Whitepaper:

MAXIMIZING THE POTENTIAL OF CONTINUOUS GLUCOSE MONITORING IN CLINICAL TRIALS: INSIGHTS, CHALLENGES, AND REGULATORY CONSIDERATIONS

Despite technological advances in diabetes, hypoglycemia remains a key obstacle to achieving glycemic control. Hypoglycemia is one of the most impactful adverse events related to persons with both type 1 and type 2 diabetes. Too much insulin, insulin-producing medications, exercise, alcohol consumption, high-stress situation, or delayed, missed, or reduced meals can all contribute to increased hypoglycemic events. When persons enroll in clinical trials that investigate therapies impacting glycemic patterns, it is essential to closely monitor glucose levels. Testing frequency may need to be increased due to potential risks of hyper or hypoglycemia from the investigational product. This is where continuous glucose monitoring (CGM) can be a useful tool in assessing overall glycemic patterns and may help reduce the risks of adverse events like hypoglycemia.

THE IMPORTANCE OF ACCURATE HYPOGLYCEMIA ASSESSMENT IN CLINICAL TRIALS

Hypoglycemia, especially severe hypoglycemia, is a serious medical condition that can result in cognitive impairment or even death. Hypoglycemia is usually defined by a plasma glucose concentration below 70 mg/dL (3.9 mmol/L), but signs and symptoms of hypoglycemia may not present until plasma glucose concentrations drop below 55 mg/dL (3.0 mmol/L).[7] The American Diabetes Association (ADA) classifies hypoglycemia into three categories:

- Level 1—glucose < 70 mg/dL (3.9 mmol/L) and ≥ 54 mg/dL (3.0 mmol/L)
- Level 2—glucose < 54 mg/dL (3.0 mmol/L)
- Level 3—a severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia

Hypoglycemia is commonly seen in diabetes, but it can occur in persons without diabetes related to things such as medications, alcohol, critical illness, counter-regulatory hormone deficiencies, non-islet cell tumors, and post-bariatric surgery to name a few. Diabetes therapies like meglitinides, sulfonylureas, or insulins increase the risk of hypoglycemia substantially. The risk of hypoglycemia is highest in type 1 diabetes due to intensive insulin therapy; however, we are now seeing an increasing incidence in type 2 diabetes as well, especially on intensive insulin regimens. Persons on intensive insulin therapy require close monitoring of blood glucose levels multiple times per day given the increased risk of hypoglycemia. Measuring blood glucose by multiple daily finger sticks adds an additional burden to an already complex regimen. When a person is required to test blood glucose levels multiple times per day, adherence to self-monitoring blood glucose becomes more difficult despite improvements in glucometers which have become smaller, faster, more accurate, and require less blood.

Hemoglobin A1c (HbA1c) has always been the standardized measurement to see how well a person with diabetes is managing their disease. The ADA has recommended HbA1c goals for different patient populations based on age, comorbid conditions, pregnancy status, and hypoglycemia awareness. These guide clinicians to recommend individualized HbA1c goals to monitor how a person's diabetes is currently being controlled. While HbA1c and fingerstick blood glucose values provide useful measurements, they cannot, either in real-time or retrospectively reveal a person's behaviors or actions to inform the patient or provider of real-time decisions. This is where CGM has changed the playing field for persons requiring multiple daily blood glucose testing. In 2016, the FDA approved the Dexcom G5 CGM system to allow for the replacement of fingerstick blood glucose testing for treatment decisions in persons 2 years of age and older with diabetes. Until that time, CGM was only approved to complement, not replace, fingerstick blood glucose

testing for treatment decisions. According to the T1D Exchange registry's recently published 2022 data from the electronic medical record (EMR) data of 60,915 patients with T1D from 26 diabetes centers in the US, there is a difference in CGM use across demographics. This data shows CGM diabetes technology use was highest in the 6 –13 age range at 64% relative to adults in the 26 –50 age range at 46%. This study outlines more work is needed for desirable management of diabetes.[16] In April 2023, Medicare expanded CGM coverage to more persons with type 2 diabetes who are on basal insulin alone or who don't take insulin but have a history of level 2 or level 3 hypoglycemia. This will contribute to increasing the number of persons with type 2 diabetes who will now qualify for CGM coverage in the United States.

