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COMMENTARY

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Minimum expectations for market authorization of continuous glucose monitoring devices in Europe—'eCGM' compliance status

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1 | INTRODUCTION

Accurate determination of blood glucose concentrations is essential for daily diabetes management, for people with type 1 diabetes (T1D), type 2 diabetes (T2D) and gestational diabetes (GDM), in particular for those using insulin in their treatment. Capillary blood glucose meters (BGM) are the most common devices used for this purpose and typically measure glucose levels from whole blood following fingerpricking.[1] However, the displayed test results actually reflect glucose concentrations in the plasma, which may be 10%–15% higher than in whole blood.[2] The accuracy of BGM systems is covered by ISO 15197:2013, which ensures they meet minimum specific design verification and performance validation standards. The use of BGM for measuring glucose levels for people with diabetes, especially T1D, is increasingly being replaced by continuous glucose monitoring (CGM) systems, which measure glucose levels in the interstitial fluid (ISF) and convert this reading into a close approximation of plasma-glucose levels, using advanced algorithms. The widespread use of CGM technology has been driven in the last decade, in part by the availability of affordable CGM systems with proven accuracy at least

as good as the majority of BGM devices, that provide continuous readings throughout the day and overnight.[3] Unlike earlier CGM systems, many currently available devices are so-called non-adjunctive systems, which mean that users can make treatment decisions based on their CGM readings alone, without the need to confirm this with a BGM finger prick test reading.[4] A wealth of randomized controlled trial (RCT) data and real-world evidence has shown that, compared to BGM devices, the use of CGM systems by people with insulin-treated T1D or people with T2D on insulin or non-insulin therapies, regardless of age, leads to improvements in measures of glycemia, including HbA1c, and reduced hypoglycemia during the day and overnight, with consequent increases in patient-reported quality of life (QoL) and psychological wellbeing.[5–10]

Alongside their value as stand-alone devices for people with diabetes, CGM sensors can also be connected with continuous subcutaneous insulin infusion (CSII) pumps, either as part of sensor-augmented pump (SAP) therapy or as components of hybrid closed-loop (HCL) automated insulin delivery (AID) systems.[11] For individuals on intensive insulin therapy using multiple daily injections (MDI), a CGM device can be paired with a smart insulin pen to improve the timing and frequency of insulin doses, with a reduction in missed doses, to significantly improve time in range (TIR).[12] For these reasons, it is vital that CGM devices are able to meet accuracy and performance standards that ensure their role in interconnected digital ecosystems is safe and effective. An unintended consequence of the successful and widespread adoption and integration of CGM systems across all areas of diabetes clinical practice is the associated risk that errors in device accuracy and performance may lead to patient harm. This possibility was highlighted early in the clinical development and use of CGM systems, with calls to action for better European Union (EU) regulation of diabetes technologies.[13] However, issues with the accuracy and safety of CGM systems are now being reported, linked to poor sensor accuracy and performance. In 2022, concerns were raised about a device selected by healthcare administrators following a winner-takes-all tender to supply CGM systems for people with diabetes on insulin therapy in the Campania region in Italy.[14,15] Despite the CGM device being CE marked, users and clinicians reported poor accuracy at low and high glucose levels, serious enough that clinicians refrained from prescribing the system and recommended that CGM users returned to using finger prick blood glucose meters, which were also reimbursed.[15] Among the approximately 400 000 people with diabetes in the region, around 20 000 individuals on intensive insulin therapy were penalized by this outcome. The matter was ultimately escalated to the Italian parliament. In June 2024, the Association of British Clinical Diabetologists (ABCD) raised concerns about the lack of published evidence to support the claimed performance of a CE-Marked HCL system included in the NHS England supply chain, which was associated with instances of hypoglycemia for users in an NHS England Pilot of HCL systems.[16] The ABCD reported similar concerns from specialists with experience of the same HCL system outside of the UK. To date, the manufacturers of the systems described have not made available the requested efficacy and safety evidence.

2 | THE NEED TO DEFINE MINIMUM ACCURACY AND PERFORMANCE STANDARDS FOR THE CONFORMITY ASSESSMENT OF CGM DEVICES IN EUROPE

The Conformité Européenne (CE) process is a requirement for many products fulfilling the definition of a medical device in the applicable legislation before they can be marketed in Europe, which includes all 29 current members of the European Union and the European Free Trade Association (EFTA). A CE mark, once issued, is intended to indicate that a product has been designed, tested, verified, validated and assessed for its conformity by the manufacturer in line with the applicable legislative and state-of-the-art requirements and, when applicable, assessed by a designated Notified Body (see Box 1). Non-adjunctive CGM systems are categorized as Class IIb medical devices with moderate to high risk. However, the current and proposed set of guidance documents and/or standards utilized in the Conformity Assessment process do not provide CGM-specific product-evaluation criteria to guarantee that a device has been adequately assessed for safety, performance and benefit in the population of people with diabetes in which the product may be used.

