term prospective randomised controlled trial has validated the relationship between time in range and long-term microvascular or macrovascular complications of diabetes.

Use of time in range 70–180 mg/dL (3·9 mmol/L) as a glycaemic measure in clinical trials should be augmented with the inclusion of metrics of hypoglycaemia (eg, time below range <70 mg/dL [3·9 mmol/L] and time below range <54 mg/dL [3·0 mmol/L]),[90] including in trials with interventions that might directly reduce glucose, such as insulin[91,92] or exercise,[93] or in populations at risk of hypoglycaemia.[94] For example, in the InRange study,[92] when comparing time in range of participants with different basal insulins, the rate of hypoglycaemia as measured by CGM was 3–6 times higher than

Panel 3: Consensus recommendations for the application of CGM sensors in a clinical trial setting

Each of the recommendations in this consensus have been assigned a level of supporting evidence (ie, A, B, C, or E), that adheres to the evidence-grading system of the American Diabetes Association Standards of Medical Care in Diabetes.[38]

- CGM data should be collected at baseline and at all specified study timepoints with the CGM device selected for the clinical trial (E)
  - If CGM is not used throughout the study, specified CGM data-collection periods should allow for sufficient data to be collected that can be representative of glucose exposure for 3 months (B)[72–74]
- Participants recruited into a study that uses blinded CGM for the study data collection and who are already using a personal CGM device for their diabetes management should be provided with and required to wear the blinded study CGM sensor during specified study data-collection periods, even if the trial CGM and personal CGM devices are the same type (E)
- For a study in which unblinded CGM is to be used, all participants should be provided with and use the same study CGM, even if they used a CGM for personal use before study enrolment (E)
- In a clinical trial, CGM should be used for a minimum of 14 consecutive days every 3 months throughout the study, including at baseline (B)
  - The aim is that a minimum of 70% of the glucose data should be obtained for each individual participant[72–74]
- All CGM data should be included in the final analysis, but the proportion of participants who met the minimum 70% data-obtainment requirement during 14 days should also be reported as part of the data completeness (E)
- Although CGM sensors have each shown accuracy, a comparison of CGM outcomes across studies that use different brands of sensors should be done with caution (C)[75,76]

	Glycaemic criteria	Duration	Description
Hypoglycaemia	<70 mg/dL (<3·9 mmol/L), including readings of <54 mg/dL (<3·0 mmol/L)	≥15 consecutive min of <70 mg/dL	Sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose reducing therapy; event ends when there is ≥15 consecutive min with a CGM sensor value of ≥70 mg/dL
Hypoglycaemia alert value (Level 1)	54–69 mg/dL (3·0–3·9 mmol/L)	≥15 consecutive min of <70 mg/dL	Sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose reducing therapy; event ends when there is ≥15 consecutive min with a CGM sensor value of ≥70 mg/dL
Clinically significant hypoglycaemia (Level 2)	<54 mg/dL (< 3·0 mmol/L)	≥15 consecutive min	Serious, clinically important hypoglycaemia; event ends when there is ≥15 consecutive min with a CGM sensor value of ≥54 mg/dL
Extended hypoglycaemia	<70 mg/dL (<3·9 mmol/L)	>120 consecutive min	No maximum agreed duration; during periods of extended hypoglycaemia, any periods of hypoglycaemia <54 mg/dL should be reported separately
High glucose (Level 1)	181–250 mg/dL (10·1–13·9 mmol/L)	≥15 consecutive min	Event ends when there is ≥15 consecutive min with a CGM sensor value of ≤180 mg/dL
Very high glucose (Level 2)	>250 mg/dL (>13·9 mmol/L)	≥15 consecutive min	Event ends when there is ≥15 consecutive min with CGM sensor value of ≤250 mg/dL
Extended hyperglycaemia	>250 mg/dL (>13·9 mmol/L)	≥90 cumulative min within a 120-min period	Often postprandial

Other non-CGM measures of symptomatic hypoglycaemia can be recorded and might be correlated with CGM-derived measures. When reporting or evaluating the frequency of hypoglycaemia with sensor glucose values, low sensor glucose values can be asymptomatic in people with diabetes and might be evident in people without diabetes,[81] especially values between 60–70 mg/dL (3·0–3·9 mmol/L). In a clinical trial, assumptions concerning impaired awareness of hypoglycaemia should be confirmed with a validated tool.[82] Severe hypoglycaemia cannot be classified by CGM-derived data, it is a clinical diagnosis defined by severe cognitive impairment requiring external assistance for recovery, and not by a specific glucose threshold.

Table 4: **Classification of CGM-detected hypoglycaemia or hyperglycaemia to be counted in clinical trials**

SMPG-detected hypoglycaemia in the same data-collection period.

The Glucose Management Indicator, coefficient of variation, and Glycemia Risk Index as other CGM metrics

Along with specific time in glucose ranges, other measures of glucose control can be calculated from CGM data that have become established in assessing diabetes health.[95] These measures include the Glucose Management Indicator (GMI), which is a mathematical derivation from the mean glucose, the coefficient of variation, and the Glycemia Risk Index (GRI; table 2).[67,96]

GMI is a function of mean glucose, expressed in the same units as HbA_{1c} (ie, as a percentage or in mmol/mol) for comparative purposes, which can be used with an HbA_{1c} test to help in-therapy adjustment.[67,97] GMI and HbA_{1c} are usually not identical as HbA_{1c} can be affected by many non-glycaemic factors that affect red blood cell lifespan.[97] The correlation between GMI and HbA_{1c} is stronger with long CGM wear (eg, 4 weeks) than with short CGM wear[77] and in the CGM collection period that immediately precedes the HbA_{1c} test.[72]

The coefficient of variation is a measure of glucose variability that is correlated with time below range[98] and is calculated as 100 × (SD divided by mean glucose). A target threshold for the coefficient of variation in type 1 diabetes is recommended to be less than or equal to 36%[5] based on the increased risk of hypoglycaemia above this amount.[98] A limitation of the coefficient of variation is that it might increase even if glycaemic variability improves if it is accompanied by a decrease in mean glucose. Other limitations of the coefficient of variation are that it does not quantify the frequency of glycaemic oscillations or show within-day or between-day variability, all of which are relevant to understanding glycaemic variability. However, despite these limitations, both GMI and the coefficient of variation are included in standard reports on CGM-derived glucose performance.

