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Improving the Clinical Value and Utility of CGM Systems: Issues and Recommendations

Joint Position Statement

European Association for the Study of Diabetes and American Diabetes Association Diabetes Technology Working Group

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Abbreviations: AACE – American Association of Clinical Endocrinologists; AADE – American Association of Diabetes Educators; ADA – American Diabetes Association; AID – Automated Insulin Delivery; AGP – Ambulatory Glucose Profile; CDER – Center for Drug Evaluation and Research; CDRH – Center for Devices and Radiologic Health; CGM – Continuous Glucose Monitoring; CI – Confidence Intervals; CONGA – continuous overall net glycemic action; CSII – Continuous Subcutaneous Insulin Infusion; CV – coefficient of variation; EASD – European Association for the study of Diabetes; isCGM – intermittent scanning continuous glucose monitoring; IDF – International Diabetes Federation; IQR – interquartile range; ISPAD – International Society for Paediatric and Adolescent Diabetes; JDRF – Juvenile Diabetes Research Foundation; LBGI – low blood glucose index; MAGE – mean amplitude of glucose excursions; MDI – Multiple Daily Injections; MODD – mean of daily difference; PRO – Patient Reported Outcomes; RCT – Randomized Controlled Trial; rtCGM – real time Continuous Glucose monitoring; SD – total standard deviation; SMBG – Self Monitoring of Blood Glucose; T1D – type 1 Diabetes; T2D – type 2 Diabetes; TIR – time in range

Abstract

The first systems for continuous glucose monitoring (CGM) became available over 15 years ago. Many then believed CGM would revolutionize the use of intensive insulin therapy in diabetes; however, progress towards that vision has been gradual. Although increasing, the proportion of individuals using CGM rather than conventional systems for self-monitoring of blood glucose on a daily basis is still low in most parts of the world. Barriers to uptake include cost, measurement reliability (particularly with earlier generation systems), human factors issues, lack of a standardized format for displaying results, and uncertainty on how best to use CGM data to make therapeutic decisions. This Position Statement makes recommendations for systemic improvements in clinical usage and regulatory (pre- and post-marketing) handling of CGM devices. The aim is to improve safety and efficacy in order to support the advancement of the technology in achieving its potential to improve quality of life and health outcomes for more people with diabetes.

Introduction and Background

Continuous glucose monitoring (CGM) is a method of continuously following glucose levels in the interstitial fluid as a basis for improving metabolic control. This includes increasing time in the target glucose range by reducing hyperglycemia and minimizing the occurrence of low glucose values (including symptomatic hypoglycemia). The international diabetes community has welcomed the introduction of CGM systems. However, daily use of these devices is associated with challenges including potential risks.

There are several ways in which CGM functions. It can either be blinded to the user or viewed in real-time. The device sends data continuously to a receiver, which allows for alerts and alarms to be provided to the wearer. Recently a form of CGM known as "flash" glucose monitoring (Freestyle Libre, Abbott) became available from one manufacturer in some countries. Although this device is based on similar technology, daily costs are lower and no calibration is required but alarms are not provided for high and low glucose values. Interstitial glucose levels are measured continuously, but as data are not transmitted continuously from the sensor, the results are available only when the sensor is scanned with a reading device. Full 24 hour data can be captured and downloaded if the sensor is scanned at least every eight hours. This latter form of CGM will be described here as intermittently-scanned continuous glucose monitoring (isCGM) (1). The glucose sensors of most CGM systems are inserted subcutaneously and worn externally by the user, although implantable CGM devices are also becoming available (2).

Following an evaluation of insulin pumps (3), the same working group of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) has now evaluated CGM and related technologies from a clinical perspective. The aim was not to replicate published position statements and overviews of CGM technology (4,5,6), but instead to consider how health care professionals, CGM manufacturers, regulatory authorities, policymakers and consumers can best ensure effective and appropriate use of CGM as the technology continues to develop.

As only limited clinical trial data are required for approval of glucose monitoring devices, larger trials are often performed at a later stage with the aims of convincing payers to provide reimbursement and providing guidance on appropriate use. As such trials usually take three or more years, the marketed version of the CGM device has often been updated or modified by the time of publication. The rapidity of this development cycle means that a Position Statement can never be definitive nor comprehensive and requires regular updating.