Just as pressing, the rapid growth in the use of interconnected diabetes devices for the management of daily glycemic health means that standards, setting minimum criteria for clinical investigations that assess performance and reliability, are needed for any CGM device that is a component of an interconnected system. Currently, for manufacturers of CGM devices and other diabetes technologies, it is possible to attain a CE mark without the support of standardized clinical investigation criteria that ensure harmonization and consistent compliance statements across the EU single market. The requirement for more rigorous CGM device regulation is accepted and, for the medium-to-long term, the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) has established a working group with the aim to develop International Organization for Standardization (ISO) minimum standards for the accuracy of CGM devices,[17] but these are not imminent. In contrast, the widespread and increasing use of CGM systems in Europe is an immediate reality. This defines an urgent unmet need for a minimum set of requirements for clinical

BOX 1 What is a Notified Body?

- Designated by EU and EFTA member states.
- Independent, transparent and impartial organizations with the expertise and resources to undertake medical device assessment based on the QMS information provided.
- Must be involved for a Class IIb medical device to be CE marked.
- Manufacturers can choose any Notified Body that is designated for the medical device under review.

testing and performance metrics for CGM systems, to provide a basic level of safety to users in Europe. Meeting this minimum set of standards may be recognized by an eCGM compliance status that denotes the system has undergone a certification process beyond what is required for CE marking.

3 | DEFINING CLINICAL INVESTIGATION OF CGM SYSTEMS IS A CRITICAL UNMET NEED

Since May 2021, the applicable EU Medical Device Regulation (MDR) has been MDR 2017/745/EU,[18] which defines a clinical investigation as 'any systematic investigation involving one or more human subjects, undertaken to assess the safety or performance of a device'. A clinical evaluation has a wider definition and '…shall follow a defined and methodologically sound procedure based on the following: (a) a critical evaluation of the relevant scientific literature currently available relating to the safety, performance, design characteristics and intended purpose of the device; (b) a critical evaluation of the results of all available clinical investigations; and (c) a consideration of currently available alternative treatment options for that purpose, if any'. As Class IIb devices, clinical investigations are mandatory for new CGM systems without a demonstrated equivalence with an already CE-Marked device. Overall, the introduction of MDR 2017/745/EU was intended to tighten regulation and ensure the safety and efficacy of medical devices, including the provision of greater oversight of Notified Bodies by national authorities.

A CE mark for a CGM system is awarded through a multistep process that requires the manufacturer to demonstrate that it can provide the CGM device and related services to the product users (customers) that consistently meet their needs and also fulfil all applicable regulatory requirements. A clear and detailed exploration of this process as it pertains to CGM devices has been recently published.[19] Briefly, the conformity assessment is achieved using a quality management system (QMS), through which the manufacturer validates that the design and production processes meet EU safety and environmental requirements, that labelling and descriptive materials accompanying the device are fit for purpose, as well as providing a summary of the risks of using the device and a risk management plan/report to address these. Importantly, the QMS must provide a clinical evaluation and, when applicable, a clinical investigation plan/report for the CGM device. Once all this information is compiled, the next step is for it to be audited by a Notified Body, which can assess compliance with applicable regulatory standards. Both the QMS process audit and the technical documentation assessment of the Notified Bodies must be compliant with applicable legislations by covering state-of-the-art standards such as ISO 13485, which covers quality management for medical device manufacturers but does not provide guidance on how to assess the quality, efficacy and safety for individual devices.

Ultimately, in the current EU regulatory landscape, medical device manufacturers and Notified Bodies are operating without clear guidance on how to assess the quality, efficacy, and safety of CGM devices entering the European single market. The existing requirements for clinical investigation or evaluation of CGM devices can be interpreted very widely and may be limited to studies in which the safety and efficacy of a system have been insufficiently validated before it is awarded a CE mark and distributed for use by people with diabetes. In this environment, it is vital that manufacturers and Notified Bodies have clear guidance as to the minimum expectations for clinical and technical data that support the award of a CE mark to a CGM device.