The GRI is a single-number summary of the quality of glycaemia based on expert analysis by 330 clinicians of 14-day ambulatory glucose profile (AGP) tracings.[96] The GRI assesses both low and high glucose profiles to calculate and rank the quality of glucose control, allocating increased weight to very low and very high glucose. The GRI can be displayed graphically on a GRI grid that can be used by clinicians and researchers to establish the glycaemic effects of prescribed and investigational treatments within an individual over time, and to compare groups of individuals.

The ambulatory glucose profile graph and report

An accepted visual summary of the features of a CGM profile is the AGP.[38,99,100] The AGP graph allows people with diabetes to identify patterns and trends in

daily glucose management. It has four important features: the target glucose range, the median line, the shaded 25th to 75th percentile band, and the outer 5th to 95th percentile band. A full description of these features is available from the International Diabetes Center. The AGP graph can be used systematically to identify trends in glucose control in each day and between different days to enable clinical decision making.[100,101]

The standardised AGP report includes a so-called stacked bar that summarises the different time in range metrics in a visual format. The stacked bars in the AGP report indicate the percentage of time below range and the percentage of time above range metrics for Level 1 and Level 2 hypoglycaemia or hyperglycaemia, with discrete percentage values for low or high and very low or very high readings. The separate colours in the stacked bar also reflect a clinical viewpoint that, by use of consistent color-coding for different glucose ranges, can optimise safety and clinical interpretation;[102] green indicates desired levels of glucose and red indicates levels of glucose that require improvement. The AGP report also contains the summary metrics for mean glucose, GMI, glucose variability, and percentage of data obtained. The potential uses of the AGP report format in diabetes research and clinical trials are described by the International Diabetes Center.

For the **full description of AGP features** see www.agpreport.org

For the **potential uses of the AGP report format** see www.agpreport.org/agp/research

Planning to use CGM in a clinical study

When considering the use of CGM in a clinical study, researchers should explicitly state their aims as different sensors have different features regarding their uses for glucose data collection and accuracy. Similarly, the glucose data requirements should be matched to the trial objectives.

CGM use throughout the study or during specified periods

During a diabetes clinical trial, it is preferable that CGM data be collected continually throughout the study period. This process reduces the likelihood of bias in the sensor glucose data collection and maximises the likelihood that the data are representative of the glycaemia of a participant for the study duration. However, in some circumstances, glucose data might only be collected during specified periods, for example, at baseline, at prespecified timepoints during the intervention, or at study end. Periodic CGM might be appropriate for trials that continue for months or years. However, periodic use of CGM might introduce bias as a consequence of a change in the self-management behaviour of a participant during these periods.

When CGM is used only during specified periods, the same CGM device should be used at each timepoint and individual data collection periods should ensure sufficient data collection for confident assessment of the glucose data. This process should include the data collected in the first 12–24 h after sensor application when post-insertion artifacts might affect accuracy. A minimum of 14 days of sensor use with more than 70% data obtainment is currently an established standard for confident prediction of glucose exposure for 3 months for any participant (panel 3).

***Panel 4:* Consensus recommendations for the interpretation of clinically meaningful differences in time in range in clinical trials**

Each of the recommendations in this consensus have been assigned a level of supporting evidence (ie, A, B, C, or E), that adheres to the evidence-grading system of the American Diabetes Association Standards of Medical Care in Diabetes.[38]

- A difference of ≥5% (absolute percentage points) in time in range is considered clinically meaningful for an individual participant in a clinical study and 3% is considered clinically meaningful for a treatment group difference in mean time in range (B)[84]
- The change in time in range should be reported separately for each study group from beginning to end of the study, and the difference between the study groups should be compared statistically with adjustment for the baseline value (E)
- Studies can be powered to detect a minimum 3% change in mean time in range between study groups (E)

CGM data collection at baselines and other timepoints

Use of blinded or unblinded CGM in a clinical study

Clinical study protocols can specify the use of blinded or unblinded CGM to collect study data. The use of blinded CGM throughout the study, or at specified data collection timepoints, might be most appropriate for studies that recruit only CGM-naive participants.[7] The use of blinded CGM in these studies can reveal the efficacy of an investigational drug or device, but might not be generalisable to the typical ambulatory population. However, as clinical practice for people with diabetes who use insulin begins incorporating CGM as standard care, participants in a study are likely to use a personal CGM device for day-to-day glucose management.[11] To require participants not use their personal devices when recruited into a trial that requires a blinded study CGM would be challenging and potentially unethical. Therefore, for studies using blinded CGM, the study CGM sensor should be supplied to participants and used to collect data for researchers, even when a participant has their own personal CGM for day-to-day diabetes self-care. This process can ensure quality control and continuity for all study participants, and manage data privacy issues by enabling investigators to know which data are for their use and analysis and which data are private for the

Panel 5: **Consensus recommendations for CGM data inclusion in the clinical trial final analysis set**

Each of the recommendations in this consensus have been assigned a level of supporting evidence (ie, A, B, C, or E), that adheres to the evidence-grading system of the American Diabetes Association Standards of Medical Care in Diabetes.[38]

- For prospective randomised clinical studies in which both intervention groups and control groups use the same CGM device throughout, all CGM data (including data collected within the first 12–24 h of sensor use and low-frequency glucose data artifacts) should be included in the analysis set (E)
- Managing missing data should be part of the statistical analysis plan so that no CGM data are excluded from the final analysis set (E)
- CGM sensor glucose data should be stored according to the regulations and laws appropriate to any other source data generated in a prospective clinical study (E)

study participant. Blinded CGM sensors can allow CGM-naive participants to get used to wearing the sensor before collection of baseline data and can allow participants who use personal CGM devices to get used to the blinded study CGM. For clinical studies in which both CGM-naive participants and CGM-users are included, randomisation should be stratified so that bias is avoided.