Our goal was to assess current clinical and regulatory aspects of CGM within this rapidly-evolving landscape in order to encourage cycles of improvement in device performance, clinical outcomes, and utilization. We make a number of recommendations (marked as numbers in rectangular brackets), each targeted at relevant stakeholders

involved in delivering safe and effective use of CGM. We gathered evidence by searching Pubmed from inception until end of November 2016 using the search terms "continuous glucose monitoring [Title/ Abstract] OR real-time glucose monitoring [Title/ Abstract] OR subcutaneous continuous glucose monitoring [Title/ Abstract] OR continuous measurement of glucose [Title/ Abstract]." We supplemented this with information from recent trial publications, abstracts, web-based resources, regulatory authorities (including from their databases), manufacturing companies and our own clinical experience.

Clinical evidence

Growing evidence supports the benefits of using CGM: the studies and clinical trials reviewed below suggest that adults with type 1 Diabetes (T1D) who wear CGM most days can improve glycemic control without increasing hypoglycemia, while those already close to target HbA1c can maintain control while reducing hypoglycemia. In children and adolescents, achieving adequate adherence remains a significant barrier, although usability has improved with current generation CGM devices in this age group [2b].

a) Type 1 Diabetes (T1D): In the JDRF trial, 322 adults and children (≥8 years of age) with HbA1c 7.0-10.0% (53-86 mmol/mol), more than 80% using continuous subcutaneous insulin infusion (CSII), were randomized to three different CGM devices (Dexcom SEVEN (Dexcom), MiniMed Paradigm Real-Time Insulin Pump and Continous Glucose-Monitoring System (Medtronic), Freestyle Navigator (Abbott Diabetes Care)) or usual self-monitoring of blood glucose (SMBG). A significant improvement in the primary outcome of change in HbA1c at 26 weeks (-0.53%, 95% Confidence Intervals (CI) -0.71 to -0.35%) (-5.7 mmol/mol, 95% CI -7.7, -3.8) was observed only in the subgroup defined by age ≥25 years. This improvement was strongly associated with wearing the device for six or more days per week (7). In the recent DIAMOND study, in which 158 adults on multiple daily injections (MDI) were randomized (2:1) to CGM (Dexcom G4) or usual care for six months, baseline HbA1c (8.6%) (70.5 mmol/mol) improved by 1.0% (11.0 mmol/mol) with CGM and by 0.4% (4.3 mmol/mol) with usual care (adjusted mean difference 0.6% (6.5 mmol/mol), p<0.001); adherence was high (8). A further large crossover trial is in progress using the same device (9) and supportive cross-sectional real world data are available (with the various marketed devices) (10). The potential for CGM to take the place of (rather than augment) SMBG recently gained support from (REPLACE-BG), an open-label randomized trial of 226 adults with well-controlled T1D (HbA1c 7.1± 0.7% (54.0±7.6 mmol/mol) at baseline) that compared "CGM only" with "CGM and SMBG": SMBG in addition to CGM had no effect on time in range (70-180 mg/dL)(3.9-10.0 mmol/L), the primary endpoint (11). For this reason, the FDA recently (December 2016) approved a specific CGM device (Dexcom G5® Mobile CGM System) to

replace fingerstick glucose measurements in people with diabetes two years of age or older, although twice daily fingerstick calibrations remain necessary (12).

Some evidence with isCGM is also now available in T1D. In the recent IMPACT trial, 241 adults with T1D and HbA1c ≤7.5% (58.5 mmol/mol) (68% treated with MDI; 32% with CSII) wore an isCGM device for 14 days (Abbott Freestyle Libre) without access to glucose results. This period was then compared with a subsequent 14-day period when access to data was provided. The primary endpoint of time spent in hypoglycemia (<70 mg/dL)(<3.9 mmol/L) was reduced by almost 90 minutes per day (p<0.0001) with isCGM while time in hyperglycemia (>240 mg/dL)(>13.3 mmol/L) was also reduced by just over 20 minutes per day (p=0.0247); there was no change in HbA1c over this short period (13).

b) Type 2 Diabetes (T2D): Currently there is limited evidence to support the use of CGM in this large group of individuals: further studies are required [4a, 4b]: In a single center controlled trial (RCT) which randomized 100 people with T2D on a variety of therapies (excluding prandial insulin) to either SMBG or intermittent use of CGM (Dexcom SEVEN), a significant improvement in HbA1c from a baseline of 8.3% (67.2 mmol/mol) was observed over 12 weeks for CGM vs SMBG (1.0±1.1 vs 0.5±0.8%)(11.0±12.0 vs 5.4±8.7 mmol/mol) (14). The improvement was sustained (although attenuated) over a 40-week observational follow-up period (0.8±1.5 vs 0.2±1.3%)(8.7±16.3 vs 2.1±14.1 mmol/mol) (15). These data require replication using other CGM devices and in other populations with T2D, but provide support for periodic use of CGM in those using basal insulin (16).