SIGNIFICANCE OF CGM ADOPTION IN CLINICAL TRIALS

The use of CGMs has become prevalent in clinical practice for more than a decade, revolutionizing the lives of people with diabetes mellitus. Their technical performance has improved to the extent that their output is accepted as medico-legal evidence in "fitness to drive" cases. For example, in the UK, DVLA no longer requires people to obtain evidence of having a "safe glucose level" by finger pricking before they set off to drive. It is enough to have a demonstration of time in range on a CGM.

These advancements have yet to be reflected in guidance from regulatory bodies. It is time to acknowledge that the requirement to prick one's finger for the sake of participating in clinical trials is an unnecessary burden, especially considering the availability of CGM outputs that provide much more insightful data compared to a single glucose reading at the testing point. The paper by Battelino, T. et al. (2023) provides guidance to the research and drug development industry to catch up with the rest of medicine in that respect.[3] It is no longer justifiable to impose an unnecessary, uncomfortable, time-consuming, and distressing action when a perfectly viable alternative exists. With the availability of CGM, individuals can seamlessly go about their lives while the CGM operates in the background. They only receive alerts, either through vibration or sound, if there is a need for immediate action to ensure their safety and prevent hypo or hyperglycemia.

Patients are already carrying the extra burdens of their conditions. While they are eager to participate in scientific advancements, they also have their own lives to lead. Thus, participation in clinical trials should not only prioritize safety but also minimize disruption to their daily routines. If participants are required to carry an additional device like a glucose testing kit, which is not a part of their regular habits, they are more likely to forget it amidst the demands of work, family, and general life responsibilities. When an event such as hypoglycemia occurs and requires capturing through an additional and unpleasant action like finger pricking using a separate device that needs to be carried alongside their everyday belongings, it becomes evident how such a requirement perpetuates study data losses and hinders concordance with the study procedures.

DEFINING AND CAPTURING HYPOCLYCEMIC EPISODES

CGM data has opened a whole new perspective in how clinicians assess a person's glycemic patterns. We have learned that traditional methods of assessing glycemic control like Hba1C and fingerstick values with a glucometer don't always tell the whole picture of how well a person's diabetes is controlled. CGM data allows us to see a much larger picture of glycemic patterns, including nocturnal hours. In 2019, evidence emerged to link time in range (TIR) to microvascular complications in diabetes which has been subsequently confirmed by other studies.[11,12] The link between TIR and macrovascular outcomes is more challenging to demonstrate as macrovascular complications take longer to develop. Nevertheless, the link between carotid intima-media thickness

and TIR has been observed.[13] Additionally, the link between cardiovascular mortality and TIR has been demonstrated, paving the road for TIR as a surrogate marker of long-term diabetes outcomes.[14]

A panel of diabetes experts developed the international consensus on TIR which provides guidance on standardized CGM metrics that clinicians interpret and use for care measurements.[2] CGM devices are efficient tools to support standard of care for both persons with type 1 diabetes and type 2 diabetes on insulin therapy. CGM use has been associated with increased TIR, reduced hyperglycemia and hypoglycemia (including nocturnal hypoglycemia) in both type 1 and type 2 diabetes.[3] As CGM users continue to grow, we will see increasing use of these devices in clinical studies allowing a detailed understanding of glucose profiles in study participants and providing useful data to support study endpoints.

The time in ranges shows the proportion of the day the person using the CGM spends with glucose readings within the three ranges as outlined in the international consensus, TIR, time below range (TBR), and time above range (TAR).[3] TIR measures the percentage of time spent with blood glucose readings between 70-180 mg/dL (3.9-10.0 mmol/L). TBR measures the percentage of time spent with glucose <70 mg/dL (<3.9 mmol/L), including readings <54 mg/dL (<3.0 mmol/L). TBR level 1 hypoglycemia measures the time spent with glucose 54-69 mg/dL (3.0-3.9 mmol/L). TBR level 2 hypoglycemia measures the time spent with glucose <54 mg/dL (<3.0 mmol/L) and is considered clinically significant and requires immediate attention.[3] TAR measures the percentage of time spent with glucose >180 mg/dL (>10.0 mmol/L); including readings >250 mg/dL (>13.9 mmol/L). TAR level 1 hyperglycemia measures the percentage of time spent with glucose 181-250 mg/dL (10.1-13.9 mmol/L). TAR level 2 hyperglycemia measures the percentage of time spent with glucose >250 mg/dL (>13.9 mmol/L). According to Battelino et al. (2022) prospective clinical studies using CGM devices should report hypoglycemia endpoints for all core metrics for TIR which include time below <70 mg/dL (3.9 mmol/L) and time below range 54 mg/dL (3.0 mmol/L), time below 70 mg/dL (3.9 mmol/L) includes time below 54 mg/dL, both <70 mg/dL (3.9 mmol/L) and time below 54 mg/dL (3.0 mmol/L) should be reported separately. In prospective clinical studies that evaluate the safety, efficacy, and clinical effects of an intervention, CGM data should also be reported separately for nocturnal (0000h to 0559h) and daytime periods (0600h to 2359h).[3] When CGM-defined TIR measures are categorized into temporal subgroups such as within a 24-hour period, diurnal, or nocturnal, they should be used when specifying endpoints.[3] This can allow different measurements and outcomes such as a change in nocturnal hypoglycemia (0000 h to 0559 h) from daytime hypoglycemia (0600h to 2359h) or within a 24-hour period.[3]