For studies using unblinded CGM, all participants should be provided with and use the same study sensor for the duration of the study (panel 3). Participants with personal CGM devices that are different to the study CGM should switch to using the study CGM. If the personal CGM of a participant is identical to the study CGM, they should be provided with a study CGM device to ensure quality control and continuity of sensors used in the study. To minimise the confounding effect of CGM improving glycaemic metrics after randomisation, participants who are not current CGM users should have 7–14 days to get used to the CGM device (panel 3). This amount of time will be sufficient to stabilise the subsequent collection of baseline CGM data that is recommended to be 10–14 days; important CGM metrics for hyperglycaemia, hypoglycaemia, and overall glucose control plateau within the first week of use of an unblinded sensor.[103]

Important CGM metrics of value to be reported

Important CGM metrics are based on recommendations from the International Consensus on Use of Continuous Glucose Monitoring and Standardizing Clinically Meaningful Outcome Measures Beyond HbA_{1c} for Type 1 Diabetes on the use of CGM in clinical practice,[4,5] and from the International Consensus on Time in Range.[6] If reporting time in range, time below range, or time above range, metrics can be defined as percentage of time per day, estimated actual amount of time in hours or minutes per day, or both. For studies using isCGMs, the frequency and timing of daily scans and any data gaps should also be reported (table 2). The application of CGM metrics as study endpoints, including endpoints that are well established as standard glucose metrics in the AGP report format and additional endpoints, can be directly collected from CGM devices but are not typically part of standard reports, and should be specified by researchers (table 3). Each study should select and report only the metrics that allow clear interpretation of the data in the context of the specified study objectives and statistical analysis plan.

Clinically relevant changes in important glucose metrics over time

What constitutes a clinically relevant change from baseline or between comparative timepoints in any CGM glucose metric is not standardised and is discussed and periodically reviewed by the expert community. International consensus[6] has accepted that a change of at least 5 percentage points in time in range is clinically meaningful for an individual participant. This conclusion is based on a retrospective analysis of blood glucose data systematically collected seven times a day once every 3 months in the Diabetes Control and Complications Trial,[84] relating change in percentage of time in range to a clinically meaningful change in HbA_{1c}. In this context, comparisons between study participants should use the mean data for each individual to acknowledge the lack of independence of observations on any individual. Further investigation and discussion of this aspect of time in range is necessary.

No consensus is established for clinically important changes in other glucose metrics. Regular clinical practice will emphasise any change that brings a metric within international consensus targets or takes it out of the agreed target daily range.

When reporting outcomes, the proportion of participants within each treatment group who met the clinically relevant change (≥5% time in range) over time should be reported, as should the proportion of participants who met the consensus target for any specific metric after the intervention compared with baseline (panel 4). For time in range, the proportion of participants with the relevant change for the trial endpoint (≥5% increase in time in range) and the proportion that met the clinically relevant target (time in range >70%) should be reported. For time below range, although there is no agreement for a clinically meaningful change in time below range, the percentage of participants who had less than 4% time at less than 70 mg/dl and who had less than 1% time at less than 54 mg/dL (3·0 mmol/L) after intervention compared with the percentage at baseline should be reported (table 3).

Clinically relevant differences between treatment groups

When establishing whether a meaningful change in CGM metrics can be reported between treatment groups, the change should be reported separately for each study group from beginning to end of the study (panel 4). The difference between study groups should be compared statistically, with adjustment for the baseline value and with adequate type 1 error control for statistical significance. For the power calculation of a trial, expert consensus is that a minimum 3% change in mean time in range between intervention and control groups represents a meaningful change in the distribution of time in range between different study groups, and that the intervention has had an effect on glycaemia (panel 4). These definitions are also important in setting non-inferiority limits.

Data handling and calculations

Time periods after sensor application

The accuracy of different CGM devices might be reduced immediately after sensor application as a consequence of local injury at the insertion site.[104] In a minority of cases, this insertion-site trauma provokes an inflammatory reaction that can reduce local glucose bioavailability for detection.[105–107] Within a clinical study, consistent use of a single CGM device in intervention and control groups can allow this period of variable accuracy to be included in comparative analysis so that discarding data collected in the initial 12–24 h after sensor application is not advised (panel 5). Many available systems have updated glucose algorithms that minimise the effects of changes in accuracy after insertion. In this context, increased inaccuracy does not imply that the metric computed for the period will be biased, especially if a control group is available for comparison.

Missing data and artifacts

As with any clinical trial, the ability of a participant to meet the requirements for optimal CGM data obtainment can vary, resulting in gaps in the CGM data record. Although the aim is to obtain at least 70% of data for each participant, managing missing data should be part of the statistical analysis plan so that almost no data are excluded from the final analysis set (panel 5).

Artifacts other than insertion-site trauma after sensor application can involve pressure-induced sensor attenuation, which occurs when direct pressure on the sensor and surrounding tissue causes a temporary reduction of localised blood and interstitial fluid exchange.[108] Sensor-filament displacement within the insertion site can also occur[104] and localised changes in temperature can affect oxygen tension and sensor output.[109] These effects can combine to create temporarily reduced sensor readings.

However, each sensor has been developed by the manufacturer with presignal algorithms authorised by regulatory bodies. To avoid post hoc data cleaning of low-frequency artifacts, we recommend including potentially artefactual data in the primary analysis set, as chance and randomisation will balance any bias between the study groups. Sensitivity analysis can be considered if artifacts are suspected. Insertion site selection, with preference for arm over abdomen, can contribute to avoiding sensor artifacts.