In the case of isCGM, a six-month trial (REPLACE, Abbott Freestyle Libre) in people with T2D on basal-bolus insulin therapy and a baseline HbA1c of 8.8% (72.7 mmol/L) showed a significant reduction in time in hypoglycemia (by almost 30 minutes), but no change in HbA1c, the primary endpoint (17).

The above mentioned clinical studies have undoubtedly moved the field forward, but our review of the CGM literature revealed common design limitations, including:

(i) Few studies (18) including individuals with a recent history of severe hypoglycemia [4a]

(ii) Few head-to-head comparisons (19) between CGM systems [3e, 4a],

(iii) Lack of standardization of outcome measures for glycemic control and glucose variability [1c], an issue recently highlighted at an FDA workshop (20)

(iv) Lack of consensus on appropriate patient reported outcomes (PRO) (21-23) [1d, 2e, 3c]

(v) Insufficient statistical power to detect important outcomes (i.e. insufficient study duration/ sample size) [2e, 3e]

(vi) Lack of a standard reporting format for CGM data [1c, 2a]

(vii) Insufficient guidance for participants on how best to make therapeutic decisions on the basis of CGM data [5c]

(viii) Lack of adequate masking between active and comparator arms (with potential for a research participation or "Hawthorne" effect) (24) [4a]

Meta-analyses

A number of formal summaries of the CGM literature have been conducted (25-32). Although this suggests that the field is coming of age, review of the existing evidence base has generated diverse conclusions, ranging from "limited evidence" (Cochrane review) (26) to fully supportive (28-30). In only two of the meta-analyses have individual patient level data been combined: both of these showed a small improvement in HbA1c with no change in rates of hypoglycemia (4, 28). The others used mean values and took different approaches to inclusion and exclusion criteria, pooled data from CGM systems with different performance characteristics, and/or focused on studies financed by particular manufacturers (27). The heterogeneity of the outcome of the meta-analyses performed indicates that a more standardized and systematic approach (33) is required to avoid reaching inappropriate conclusions that could undermine the value of CGM [2f].

Design and remaining limitations of CGM systems

The design of most CGM systems has improved markedly over the years. For example, changes which are fundamental from a safety perspective have occurred at least in part because the FDA and other regulatory authorities began to require human factor studies prior to market approval (34) [1a, 3b]: these include more accurate glucose measurement, more audible alarms, and easier to read displays.

The remaining limitations can be grouped as follows:

Technical issues:
- Measurement of capillary blood glucose levels using a standard SMBG system is currently required for initial calibration and regular daily re-calibrations for all devices except isCGM.
- Episodic differences in sensor performance can be observed in the same individual (may or may not be attributable to the technology)
- Sensors are approved for use for only varying lengths of time, with implantable sensors lasting longest

User issues:
- Wearing a device continuously can be a burden
- A skin puncture is required each time for insertion of the glucose sensor into the subcutaneous skin tissue (or a small surgical procedure for an implantable device)
- Limited scope to personalize the user interface [2b]

Safety issues

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- Site reactions, skin rashes (to adhesives), pulling off, falling off, sweating off, losing transmitter, receiver, issues with transmission at night, malfunctioning sensors, silencing of alarms if smart phone is on vibrate or silent mode are frequently reported. [1a, 2g]

Costs

- High costs for sensors and replacing system components
- In some settings, prohibitive amounts of paperwork to obtain approval for coverage

Optimizing the technology to overcome as many of these issues as possible requires a high level of cooperation [5d] between all relevant stakeholders: regulatory agencies, manufacturing companies, academic researchers, research funding bodies, health professionals, medical associations, and patient groups (as per the specific recommendations below)**.**

Combination of CGM with insulin pumps: automated insulin delivery

A number of different combinations of CGM systems with insulin pumps are available on the market in the EU and more recently in the US. Trends towards reductions in the occurrence of mild and severe hypoglycemic events when using such combinations have been reported (35, 36), but also challenged (37). These represent an intermediate step towards automated insulin delivery (AID) systems (38): rapid development has led to the recent market approval and launch of the first hybrid closed loop system (Minimed 670G (Medtronic)) (39).