INTEGRATION OF CGM IN CLINICAL TRIALS

Randomized controlled trials in persons with type 1 and type 2 diabetes have routinely used glucose meters and HbA1c value as measures of blood glucose levels for approval of investigational medicinal products in clinical trials. HbA1c provides an estimate of blood glucose levels over a three-month period and does not report intra- and inter-day glycemic excursions, including the potential occurrence of acute hypoglycemia or post-prandial hyperglycemia. Glucose meters report a one-time snapshot of a glucose value at a specific point in time and cannot foresee oncoming hypoglycemia or send alerts for hypoglycemia. With the evolving improvement of CGM and their rapidly advancing use in type 1 and type 2 diabetes communities, Sponsors are increasingly interested in using CGM as a source of continuous streaming data to gain a more accurate picture of glucose values in clinical trial outcomes.

CGM provides glucose data at one-to-five-minute time spans and importantly measures nocturnal, unrecognized, and post-prandial hypoglycemia. The 7- point self-monitoring of blood glucose (SMBG) only reports intermittent data at certain time points and increases patient burden with a need to awaken in the middle of the night to perform a fingerstick. CGM can report the percentage of time in range (TIR) which measures in hours and minutes, time spent in a target blood glucose range, and time below range.

The precedent for the use of CGM as a source of primary outcome in diabetes was set by Goldberg et al. and provided a mean for head-to-head comparison between drugs in diabetes that could help define a unique selling point for one drug over the other.[15]

CGM has the capability to send alerts to patients and caregivers for safety through a smartphone or receiver at a level determined by the study as well as sending CFR part 11 compliant data to the vendor platform for

determining outcomes. An e-diary app can be uploaded on the subject's smartphone for integrating data including the signs and symptoms along with nutrition and exercise. Integrated Bluetooth glucometers can stream near-real-time data to the platform to minimize loss of data.

Medpace understands the importance of reliability and patient convenience using CGM devices in randomized controlled trials. With the collaboration of endocrinologists, endocrine nurse practitioners, and diabetes educators, Medpace individualizes clinical trials to recommend the appropriate device to reduce patient burden and considerations for safety while maximizing data flow. Medpace offers familiarity with different software and hardware vendors, supplies and processes. Sponsors have access to a broad partnership for successful trials using CGM devices in diabetes and other rare disorders.

GUIDELINES FOR CGM USE IN PEDIATRIC POPULATIONS

Guidelines recommend individualized glycemic targets for children and adolescents. Continuous glucose monitors and other newer technology such as smart pumps and algorithm-controlled insulin delivery can help achieve lower HbA1c goals without the risk of severe hypoglycemia. The ADA recommends all youth with type 1 diabetes monitor glucose levels by either a glucose meter prior to meals, snacks, bedtime, prior to driving and other circumstances, or monitor by continuous glucose monitoring.[1] The ADA further advocates either real-time or intermittently scanned glucose monitoring should be offered for diabetes management in youth with diabetes who are on multiple daily injections or insulin pump therapy and who could use the technology safely by themselves or with caregiver support. The ADA also states CGM could be considered in youth with type 2 diabetes requiring frequent blood glucose monitoring for diabetes management.[1] It is important in clinical trials with children with type 1 or type 2 diabetes to consider technology and/or continuous glucose monitoring as a stratification for randomization and/or as an important eligibility consideration.