Search strategy and selection criteria

Papers for this Review were identified via searches of PubMed for articles published between Jan 1, 1989, and June 30, 2022, by use of the terms "randomized controlled trial", "randomized clinical trial", "real world study", "observational study", "continuous glucose monitoring", "CGM", "intermittently scanned continuous glucose monitoring", "isCGM", "flash glucose monitoring", "time in range", "time below range", "time above range", "MARD", "GMI", "GRI", "ambulatory glucose profile", and "diabetes". Appropriate papers that were identified via this search and relevant references cited in those articles were reviewed. Only published articles were reviewed and all searches were restricted to studies on humans and published in English.

Conclusion

Prospective and randomised controlled clinical studies in diabetes, especially with new pharmaceutical agents, can benefit from incorporating CGM devices for both the comparative monitoring of the intervention and as clinically relevant outcome measures that complement established HbA_{1c} outcomes. Additionally, the use of CGM-derived metrics can identify selective treatment targets related to hypoglycaemia, postprandial hyperglycaemia, and glucose variability. The efficacy, safety, and ability of CGM devices themselves to positively affect a range of measures of glycaemic control is a challenge to effective trial design. Although the use of blinded sensors can minimise the confounding effect of CGM, the use of unblinded CGM should also be accommodated, particularly in type 1 diabetes in which the use of personal GCM devices is now widespread.

To optimise study objectives, careful consideration should be given to the selection and use of CGM devices used for data collection. Different features of different systems will be appropriate for different study protocols and participant cohorts. Equally, among the diverse range of study endpoints that can be supported by CGM devices, it is crucial to choose those that have the most relevance to the study objectives. The recommendations within this consensus statement focus on providing clear guidance regarding how the use of CGM devices can be most effectively incorporated into protocols for prospective clinical studies so that the resulting glucose metrics can be collected, managed, and interpreted with confidence in the context of the trial objectives

and outcomes. Importantly, the clinical significance of some CGM metrics, such as time below range, needs to be considered according to patient-related outcomes.

Contributors

TB, JH, and MP provided topics that can be considered as part of the discussion about continuous glucose monitoring (CGM) and CGM data in clinical trials. CMA, SAA, GA-R, RWB, RMB, BAB, JC, AC, EC, PC, KC, TD, SD, RG, SG, JH, IBH, TK, JK, BK, LL, DMau, CM, DMaa, RNim, RNis, MS, SDP, ER, JR, BS, KU, GEU, and SAW provided feedback on the conceptualisation of this Review. A consolidated draft consensus manuscript and consensus recommendations were developed by all authors. The draft was then revised by all authors. The final draft was approved by all authors.

Declaration of interests

TB has received honoraria for participation on advisory boards for Novo Nordisk, Sanofi, Eli Lilly,Boehringer-Ingelheim, Medtronic, and Indigo Diabetes, and as a speaker for AstraZeneca, Eli Lilly, Novo Nordisk, Medtronic, Sanofi, and Roche. TB owns stocks of DreaMed Diabetes and his institution (University Medical Centre Ljubljana, University Children's Hospital) has received research grant support and travel expenses from Abbott Diabetes Care, Medtronic, Novo Nordisk, Sanofi, Sandoz, Novartis. SAA has served on advisory boards for Novo Nordisk and Medtronic and has spoken at educational events sponsored by Novo Nordisk and Sanofi in the last 12 months. She is a co-investigator on the EU IMI Hypoglycaemia Redefining Solutions for Better Lives programme, which has the industry partners Abbott Diabetes Care, Eli Lilly, Medtronic, Novo Nordisk, and Sanofi-Aventis. 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References

1 Stratton IM, Adler AI, Neil HAW, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000; **321:** 405–12.

2 Nathan DM, Genuth S, Lachin J, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993; **329:** 977–86.

3 The DCCT Research Group. The Diabetes Control and Complications Trial (DCCT). Design and methodologic considerations for the feasibility phase. *Diabetes* 1986; **35:** 530–45.

4 Agiostratidou G, Anhalt H, Ball D, et al. Standardizing clinically meaningful outcome measures beyond HbA_{1c} for type 1 diabetes: a consensus report of the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endocrine Society, JDRF International, The Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society, and the T1D Exchange. *Diabetes Care* 2017; **40:** 1622–30.

5 Danne T, Nimri R, Battelino T, et al. International consensus on use of continuous glucose monitoring. *Diabetes Care* 2017; **40:** 1631–40.

6 Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. *Diabetes Care* 2019; **42:** 1593–603.

7 Goldenberg RM, Aroda VR, Billings LK, et al. Effect of insulin degludec versus insulin glargine U100 on time in range: SWITCH PRO, a crossover study of basal insulin-treated adults with type 2 diabetes and risk factors for hypoglycaemia. *Diabetes Obes Metab* 2021; **23:** 2572–81.

8 Ceriello A, Prattichizzo F, Phillip M, Hirsch IB, Mathieu C, Battelino T. Glycaemic management in diabetes: old and new approaches. *Lancet Diabetes Endocrinol* 2022; **10:** 75–84.

9 Battelino T, Dovč K. Glycemic variability: the danger of a physiologically stable metric. *J Clin Endocrinol Metab* 2020; **105:** e3815–17.

10 Lind M, Polonsky W, Hirsch IB, et al. Continuous glucose monitoring vs conventional therapy for glycemic control in adults with type 1 diabetes treated with multiple daily insulin injections: the GOLD randomized clinical trial. *JAMA* 2017; **317:** 379–87.

11 Aleppo G, Ruedy KJ, Riddlesworth TD, et al. REPLACE-BG: a randomized trial comparing continuous glucose monitoring with and without routine blood glucose monitoring in adults with well-controlled type 1 diabetes. *Diabetes Care* 2017; **40:** 538–45.