Reliable CGM system performance with accurate, uninterrupted glucose information is a key component of a safe and effective performance of any such AID systems, i.e. ongoing automated adjustment of subcutaneous insulin infusion (with or without glucagon) according to ambient glucose levels. However, if there is an undetected malfunction, missing data transfer, or the algorithms do not handle the CGM data adequately, a clinically relevant adverse event can clearly ensue [3a]. As with CGM, there are likely to be rapid improvements in AID systems from one generation to the next that will challenge the pace of clinical evaluation (see above) and ask for standardized outcome measures (19-21) [1c].

Glucose measurement in interstitial fluid

The glucose sensors of CGM systems measure glucose in interstitial fluid as opposed to SMBG which measures glucose in capillary blood. Although few formal studies have been published with modern sensors, the assumption that interstitial glucose measurement results can be calibrated to capillary blood glucose accurately and reliably used as a basis for therapeutic decisions may be less warranted during periods of rapid changes in glycemia. In the post-absorptive state, there are measurable differences between capillary blood and interstitial fluid glucose. A study published in 2003 estimated that at an ambient glucose around 200 mg/dL, change in interstitial glucose over time was ≅15% lower when glucose

was increasing and ≅20% higher when glucose was decreasing [3a] (40). Such discrepancies between blood and interstitial fluid are potentially compounded by both physiological and "instrumental" time delay (i.e. while the measurement takes place) (39) and also by exercise. Adjusting the insulin dose on the basis of CGM glucose values therefore carries - at least a theoretical - risk of over- or underestimation with obvious attendant risks (41). However, despite these concerns, interstitial glucose concentrations from CGM appear sufficiently robust for successful use with AID systems (38, 39), and recent data suggest *increased* time in target when insulin dosing decisions are taken on the basis of CGM as opposed to SMBG (11). Time trends in glucose concentrations may be more informative than infrequent single time point estimates using SMBG, even if the latter are more accurate from an analytical point of view.

Data handling and reporting

At present, each manufacturer of CGM systems has its own format for display of glucose data. In addition, there are a number of tools in use for data display and analysis [e.g. Glooko/ Diasend (these two companies merged in 2016), Tidepool]. From a user and clinical perspective, a key aspect is how much time a given individual spent in a defined glucose range i.e. time in range (TIR). While individualized ranges may be appropriate for some individuals and situations, we believe that a standard and universal definition range for glucose TIR [e.g. 70-180 mg/dl (3.9-10.0 mmo/L)] would be desirable as an endpoint for clinical trials. However, a number of other parameters are in current use for characterization of:

(a) glucose control – mean glucose (of all readings), median glucose for all readings, area under the curve (AUC) [for 24 hours, normalized hourly, excess for 24 hours], low blood glucose index (LBGI); and

(b) glucose variability - total standard deviation (SD) [within-day or between-day], interquartile range (IQR), co-efficient of variation (CV), mean amplitude of glucose excursions (MAGE), mean of daily difference (MODD) and continuous overall net glycemic action (CONGA) and others have been described (20, 41, 42). As stated above, reporting results from CGM trials with these diverse and non-standardized measures prevents robust comparisons between and amongst studies, hampers meta-analyses, and complicates interpretation of the evidence by payers and regulatory agencies [1d]. The Ambulatory Glucose Profile (AGP) has been recommended as a potential universal software report that could be adopted to standardize summary metrics amongst devices and manufacturers (43).

As with regular blood glucose meters, in daily practice most CGM users never actually download data from their devices (10). No systematic evaluations have been reported on the information most often used in daily life to guide insulin adjustment decisions:

i.e. whether individuals with diabetes mostly rely for decisions on insulin dose adjustment on the current glucose value, the glucose profile over the previous few hours, or the "trend arrow" (which indicates when the blood glucose is rapidly falling or rising but differs in format between devices) (44,45). [3e]

Safety of CGM usage

Scientific knowledge concerning the safety of CGM usage in daily life is limited. Many interesting user comments on safety aspects of CGM systems can be found on internet blogs, but are of limited generalizability. The manufacturers (as with insulin pumps and other medical devices) are required by the regulatory agencies to collect and report the customer complaints they receive for their product. However, the total number of CGM users is unknown as the numbers sold and operating are not currently reported (i.e. there is no denominator) and data are not reported in formats that are sufficiently consistent or easily searchable to be helpful in improving safety.