4 | PERFORMANCE OF CGM DEVICES — ACCURACY AND PRECISION

Demonstrated accuracy and precision in the detection of glucose in the ISF is an essential prerequisite of CGM systems, which empowers people with diabetes to make appropriate treatment decisions in daily life. This accuracy can be measured as analytical point accuracy, clinical point accuracy and trend accuracy.[3] Precision refers to the consistency of the system and is often assessed by comparing how close a series of glucose readings from separate sensors, used at the same time on a study subject, are to each other. All metrics of precision and accuracy for CGM sensors are influenced by the glucose range being investigated, the dynamic of glucose fluctuations, the study design and the number of paired readings that are evaluated. It is not the task of this consensus opinion to discuss the relative benefits and deficiencies of the currently applied metrics of accuracy and precision of CGM devices, and we refer the reader to other authoritative reviews and opinions on these topics.[19,20] However, it is important that any measure of accuracy for a CGM device has been validated thoroughly against accepted reference values and using the most appropriate protocols currently adopted by international agencies. When performing in-clinic studies guided by frequent sampling period (FSP) protocols, the selection of the comparator blood glucose sample against which CGM performance will be checked is an important consideration.[21] Capillary and venous blood samples will provide differing comparator values for the ISF readings obtained by the CGM sensor being tested. Thus, when performing head-to-head comparisons of CGM readings with those from a clinical laboratory grade analyser, the test sample must be consistently obtained from either capillary or venous blood. A detailed exploration of potential study protocols and bench testing scenarios are outside the scope of this current article, but can be reviewed in a comprehensive 2024 article from the Working Group on Continuous Glucose Monitoring,[21] established by the IFCC.[17]

What is proposed herein are a set of minimum requirements, both for the accuracy and precision of a candidate CGM system and for the tested clinical efficacy of the candidate system in defined populations of people with diabetes, against which formal approval for marketing approval can be evaluated. For example, accuracy claims for distinct age ranges must be accompanied by study data collected in distinct age groups according to a standardized study design.

5 | MINIMUM REQUIREMENTS FOR PRE-MARKET CLINICAL INVESTIGATION OF CGM SYSTEMS

We propose a set of minimum requirements that must be met by any manufacturer submitting evidence to an accredited Notified Body for CE marking conformity assessment of a CGM device in the European healthcare marketplace (Table 1; Figure 1). Minimum accuracy and performance standards for CGM user protection already exist in the United States, through the Federal Drug Administration integrated CGM (iCGM) requirement 21CFR862.1355. It is accepted that CGM devices not meeting these proposed requirements for conformity assessment in Europe may exceptionally be accepted as safe and effective if they have previously been assessed against comparable minimum standards outlined here. For example, where US FDA pre-market CGM-specific evaluation of safety and efficacy has been confirmed in the population of people with diabetes. However, meeting the minimum requirements proposed here allows a faster regulatory pathway.

For what we propose, the clinical data used to support conformity assessment and CE marking in Europe must be obtained from clinical investigations that fully test the performance of the device in each of the intended use populations (accepting reasonable exclusions, for example, very young children, pregnant women), across the measuring range of the device and throughout the designated wear life of the system. To ensure data transparency, performance data should be presented in the instructions for use, included in the package inserts that accompany the device, published in peer-reviewed journals registered in the Science Citation Index (SCI) or otherwise made available in publicly accessible databases, per applicable legislative requirements. The CGM devices covered by the proposed minimum standard will be those designed for non-adjunctive use, with or without a requirement for user calibration, which is not in itself a barrier. Factory-calibrated CGM systems eliminate user calibration errors which compromise accuracy, and reduce burden for users. Devices currently on the market that already meet the proposed minimum expectations, including the requirement for full disclosure of their performance data as described above, can be assigned eCGM compliance status.

The performance requirements for adult CGM users should meet all the criteria detailed in Table 1, which together assess accuracy and precision in hypoglycemia, hyperglycemia, euglycemia and rates of dynamic change between these states. Management of each of these aspects of daily glucose are critical to the health and safety of a person with diabetes. When assessing the performance in each glucose range, it is more important to have a greater number of people with CGM data in the different concentration ranges, rather than fewer people with a lot of paired readings (test device and reference blood glucose analyser pairs). Sample size calculations indicate that approximately 100 subjects should be included in the performance assessment study to generate sufficient paired readings for objective statistical confirmation of a clinically relevant difference.[22] For example, a study with 100 subjects with 3 in-clinic visits of 10 hours each, drawing blood every 15 mins, would provide around 12 000 paired data points to compare.