Key guidance organizations such as the European Association for the Study of Diabetes (EASD), and the International Society for Pediatric and Adolescent Diabetes (ISPAD) with the support of the Juvenile Diabetes Research Foundation (JDRF) provide guidance on the use of technology to determine glucose around exercise for adults, children, and adolescents with type 1 diabetes.[8] The direction of trend arrows in CGM pre-exercise points to mitigations recommended prior to exercise to avoid hypoglycemia, hyperglycemia, and diabetic ketoacidosis (DKA). Standards of care in children and adolescents with diabetes acknowledge that CGM abolishes the need for the use of a glucometer. We suggest clinical trials in this population should not impose a burden beyond what is required by the standard of care. Hopefully, clinical trials in the pediatric population may be the first to adopt the routine use of CGM as a primary source of glucose data.Within the rapidly changing landscape of wearable technology in diabetes treatment and care for children and adolescents, recommendations are frequently changing. The Medpace team has the knowledge and experience to guide Sponsor's clinical trials in this very important area.

REGULATORY CONSIDERATIONS FOR THE USE OF CGM DEVICES IN CLINICAL TRIALS

The first transdermal implantable glucose sensors were approved for use by diabetes patients over 20 years ago and significant advances in technology, accuracy, and lifespan for these devices have been achieved since then. To date however, no drug approvals have been supported by data from CGM devices that measure a primary efficacy endpoint of hypoglycemia. Regulators have been recommending that HbA1c be used as the primary efficacy endpoint to support drug approvals for the improvement of glycemic control. Despite increasing experience with CGM devices in the clinical trial setting, with a rise

in usage from <5% before 2005 to 12.5% by 2019,[10] and an international consensus statement endorsed by a number of clinical organizations, on the use of CGM in clinical trials along with recommendations on standardized approaches to data collection and reporting in this context,[3] it is only now that the use of CGMs for a hypoglycemia primary efficacy endpoint to support a drug approval may be accepted by the regulators.

The FDA has issued a new draft guidance (May 2023) on efficacy endpoints for clinical trials investigating antidiabetic drugs and biological products for the treatment of diabetes mellitus. This is a timely release from the FDA as current guidance, issued in 2020, was available for safety evaluations of drugs for improving glycemic control in T2DM but did not provide clear recommendations for efficacy endpoints and treatment goals, as well as a lack of recommendations for T1DM. FDA's new guidance considers that reduction in hypoglycemia is an acceptable endpoint for these trials and also provides considerations for the use of CGM in support of hypoglycemia labeling claims. However, this new guidance does not address endpoints related to clinical complications (such as cardiovascular disease risk reduction) of diabetes, endpoints required for prevention or delay of T1DM, use of hypoglycemia endpoints in trials for other indications such as PBH (post-bariatric hypoglycemia), trial design considerations, or recommendations for evaluation of safety. The guideline clearly states that change from baseline in HbA1c is an accepted primary endpoint in clinical trials for a glycemic-control indication and that reduction in HbA1c is considered to be a validated surrogate endpoint for microvascular risk reduction to support traditional regulatory drug approval. In contrast, hypoglycemia endpoints have primarily been used to evaluate safety and only rarely used as endpoints for comparative efficacy or safety claims, mainly due to lack of agreed hypoglycemia definitions linked to clinical outcomes and lack of appropriate measurement tools. The guidance defines hypoglycemia using the definitions described by the ADA and that level 3 and level 2 hypoglycemia are acceptable endpoints to support claims related to improved glycemic control and iatrogenic hypoglycemia.

Accurate measurement of endpoints is essential, and the FDA recommends early engagement to discuss how best to measure primary endpoints and to justify the proposed CGM device to be used in clinical trials. The guidance acknowledges that SMBG systems and CGM are commonly utilized approaches although, it is noted that CGM provides near real-time glucose data and trend information on fluctuating glucose levels throughout the day and is increasingly used in clinical practice. This has driven the use of CGM in clinical trials, especially with the improvement in technology and resolution of previous performance issues. As CGMs are more likely to capture hypoglycemic events due to the continuous nature of glucose data collection by these devices, which is an advantage over SMBG test systems, as well as CGMs being able to limit subject bias and can better capture nocturnal hypoglycemia and patients with hypoglycemia unawareness they are likely to be the preferred measurement device in the clinical trial setting. The FDA acknowledges that regulatory acceptability for the use of CGM systems in clinical trials continues to evolve. They recommend drug developers discuss CGM considerations such as CGM-based hypoglycemia endpoints, data analysis and format for submission, and the intended patient populations, with the agency. The guidance also states that a single CGM model, which is authorized in the US and has an acceptable level of performance characteristics (accuracy and precision) in the hypoglycemic range, should be used throughout clinical development.