For example, on the FDA database for medical devices (MAUDE), issues attributed to user error cannot be filtered from those considered potentially device-related. A search for reports involving "Enlite" or Dexcom (as examples of specific CGM systems) showed quite different results. Problems specific to CGM systems such as skin reactions, sensor failure or hypoglycemia are not searchable terms. As the database can be searched by "event type" (death, injury, malfunction, other) and due to our focus on safety, we searched under "death" and "injury", restricting to one month each year due to the large number of monthly events listed.

From Table 2, it is clear that reporting procedures for these two device manufacturers differ substantially and change over time. Many of the reports of death could not have been related to the CGM systems as the harmed individual was not wearing the glucose sensor at the time of death, but were notified by the manufacturer as CGM supplies were no longer required. Although we found several reports of death due to hypoglycemia while wearing a CGM system, none were considered a device issue.

Our working group initiated discussions with the FDA with a view to reaching a better understanding of current safety reporting procedures. The FDA was willing to communicate directly with us but as the responsibility for reporting customer and complaints rests with individual device companies, we did not obtain any data additional to those already publicly available via MAUDE. [2c]

We also sent a set of five questions to the four CGM system manufacturing companies: Medtronic, Dexcom, Abbott and Roche. All provided complete and informative responses. The most interesting variation was in response to the question ("most common patient complaints reported through FDA's MAUDE system"): while one company provided

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specific answers, another replied that it considered this information confidential. In our view, this latter approach illustrates a fundamental impediment to improving the safety of CGM systems: if safety data reported for regulated health products are considered proprietary and are not made publicly-available, a cycle of safety improvement cannot occur. [1f, 2c]

Education and training

CGM is primarily a diagnostic technique and cannot be expected to improve glucose control *per se* any more than weighing scales can be expected to reduce weight. Without appropriate training, users of CGM may not be able to make optimal usage of the information provided.

Even in diabetes clinics, CGM data may not be optimally used. For example, physicians and other healthcare workers may vary in familiarity with the different approaches used in the different systems and/or data interpretation software available from each manufacturer [5b]. In addition, time and/ or financial constraints often do not permit sufficient discussion with individuals, so that the potential benefit of CGM is often not achieved.

To date, as most training programs have been developed and delivered by manufacturing companies, they focus on technical aspects of their own products rather than optimal usage of CGM as a technology to improve diabetes therapy. Training is not routinely available either to providers or users on how to react to the measurement results, either in real time or retrospectively and few programs have been systematically evaluated to determine their effectiveness. There are only a few company-independent teaching programs [SPECTRUM in Germany (46), AID Training Program in the US (47), and one website (42, 48)] supporting visualization and analysis of glucose data from SMBG, CGM and isCGM [2d, 5b, 5c]. isCGM is increasingly being used without training because it can be ordered direct from the manufacturer online and be used without input from health care professionals; however, a training program is under development.

Cost-benefit and reimbursement

At present, costs of CGM are reimbursed for people with type 1 (but not type 2) diabetes <65 years of age by most commercial insurance companies in the US.   In the US, following the FDA ruling in December 2016, Medicare Ruling 1682R in January 2017 approved coverage of "therapeutic CGM" (i.e. to replace fingerstick testing) in insulin treated individuals with type 1 and type 2 diabetes (using the Dexcom G5) (49). In Europe CGM is reimbursed in only a few countries (including Germany).(50, 51). This heterogeneous coverage also reflects the weaknesses and gaps in clinical evidence highlighted above. The few formal cost-benefit studies that have been published are open to interpretation and sensitive to assumptions

made in the underlying models (51,52) [1e, 3d]. Perhaps not surprisingly, CGM studies supported by manufacturers are more supportive than those performed by payers. However, some companies perform studies by providing funds and devices to an independent site that acts as a coordinating center and has independent oversight of the trial conduct and data analysis.