Paediatric data should be collected similarly to the adult performance requirements but, because of the more-restricted amount of paired data possible in children, the same performance requirements may not be met. Venous reference pairs are not collected for children <6 years old, in whom approximately 100 simple BGM reference pairs are collected (using an ISO standard-conformant BGM meter), to get around 100 or so paired points total for each subject. For children 6–17 years, the amount of blood that can be drawn depends on their weight, again limiting the number of paired readings. Glycemic challenges are done only for children 11 years and older. With these caveats, about 4000 paired data points is a reasonable estimate for paediatric subjects. This may not be sufficient to meet the proposed minimum CGM performance requirements as per Table 1, but it is important that the available paired data show concordance with adult datasets.

TABLE 1 Proposed minimum performance requirements for regulatory approval of CGM devices in Europe.

Glucose range	Performance against reference reading	Lower boundary of 95% confidence interval (CI)
<70 mg/dL mg/dL (<3.9 mmol/L)	Within ± 15 mg/dL	>85% of readings
70–180 mg/dL (3.9–10.0 mmol/L)	Within ± 15%	>70% of readings
>180 mg/dL (>10.0 mmol/L)	Within ± 15%	>80% of readings
<70 mg/dL (<3.9 mmol/L)	Within ± 40 mg/dL	>98% of readings
70–180 mg/dL (3.9–10.0 mmol/L)	Within ± 40%	>99% of readings
>180 mg/dL (>10.0 mmol/L)	Within ± 40%	>99% of readings
Across the reportable range	Within ± 20%	>87%
Overall, across all glucose measuring ranges	Within ± 20%	>87% of readings
CGM <70 mg/dL (<3.9 mmol/L) when reference > 180 mg/dL (>10.0 mmol/L)		0% of readings
CGM >180 mg/dL (>10.0 mmol/L) when reference < 70 mg/dL (<3.9 mmol/L)		0% of readings
CGM ROC > − 1 mg/dL/min when reference ROC < −2 mg/dL/min		<1% of readings
CGM ROC < −1 mg/dL/min when reference ROC > −2 mg/dL/min		<1% of readings

Abbreviations: CGM, continuous glucose monitor; CI confidence interval; ROC, rate of change.