12 Beck RW, Riddlesworth T, Ruedy K, et al. Effect of continuous glucose monitoring on glycemic control in adults with type 1 diabetes using insulin injections: the DIAMOND randomized clinical trial. *JAMA* 2017; **317:** 371–78.

13 Šoupal J, Petruželková L, Grunberger G, et al. Glycemic outcomes in adults with t1d are impacted more by continuous glucose monitoring than by insulin delivery method: 3 years of follow-up from the COMISAIR study. *Diabetes Care* 2020; **43:** 37–43.

14 Campbell FM, Murphy NP, Stewart C, Biester T, Kordonouri O. Outcomes of using flash glucose monitoring technology by children and young people with type 1 diabetes in a single arm study. *Pediatr Diabetes* 2018; **19:** 1294–301.

15 Leelarathna L, Evans ML, Neupane S, et al. Intermittently scanned glucose monitoring for type 1 diabetes. *N Engl J Med* 2022; **387:** 1477–87.

16 Battelino T, Conget I, Olsen B, et al. The use and efficacy of continuous glucose monitoring in type 1 diabetes treated with insulin pump therapy: a randomised controlled trial. *Diabetologia* 2012; **55:** 3155–62.

17 Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Effectiveness of continuous glucose monitoring in a clinical care environment: evidence from the Juvenile Diabetes Research Foundation continuous glucose monitoring (JDRF-CGM) trial. *Diabetes Care* 2010; **33:** 17–22.

18 Martens T, Beck RW, Bailey R, et al. Effect of continuous glucose monitoring on glycemic control in patients with type 2 diabetes treated with basal insulin: a randomized clinical trial. *JAMA* 2021; **325:** 2262–72.

19 Beck RW, Riddlesworth TD, Ruedy K, et al. Continuous glucose monitoring versus usual care in patients with type 2 diabetes receiving multiple daily insulin injections: a randomized trial. *Ann Intern Med* 2017; **167:** 365–74.

20 Wright EE Jr, Kerr MSD, Reyes IJ, Nabutovsky Y, Miller E. Use of flash continuous glucose monitoring is associated with A1C reduction in people with type 2 diabetes treated with basal insulin or noninsulin therapy. *Diabetes Spectr* 2021; **34:** 184–89.

21 Wada E, Onoue T, Kobayashi T, et al. Flash glucose monitoring helps achieve better glycemic control than conventional self-monitoring of blood glucose in non-insulin-treated type 2 diabetes: a randomized controlled trial. *BMJ Open Diabetes Res Care* 2020; **8:** e001115.

22 Bolinder J, Antuna R, Geelhoed-Duijvestijn P, Kröger J, Weitgasser R. Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial. *Lancet* 2016; **388:** 2254–63.

23 Haak T, Hanaire H, Ajjan R, Hermanns N, Riveline J-P, Rayman G. Flash glucose-sensing technology as a replacement for blood glucose monitoring for the management of insulin-treated type 2 diabetes: a multicenter, open-label randomized controlled trial. *Diabetes Ther* 2017; **8:** 55–73.

24 Riddlesworth T, Price D, Cohen N, Beck RW. Hypoglycemic event frequency and the effect of continuous glucose monitoring in adults with type 1 diabetes using multiple daily insulin injections. *Diabetes Ther* 2017; **8:** 947–51.

25 Bergenstal RM, Mullen DM, Strock E, Johnson ML, Xi MX. Randomized comparison of self-monitored blood glucose (BGM) versus continuous glucose monitoring (CGM) data to optimize glucose control in type 2 diabetes. *J Diabetes Complications* 2022; **36:** 108106.

26 Díez-Fernández A, Rodríguez-Huerta MD, Mirón-González R, Laredo-Aguilera JA, Martín-Espinosa NM. Flash glucose monitoring and patient satisfaction: a meta-review of systematic reviews. *Int J Environ Res Public Health* 2021; **18:** 3123.

27 Gilbert TR, Noar A, Blalock O, Polonsky WH. Change in hemoglobin A1c and quality of life with real-time continuous glucose monitoring use by people with insulin-treated diabetes in the landmark study. *Diabetes Technol Ther* 2021; **23:** S35–39.

28 Polonsky WH, Hessler D, Ruedy KJ, Beck RW. The impact of continuous glucose monitoring on markers of quality of life in adults with type 1 diabetes: further findings from the DIAMOND randomized clinical trial. *Diabetes Care* 2017; **40:** 736–41.

29 Charleer S, Mathieu C, Nobels F, et al. Effect of continuous glucose monitoring on glycemic control, acute admissions, and quality of life: a real-world study. *J Clin Endocrinol Metab* 2018; **103:** 1224–32.

30 Charleer S, De Block C, Van Huffel L, et al. Quality of life and glucose control after 1 year of nationwide reimbursement of intermittently scanned continuous glucose monitoring in adults living with type 1 diabetes (FUTURE): a prospective observational real-world cohort study. *Diabetes Care* 2020; **43:** 389–97.

31 Roussel R, Riveline J-P, Vicaut E, et al. Important drop in rate of acute diabetes complications in people with type 1 or type 2 diabetes after initiation of flash glucose monitoring in France: the RELIEF study. *Diabetes Care* 2021; **44:** 1368–76.

32 Riveline J-P, Roussel R, Vicaut E, et al. Reduced rate of acute diabetes events with flash glucose monitoring is sustained for two-years after initiation: extended outcomes from the RELIEF study. *Diabetes Technol Ther* 2022; **24:** 611–18.

33 Beck RW, Bergenstal RM. Continuous glucose monitoring for type 2 diabetes: how does it compare with type 1 diabetes? *Diabetes Technol Ther* 2022; **24:** 153–56.