Remote usage of CGM data: opportunities and challenges

Having realized the potential of remotely accessed CGM for monitoring their children's glucose control when away at school or university, and frustrated that no commercial devices offering this facility had reached the market until recently (53), some parents of children with type 1 diabetes developed custom-made solutions by "hacking" commercially-available CGM products and releasing code for other users (www.nightscout.com) (54). [2g] While the underlying motivation is completely understandable and will likely stimulate larger companies to continue to innovate, such informal solutions raise safety concerns and present a challenge for the regulatory establishment as open source software is not regulated by regulatory agencies like the FDA. There are also issues of privacy and consent. [1g,2h]

The Nightscout community continues to grow on Facebook, although the first cloud-based CGM systems with remote connectivity are now commercially available. Such remote support is not reimbursed but, insofar as they are used, manufacturers increasingly have the capacity and means to interact directly with users, supporting sharing of measured glucose values with health care professionals, and learning from anonymized "big" data (55). This approach has enormous potential, but automatic downloading of CGM results on servers owned by manufacturers also carries risks and complexities in terms of liability, consent, privacy and data protection (56). Use of CGM in school settings is a new challenge to be addressed. Due to differences in legal tradition, there is higher sensitivity on these issues in Europe, particularly when data are transferred across national boundaries to largely US-based manufacturers. Guidance on cybersecurity of medical devices has recently been published (57) and the use of an international data "safe harbor" has been proposed as a solution (58). [1g, 2h]

Use of CGM for therapeutic product development and regulatory purposes in clinical trials

In clinical trials the roles of SMBG and CGM technologies substantially overlap. CGM has great potential for supporting clinical development of e.g. new insulin products and other glucose-lowering agents in people with both type 1 and type 2 diabetes. Analysis of continuously registered glucose profiles provides much more information about the impact of

drugs on ambient glucose levels than any form of episodic SMBG (e.g. 7-point glucose profiles). For example, frequency of nocturnal or total daily hypoglycemic events as determined by CGM could be used as clinical trial endpoints [1d]: no other feasible alternative technology for accessing nocturnal hypoglycemia is available. For CGM to provide evaluable endpoints, consensus on definitions of the various levels of time in range and hypoglycemia (in clinical practice and by CGM) is urgently required amongst payers and providers (21, 43). On this topic there has been some very recent progress (59).

If the FDA and other regulators were to accept such consensus definitions, CGM could have significant impact on the development and refining of new diabetes treatment options. The same technology could be used for better studies of physiology and pathophysiology, e.g. understanding glucose metabolism during exercise and feeding in health and disease. A virtuous cycle could be created with increasing evidence for the value of monitoring technologies, improvement in these technologies, and demonstration of the favorable economics of wider availability. FDA's Center for Drug Evaluation and Research (CDER), which regulates drug therapies, recently examined new definitions and standards for measuring glycemia and other patient reported outcomes beyond HbA1c in clinical trials and expressed willingness to continue a series of meeting in an attempt to reach a consensus (21). FDA's Center for Devices and Radiologic Health (CDRH), which regulates devices and diagnostics, is supportive of the use of data from appropriately standardized CGM devices for clinical trials, as it has approved numerous trials using devices that regulate insulin delivery based on CGM values (36, 39, 60). CDRH has generally requested that investigators utilize the key glucose outcome metrics outlined by Maahs et al. in the consensus report on artificial pancreas outcome measures for clinical trials (21).

Conclusions and outlook

Great progress has been made in CGM technology in recent years (61), but several barriers remain before it can reach its full potential either as a method for improving glycemic control in diabetes (with sufficient rigor for payers to reimburse), or as a means of assessing the efficacy of diabetes therapies (e.g. a novel insulin potentially associated with less hypoglycemia).

Insufficient evidence of clinical utility and reliability and the lack of consistent reimbursement contributes to limited use of CGM across large populations of people with diabetes who could potentially benefit. A more concerted commitment to seeking robust evidence by industry, regulators, clinical and technical experts, as well as funding and patient organizations is necessary for the necessary trials to be conducted and for the field to progress.

CGM is a critically important technology for enabling AID systems. With further confirmation of the safety and utility of freestanding CGM technology, a more widespread uptake might be achieved.

Our recommendations can be categorized under the following themes:

- More systematic and structured pre-marketing evaluation of the performance of CGM systems [1a, 1b]

- Greater investment in trials to provide evidence of CGM value and reliability for all patient groups [4a, 4b]

- Standardization of CGM-measured glucose data reporting from clinical trials [1c]

- Improved consistency and accessibility of safety reports to regulatory authorities after market approval

- Increased communication and cooperation across stakeholder groups [2h]

We envision an ongoing role of ADA, EASD, and other professional medical associations in supporting the virtuous cycle of CGM innovation, confirmation of value to users, increased utilization, and greater resources reinvested to support innovation. For this vision to be realized without further delay, we call upon regulators and manufacturing companies to work urgently with health professionals and people with diabetes to create an environment with much greater standardization of outcome measures, a high level of attention to safety issues, and full transparency of adverse event reporting.