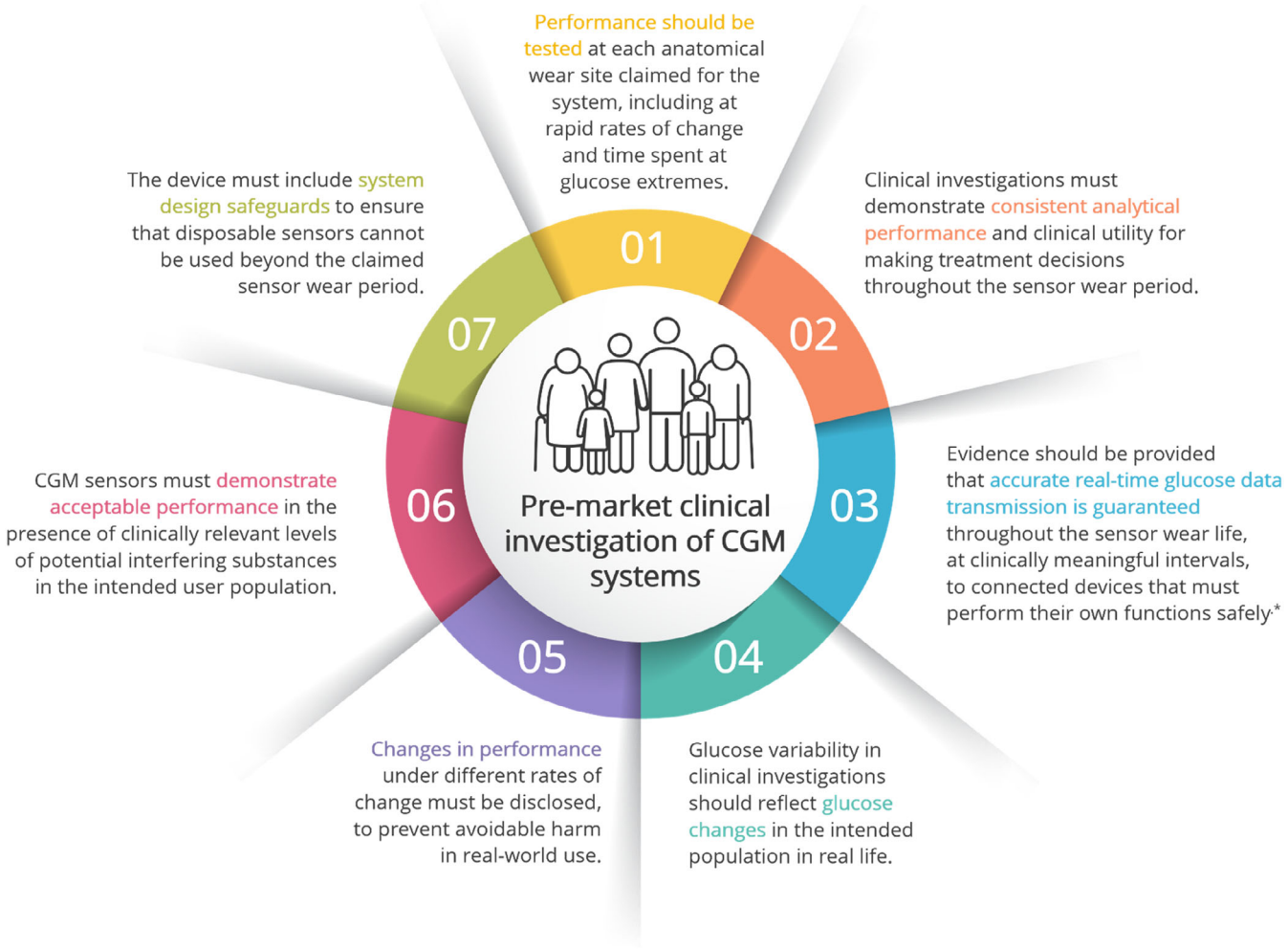

FIGURE 1 Minimum accuracy and performance requirements for safeguarding people with diabetes when using CGM systems. The figure illustrates the proposed minimum requirements for conformity assessment and CE marking of CGM devices within the EU and EFTA regions. *CGM data privacy and cybersecurity safeguards must meet European data protection laws. All clinical data from studies submitted for conformity assessment and CE marking must be fully disclosed on the product label at the point of marketing. CGM, continuous glucose monitoring; EU, European Union; EFTA, European Free Trade Association.

5.1 | Proposed parameters for clinical investigation and device validation

We propose that the accuracy and precision metrics, provided in support of European conformity assessment and CE marking for a CGM system, should meet a standard sufficiently rigorous as to have credibly minimized the risk for harm to a person with diabetes using the system. The performance and safety in all possible user groups must be assessed in as many real-world situations as can reasonably be expected to generate accuracy and performance data. Conformity assessment and CE marking should not rely solely on data generated in clinical investigations that have been designed to limit or minimize variables that may adversely affect performance, since such data are likely to be inadequate for the assessment of CGM accuracy in daily life for a person with diabetes.

Clinical investigations should also anticipate advances in diabetes technology interconnectivity and data should also be collected during clinical investigations in regard of the user experience, as recommended by expert opinion,[23] to mitigate against devices that are not compliant with user needs (for example, adverse skin reactions, ease of use, sensor failure, disruption or displacement within the claimed wear life). With these considerations in mind, the proposed mandatory parameters for clinical investigation and device validation include the assessment of clinical performance; accuracy of glucose measurement; sensor lifetime and stability: data security and integrity; and transparency of assessment. These are listed below.

1. Performance should be tested at each anatomical wear site claimed for the system. Meal and insulin challenges, which investigate rapid rates of change and time spent at glucose extremes, should be included in this dataset. A minimum of 8% of paired comparator readings should be in the <70 mg/dL (<3.9 mmol/L) range and >5% of readings in the >300 mg/dL (>16.7 mmol/L) range.[24]