34 Petrie JR, Peters AL, Bergenstal RM, Holl RW, Fleming GA, Heinemann L. Improving the clinical value and utility of CGM systems: issues and recommendations: a joint statement of the European Association for the Study of Diabetes and the American Diabetes Association Diabetes Technology Working Group. *Diabetologia* 2017; **60:** 2319–28.

35 Schnell O, Barnard K, Bergenstal R, et al. Role of continuous glucose monitoring in clinical trials: recommendations on reporting. *Diabetes Technol Ther* 2017; **19:** 391–99.

36 Freckmann G, Pleus S, Grady M, Setford S, Levy B. Measures of accuracy for continuous glucose monitoring and blood glucose monitoring devices. *J Diabetes Sci Technol* 2019; **13:** 575–83.

37 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:** 787–94.

38 American Diabetes Association. Diabetes technology: standards of medical care in diabetes—2021. *Diabetes Care* 2021; **44** (suppl 1)**:** S85–99.

39 Alva S, Bailey T, Brazg R, et al. Accuracy of a 14-day factory-calibrated continuous glucose monitoring system with advanced algorithm in pediatric and adult population with diabetes. *J Diabetes Sci Technol* 2022; **16:** 70–77.

40 Shah VN, Laffel LM, Wadwa RP, Garg SK. Performance of a factory-calibrated real-time continuous glucose monitoring system utilizing an automated sensor applicator. *Diabetes Technol Ther* 2018; **20:** 428–33.

41 Christiansen MP, Garg SK, Brazg R, et al. Accuracy of a fourth-generation subcutaneous continuous glucose sensor. *Diabetes Technol Ther* 2017; **19:** 446–56.

42 Kropff J, Choudhary P, Neupane S, et al. Accuracy and longevity of an implantable continuous glucose sensor in the PRECISE Study: a 180-day, prospective, multicenter, pivotal trial. *Diabetes Care* 2017; **40:** 63–68.

43 Garg SK, Kipnes M, Castorino K, et al. Accuracy and safety of Dexcom G7 continuous glucose monitoring in adults with diabetes. *Diabetes Technol Ther* 2022; **24:** 373–80.

44 Garg SK, Liljenquist D, Bode B, et al. Evaluation of accuracy and safety of the next-generation up to 180-day long-term implantable eversense continuous glucose monitoring system: the PROMISE study. *Diabetes Technol Ther* 2022; **24:** 84–92.

45 Wadwa RP, Laffel LM, Shah VN, Garg SK. Accuracy of a factory-calibrated, real-time continuous glucose monitoring system during 10 days of use in youth and adults with diabetes. *Diabetes Technol Ther* 2018; **20:** 395–402.

46 Lorenz C, Sandoval W, Mortellaro M. Interference assessment of various endogenous and exogenous substances on the performance of the Eversense long-term implantable continuous glucose monitoring system. *Diabetes Technol Ther* 2018; **20:** 344–52.

47 Maahs DM, DeSalvo D, Pyle L, et al. Effect of acetaminophen on CGM glucose in an outpatient setting. *Diabetes Care* 2015; **38:** e158–59.

48 Heinemann L. Interferences with CGM systems: practical relevance? *J Diabetes Sci Technol* 2022; **16:** 271–74.

49 van der Linden J, Welsh JB, Walker TC. Sustainable use of a real-time continuous glucose monitoring system from 2018 to 2020. *Diabetes Technol Ther* 2021; **23:** 508–11.

50 Joseph JI. Review of the long-term implantable Senseonics continuous glucose monitoring system and other continuous glucose monitoring systems. *J Diabetes Sci Technol* 2021; **15:** 167–73.

51 Ward JEF, Stetson BA, Mokshagundam SPL. Patient perspectives on self-monitoring of blood glucose: perceived recommendations, behaviors and barriers in a clinic sample of adults with type 2 diabetes. *J Diabetes Metab Disord* 2015; **14:** 43.

52 Sølvik UØ, Risa M, Jacobsen CE, Monsen G, Sandberg S. Performance of 10 systems for self-monitoring of blood glucose by trained healthcare professionals and in the hands of the users. *Clin Chem* 2015; **61:** 772–74.

53 Garg SK, Akturk HK. A new era in continuous glucose monitoring: Food and Drug Administration creates a new category of factory-calibrated nonadjunctive, interoperable class II medical devices. *Diabetes Technol Ther* 2018; **20:** 391–94.

54 Bailey TS, Alva S. Landscape of continuous glucose monitoring (CGM) and integrated CGM: accuracy considerations. *Diabetes Technol Ther* 2021; **23:** S5–11.

55 Phillip M, Nimri R, Bergenstal RM, et al. Consensus recommendations for the use of automated insulin delivery (AID) technologies in clinical practice. *Endocr Rev* 2022; bnac022.

56 Ajjan RA, Cummings MH, Jennings P, Leelarathna L, Rayman G, Wilmot EG. Accuracy of flash glucose monitoring and continuous glucose monitoring technologies: implications for clinical practice. *Diab Vasc Dis Res* 2018; **15:** 175–84.

57 Klonoff DC, Lias C, Vigersky R, et al. The surveillance error grid. *J Diabetes Sci Technol* 2014; **8:** 658–72.

58 Heinemann L, Schoemaker M, Schmelzeisen-Redecker G, et al. Benefits and limitations of MARD as a performance parameter for continuous glucose monitoring in the interstitial space. *J Diabetes Sci Technol* 2020; **14:** 135–50.

59 Beck RW, Riddlesworth TD, Ruedy KJ, et al. Effect of initiating use of an insulin pump in adults with type 1 diabetes using multiple daily insulin injections and continuous glucose monitoring (DIAMOND): a multicentre, randomised controlled trial. *Lancet Diabetes Endocrinol* 2017; **5:** 700–08.