Recommendations:

A high level of cooperation and engagement is required amongst the following stakeholders. Specifically, we recommend:

1) Regulatory agencies should:

a) Introduce a systematic, independent and structured pre-marketing and post approval evaluation of the performance of CGM systems including assessment of "human factors"

b) Promote the development of a consensus on which parameters should be analyzed and reported to characterize the performance of a CGM system

c) Specify a standardized CGM output format for reporting time in range and hypoglycemia for use in clinical trials

d) Review available outcomes measures (including patient-related outcomes) and specify those best used in CGM and AID studies

e) Assess available models for cost-benefit calculations and specify which should be used for CGM studies

f) Rapidly and transparently disseminate safety-related data reports on CGM to healthcare professionals

g) Protect the security and confidentiality of patient data in the era of connectivity

2) Manufacturing companies should:

a) Cooperate to standardize output formats ± software used for analysis

b) Provide interfaces that can be personalized according to the needs of the user

c) Report all safety related data transparently to the regulatory authorities

d) Cooperate with academia and healthcare professionals on providing balanced and adequate information to people with diabetes and package the output data in standardized formats to make it easy for major electronic health record (EHR) companies to access and incorporate for clinical use.

e) Incorporate a wider range of existing outcome measures including patient-reported outcomes in study designs of adequate statistical power

f) Publish all relevant data / information collected during the clinical development of a given CGM system, e.g. the results of Human Factor studies.

g) Communicate frequently and regularly with users, user groups and families affected by diabetes in order that real needs can be identified and promptly addressed as soon as the relevant technology becomes available (e.g. remote monitoring)

h) Observe high standards of data security and patient confidentiality

3) Researchers/ academics should:

a)   Develop better algorithms to improve the performance of CGM and AID systems

b)   Openly report and share the patient level results of all clinical studies

c)   Develop and validate specific and appropriate patient-related outcome measures

d)   Develop better models for cost-benefit analyses (in partnership with industry and regulatory bodies)

e)   Work to develop and perform studies that fill genuine "gaps" in the evidence

f)   Follow the recommendations made by Pickup (33) when interpreting or performing meta-analyses [including 3) b)],

g)   Involve people with diabetes and their family members/caregivers in the development of CGM and AID systems for guidance and feedback.

4) Research funding bodies should:

a)   Fund fewer small, underpowered studies of specific devices; instead well-designed larger "class" studies with clinically relevant endpoints using more than one CGM system and including head-to-head comparisons

b)   Fund large independent registry studies.

5) **Patient groups, health professionals, and medical associations should:**

a)   Provide and regularly update recommendations on CGM.

b)   Provide minimum standards of training for providers and people with diabetes using CGM, isCGM, and AID

c)   Work to develop and disseminate structured company-independent education programs e.g. SPECTRUM and standardized output of glucose metrics and glucose and insulin profiles e.g. Ambulatory Glucose Profile (AGP).

d)   Work together (AACE, AADE, ADA, EASD, Endocrine Society, IDF, ISPAD, JDRF and other patient advocacy groups) to provide wider access to CGM for all people with diabetes who are willing and able to use these devices on a near daily basis

6) Consumers of CGM technology—patients, family members, caregivers—should:

a) Report device errors and malfunctions to the manufacturers and appropriate regulatory agencies

b) Provide input to the policy development processes of professional and patient advocacy associations and regulatory authorities

c) Advocate for standardization and improved accessibility of CGM safety data to facilitate product comparisons.

Acknowledgement

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Table 1

Search results from the MAUDE database of the FDA (number of hits)

	Dexcom				Enlite			
	Jul 2013	Jul 2014	Jul 2015	Jul 2016	Jul 2013	Jul 2014	Jul 2015	Jul 2016
All	31	1979	3564	7453	0	492	366	302
Injury	20	31	78	167	0	34	163	6
Death	0	0	8	10	0	0	0	0

Adverse events are not necessarily caused by the device. N.B. these data cannot be used to compare devices due different practices in reporting of adverse events (as discussed under heading "Safety of CGM usage).