2. Clinical study results must demonstrate consistent analytical and clinical performance throughout the sensor wear period. The sensor is required to be tested at a minimum; at the beginning (days 1–3), middle and end of the sensor life,[24] including periods of rapid glucose fluctuation.
3. Performance should be tested in clinical investigations that can be expected to reflect glucose changes in the intended population in real life,[†] including glucose variability. Changes in performance under different rates of change (trend accuracy) must be disclosed as with other performance data.
4. CGM sensors must demonstrate clinically acceptable accuracy in the presence of clinically relevant levels of potential interfering substances that may reasonably be expected to be present in the intended user population. This should include, but not be limited to, endogenous substances and metabolites, foods, dietary supplements, and medications.
5. The device must include system design safeguards to ensure that disposable sensors cannot be used beyond the claimed sensor wear period.
6. Design verification and validation of a CGM system must provide evidence that secure and reliable real-time glucose data transmission is guaranteed at clinically meaningful time intervals to other connected devices intended to receive the real-time glucose data stream and perform their own functions safely.
7. Performance data must demonstrate that there are no clinically important gaps[‡] in the availability of sensor glucose data throughout the sensor wear life, as tested in conformity assessment studies, which would prevent other digitally connected devices from achieving their intended use in a safe and effective manner.
8. System design and data management specifications should provide for data privacy and cybersecurity safeguards that meet European data protection laws.
9. All data from clinical investigations must be fully disclosed in the product label, for each intended user population, at the point of marketing.
10. CGM performance should be assessed using at least three separate sensor manufacturing lots, which should be verified for regulatory purposes.

In addition to the minimum requirements specified, the following requirement is recommended: at each anatomical insertion site, the number of paired reference readings must be sufficient for confident determination of the accuracy claimed. For younger children, this should be a minimum of 2500 paired readings and at least 10 000 paired readings for adults.

6 | CONCLUSIONS

The minimum set of requirements for CGM accuracy and performance proposed above will create an environment in which clinical investigations, data collection and data transparency will underpin each claim made for a candidate CGM system entering the European single marketplace following conformity assessment and CE marking. In this, they will parallel the rigour of the iCGM requirements already mandated by the US FDA for CGM devices. This will also mean that CGM marketing approval, once achieved in one European territory, will automatically fulfil the requirements of another.

AUTHOR CONTRIBUTIONS

The authors contributed equally to discussions and development of the opinions expressed in this article. All authors reviewed and contributed to serial drafts of the manuscript and approved the final content. Chantal Mathieu and Tadej Battelino are the overall guarantors. The authors thank Dr. Steffen Thirstrup, Chief Medical Officer of the European Medicines Agency (EMA) for reading the manuscript.

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CONFLICT OF INTEREST STATEMENT

CM serves or has served on the advisory panel for Dexcom, Medtronic and Insulet. Financial compensation for these activities has been received by KU Leuven; KU Leuven has received research support for CM from Medtronic; CM serves or has served on the speakers bureau for Medtronic. Financial compensation for these activities has been received by KU Leuven. CM is the president of EASD. All external support of EASD is to be found on www.easd.org. CI has provided advisory board services for Roche Diabetes Care Italy, Abbott, Ascensia and Senseonics and has received speaker fees from Roche Diabetes Care Italy, Abbott and Ascensia. EGW has received personal fees from Abbott, Dexcom, Embecta, Insulet, Medtronic, Roche, Sinocare and Ypsomed and research support from Abbott, Embecta and Insulet. BA has participated in EU Medical Device Regulation and has represented Notified Bodies at EU Level. SDP has served as president of EASD/European Foundation for the Study of Diabetes (EFSD) (2020–2022) and is the president of the European Diabetes Forum and of the Menarini Foundation; he has served as an advisor for Abbott. PA has received honoraria for speaking engagements from Dexcom, Insulet, Medtronic, Nordic InfuCare, Rubin Medical and Tandem and is on an advisory board for Insulet, Medtronic and Roche. PA has received an unrestricted grant from Rubin Medical, Sweden, which is a reseller of Tandem insulin pumps. TK has received research support from Medtronic; participated in advisory boards for Medtronic, Dexcom and Ascencia; and received speaker honoraria from Medtronic, Dexcom, Abbott and Ascencia. ER declares consultant/speaker fees from Abbott, Dexcom, Medtronic and Roche and research support from Abbott, Dexcom and Roche. TB has served on advisory panels for Medtronic, Abbott and Indigo Diabetes and received honoraria for participating on the speaker's bureau of Medtronic, Abbott, Dexcom and Roche. TB's Institution has received research grant support from Abbott, Medtronic, the Slovenian Research and Innovation Agency, the National Institutes of Health and the European Union.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Any data associated with this proposal are available from the corresponding author on reaasonable request.

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ENDNOTES

† Including in a population with a minimum of 70%–75% of people living with T1D to ensure performance in glucose variability. The comparator method selected should be one of laboratory grade (e.g. Yellow Spring Instruments or equivalent), with the sampling component clearly documented (venous blood, arterio-venous blood, capillary blood).[24]

‡ That is, CGM data is unavailable when a treatment decision must be managed, either by the user themselves or by an enabled interconnected device. For example, an insulin dosing event, an insulin dose estimation, or impending low or high glucose.

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