60 Bajaj HS, Chu L, Bansal N, et al. Randomized comparison of initiating the fixed-ratio combination of iGlarLixi or biosimilar insulin glargine together with gliclazide in participants of south Asian origin with type 2 diabetes: VARIATION 2 SA trial. *Can J Diabetes* 2022; **46:** 495–502.

61 Ogawa W, Hirota Y, Osonoi T, et al. Effect of the FreeStyle Libre flash glucose monitoring system on glycemic control in individuals with type 2 diabetes treated with basal-bolus insulin therapy: an open label, prospective, multicenter trial in Japan. *J Diabetes Investig* 2021; **12:** 82–90.

62 Dexcom. User manual. www.dexcom.com/en-GB/downloadsandguides/search (accessed Oct 1, 2022).

63 Denham D. Effect of repeated doses of acetaminophen on a continuous glucose monitoring system with permselective membrane. *J Diabetes Sci Technol* 2021; **15:** 517–18.

64 Dunn TC, Xu Y, Hayter G, Ajjan RA. Real-world flash glucose monitoring patterns and associations between self-monitoring frequency and glycaemic measures: a European analysis of over 60 million glucose tests. *Diabetes Res Clin Pract* 2018; **137:** 37–46.

65 Lane WS, Weinrib SL, Lawrence MJ, Lane BC, Jarrett RT. Basal Insulin degludec and glycemic control compared to aspart via insulin pump in type 1 diabetes (BIGLEAP): a single-center, open-label, randomized, crossover trial. *Endocr Pract* 2022; **28:** 165–72.

66 Renard E, Tubiana-Rufi N, Bonnemaison-Gilbert E, et al. Closed-loop driven by control-to-range algorithm outperforms threshold-low-glucose-suspend insulin delivery on glucose control albeit not on nocturnal hypoglycaemia in prepubertal patients with type 1 diabetes in a supervised hotel setting. *Diabetes Obes Metab* 2019; **21:** 183–87.

67 Bergenstal RM, Beck RW, Close KL, et al. Glucose management indicator (GMI): a new term for estimating A1C from continuous glucose monitoring. *Diabetes Care* 2018; **41:** 2275–80.

68 Perlman JE, Gooley TA, McNulty B, Meyers J, Hirsch IB. HbA_{1c} and glucose management indicator discordance: a real-world analysis. *Diabetes Technol Ther* 2021; **23:** 253–58.

69 DiMeglio LA, Acerini CL, Codner E, et al. ISPAD Clinical Practice Consensus Guidelines 2018: glycemic control targets and glucose monitoring for children, adolescents, and young adults with diabetes. *Pediatr Diabetes* 2018; **19** (suppl 27)**:** 105–14.

70 Boscari F, Ferretto S, Cavallin F, Bruttomesso D. Switching from predictive low glucose suspend to advanced hybrid closed loop control: effects on glucose control and patient reported outcomes. *Diabetes Res Clin Pract* 2022; **185:** 109784.

71 Battelino T, Bergenstal RM, Rodríguez A, et al. Efficacy of once-weekly tirzepatide versus once-daily insulin degludec on glycaemic control measured by continuous glucose monitoring in adults with type 2 diabetes (SURPASS-3 CGM): a substudy of the randomised, open-label, parallel-group, phase 3 SURPASS-3 trial. *Lancet Diabetes Endocrinol* 2022; **10:** 407–17.

72 Riddlesworth TD, Beck RW, Gal RL, et al. Optimal sampling duration for continuous glucose monitoring to determine long-term glycemic control. *Diabetes Technol Ther* 2018; **20:** 314–16.

73 Rama Chandran S, Jacob P, Choudhary P. Baseline glucose variability and interweek variability affects the time to stability of continuous glucose monitoring-derived glycemic indices. *Diabetes Technol Ther* 2020; **22:** 937–42.

74 Herrero P, Alalitei A, Reddy M, Georgiou P, Oliver N. Robust determination of the optimal continuous glucose monitoring length of intervention to evaluate long-term glycemic control. *Diabetes Technol Ther* 2021; **23:** 314–19.

75 Seibold A, Schlaeger C. Comparison of continuous and flash glucose monitoring in type 1 diabetes: methodological inconsistency precludes hypoglycaemia conclusions. *Diabet Med* 2018; **35:** 1618–19.

76 Oliver N, Reddy M. Reply to Seibold and Schlaeger: comparison of continuous and flash glucose monitoring in type 1 diabetes: methodological inconsistency precludes hypoglycaemia conclusions. *Diabet Med* 2018; **35:** 1619–20.

77 Xing D, Kollman C, Beck RW, et al. Optimal sampling intervals to assess long-term glycemic control using continuous glucose monitoring. *Diabetes Technol Ther* 2011; **13:** 351–58.

78 Camerlingo N, Vettoretti M, Sparacino G, et al. Design of clinical trials to assess diabetes treatment: minimum duration of continuous glucose monitoring data to estimate time-in-ranges with the desired precision. *Diabetes Obes Metab* 2021; **23:** 2446–54.

79 Holt RIG, DeVries JH, Hess-Fischl A, et al. The management of type 1 diabetes in adults. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia* 2021; **64:** 2609–52.

80 Hermanns N, Ehrmann D, Heinemann L, Freckmann G, Waldenmaier D, Calhoun P. Real-time continuous glucose monitoring can predict severe hypoglycemia in people with type 1 diabetes: combined analysis of the HypoDE and DIAMOND trials. *Diabetes Technol Ther* 2022; **24:** 603–10.

81 Shah VN, DuBose SN, Li Z, et al. Continuous glucose monitoring profiles in healthy nondiabetic participants: a multicenter prospective study. *J Clin Endocrinol Metab* 2019; **104:** 4356–64.

82 Gold AE, MacLeod KM, Frier BM. Frequency of severe hypoglycemia in patients with type I diabetes with impaired awareness of hypoglycemia. *Diabetes Care* 1994; **17:** 697–703.

83 Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. *Diabetes Care* 2009; **32:** 1335–43.

84 Beck RW, Bergenstal RM, Riddlesworth TD, et al. Validation of time in range as an outcome measure for diabetes clinical trials. *Diabetes Care* 2019; **42:** 400–05.

85 Lu J, Ma X, Zhou J, et al. Association of time in range, as assessed by continuous glucose monitoring, with diabetic retinopathy in type 2 diabetes. *Diabetes Care* 2018; **41:** 2370–76.

86 Li F, Zhang Y, Li H, et al. TIR generated by continuous glucose monitoring is associated with peripheral nerve function in type 2 diabetes. *Diabetes Res Clin Pract* 2020; **166:** 108289.

87 Yang J, Yang X, Zhao D, Wang X, Wei W, Yuan H. Association of time in range, as assessed by continuous glucose monitoring, with painful diabetic polyneuropathy. *J Diabetes Investig* 2021; **12:** 828–36.

88 Lu J, Ma X, Shen Y, et al. Time in range is associated with carotid intima-media thickness in type 2 diabetes. *Diabetes Technol Ther* 2020; **22:** 72–78.

89 Lu J, Wang C, Shen Y, et al. Time in range in relation to all-cause and cardiovascular mortality in patients with type 2 diabetes: a prospective cohort study. *Diabetes Care* 2021; **44:** 549–55.

90 Montaser E, Fabris C, Kovatchev B. Essential continuous glucose monitoring metrics: the principal dimensions of glycemic control in diabetes. *Diabetes Technol Ther* 2022; **24:** 797–804.

91 Conget I, Mangas MÁ, Morales C, et al. Effectiveness and safety of insulin glargine 300 U/ml in comparison with insulin degludec 100 U/ml evaluated with continuous glucose monitoring in adults with type 1 diabetes and suboptimal glycemic control in routine clinical practice: the OneCARE study. *Diabetes Ther* 2021; **12:** 2993–3009.

92 Battelino T, Danne T, Edelman SV, et al. CGM-based time-in-range using insulin glargine 300 Units/mL versus insulin degludec 100 Units/mL in type 1 diabetes: the head-to-head randomized controlled InRange trial. *Diabetes Obes Metab* 2022; dom.14898.

93 Paldus B, Morrison D, Zaharieva DP, et al. A randomized crossover trial comparing glucose control during moderate-intensity, high-intensity, and resistance exercise with hybrid closed-loop insulin delivery while profiling potential additional signals in adults with type 1 diabetes. *Diabetes Care* 2022; **45:** 194–203.

94 McAuley SA, Trawley S, Vogrin S, et al. Closed-loop insulin delivery versus sensor-augmented pump therapy in older adults with type 1 diabetes (ORACL): a randomized, crossover trial. *Diabetes Care* 2022; **45:** 381–90.

95 Kovatchev BP. Metrics for glycaemic control—from HbA_{1c} to continuous glucose monitoring. *Nat Rev Endocrinol* 2017; **13:** 425–36.

96 Klonoff DC, Wang J, Rodbard D, et al. A Glycemia Risk Index (GRI) of hypoglycemia and hyperglycemia for continuous glucose monitoring validated by clinician ratings. *J Diabetes Sci Technol* 2022; 19322968221085273.

97 Gomez-Peralta F, Choudhary P, Cosson E, Irace C, Rami-Merhar B, Seibold A. Understanding the clinical implications of differences between GMI and HbA_{1c}. *Diabetes Obes Metab* 2022; **24:** 599–608.

98 Monnier L, Colette C, Wojtusciszyn A, et al. Toward defining the threshold between low and high glucose variability in diabetes. *Diabetes Care* 2017; **40:** 832–38.

99 Mazze RS, Lucido D, Langer O, Hartmann K, Rodbard D. Ambulatory glucose profile: representation of verified self-monitored blood glucose data. *Diabetes Care* 1987; **10:** 111–17.

100 Bergenstal RM, Ahmann AJ, Bailey T, 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.

101 Kröger J, Reichel A, Siegmund T, Ziegler R. Clinical recommendations for the use of the ambulatory glucose profile in diabetes care. *J Diabetes Sci Technol* 2020; **14:** 586–94.

102 Bergenstal RM, Simonson GD, Heinemann L. More green, less red: how color standardization may facilitate effective use of CGM data. *J Diabetes Sci Technol* 2022; **16:** 3–6.

103 Raghinaru D, Calhoun P, Bergenstal RM, Beck RW. The optimal duration of a run-in period to initiate continuous glucose monitoring for a randomized trial. *Diabetes Technol Ther* 2022; dia.2022.0274.

104 Klueh U, Liu Z, Feldman B, et al. Metabolic biofouling of glucose sensors in vivo: role of tissue microhemorrhages. *J Diabetes Sci Technol* 2011; **5:** 583–95.

105 Kenneth Ward W. A review of the foreign-body response to subcutaneously-implanted devices: the role of macrophages and cytokines in biofouling and fibrosis. *J Diabetes Sci Technol* 2008; **2:** 768–77.

106 Gerritsen M, Jansen JA, Kros A, et al. Influence of inflammatory cells and serum on the performance of implantable glucose sensors. *J Biomed Mater Res* 2001; **54:** 69–75.

107 Ribet F, Stemme G, Roxhed N. Real-time intradermal continuous glucose monitoring using a minimally invasive microneedle-based system. *Biomed Microdevices* 2018; **20:** 101.

108 Helton KL, Ratner BD, Wisniewski NA. Biomechanics of the sensor-tissue interface-effects of motion, pressure, and design on sensor performance and foreign body response-part II: examples and application. *J Diabetes Sci Technol* 2011; **5:** 647–56.

109 Ertefai S, Gough DA. Physiological preparation for studying the response of subcutaneously implanted glucose and oxygen sensors. *J Biomed Eng* 1989; **11:** 362–68.