In the EU, current regulatory guidance (issued in 2018) for clinical trials for the development of medicinal products to treat diabetes mellitus recommends that for confirmatory studies, HbA1c is an appropriate primary endpoint in clinical trials to support drug approvals based on glycemic control. According to the guidance from the EMA, changes in fasting plasma glucose are considered an acceptable secondary endpoint and should be measured at regular intervals. The use of CGM is encouraged to provide additional information, especially in situations where nocturnal hypoglycemia could be a risk for the trial population or in cases involving post-prandial hyperglycemia. It is noted that hypoglycemia definitions should be standardized and cites the classifications published by the International Hypoglycemia Study group as a recommended approach.

Standardization of metrics from CGM devices has been an important goal in recent years, with a number of stakeholder groups being involved in defining and

gaining consensus on glycemic measurement ranges, definitions of hypoglycemia, time in range, and hyperglycemia.[3] For additional efficacy endpoints, the FDA's position is that TIR is a biomarker that has not yet been established as a surrogate for clinical outcome and so is not considered acceptable as a primary endpoint for a glycemic control indication. Inclusion of relevant CGM-based metrics results in the clinical studies section of labeling for drugs approved for a glycemic-control indication could be considered where efficacy has been demonstrated by a change in HbA1c or an appropriate hypoglycemia endpoint.

This guidance provides considerations for the use of hypoglycemia endpoints, and the potential use of CGM systems for hypoglycemic measurements, to support regulatory approval of hypoglycemia label claims will be seen as a positive step for drug developers. However, some questions remain to be addressed including extrapolation of this guidance to other hypoglycemic-related indication and what will be required to achieve acceptance of CGM-based metrics as clinical endpoints. Further development of CGM systems is inevitable and will require regulators to continue to assess new data, provide further guidance and evolve their position on regulatory acceptability in support of new therapies.

The most recent versions of CGMs that incorporate software, technology platforms, connectivity, and sensors are expected to meet the definition of digital health technology, and this is an additional aspect to be addressed when Sponsors are designing clinical trials that will use CGMs. The FDA's draft guidance on Digital Health Technologies for Remote Data Acquisition in Clinical Investigations (December 2021) and Framework for the Use of DHTs in Drug and Biological Product Development (March 2023) outlines the challenges and expectations for the use of CGM devices including selection of devices that are fit-for-purpose, verification and validation for use in clinical trials, use of DHTs to collect data for trial endpoints and identification and management of risks in clinical trials. These considerations will provide additional support for the predicted increase in use of CGMs in clinical trials, set clear expectations for regulatory acceptance of CGM-based data and ensure that these devices collect high-quality clinical data.

IMPLICATIONS FOR CORE LABS IN CGM TRIALS

Wearables and other patient-centric portable devices that remotely collect individual biometric data are transforming clinical trials. These devices can be used to evaluate the effectiveness of a medical therapy while delivering many other vital operational and analytical advantages. CGM is the primary and biggest contributor to this evolution and quickest adoption.

A core lab is uniquely positioned to provide an end-to-end suite of solutions for a CGM trial to enhance and expedite type 1 and type 2 diabetes trials of all phases. It is consistently on the endeavor of modernizing clinical development with industry-leading innovation to drive faster and increased data collection, with a better patient-centric experience, by collecting a more complete and dynamic view of the daily measures of glucose levels and variability than traditional measures of glucose control by SMBG and HbA1c.

To keep pace with the technology evolvement and offer the best-suited solution for a type 1 or type 2 diabetes trial, a core lab is strategically designed to constantly work with their technology and device partners and integrate a wide range of CGM devices in the market into our e-source platforms and data collection applications deployed through a smart device, that develops the best-suited data workflow ensuring enhanced user experiences and compliance.

The core lab wearable technology and portfolio of digital and connected CGM solutions work together to mitigate risk and consolidate, verify, and analyze continuous bidirectional data flow, all in a centralized view within Medpace's ClinTrak® platform.

The ability to remotely collect CGM data, centrally aggregate the data, and provide a near real-time data analysis can impact study design, patient selection, and go/no-go decisions.

- Decreased site visits: reduced site and resource burden leads to cost savings
- Improvement of patient recruitment and compliance: fewer office visits and improved adherence with trial protocol requirements leads to reduced protocol deviations
- Better monitoring of patient's overall glycemic health for site coordinators and investigators

The CGM technologies selected and vetted by Medpace's therapeutically aligned teams meet tailored study design requirements, streamline vendor management, and accelerate study start-up. Medpace seamlessly collects, harmonizes, and integrates glucose data from CGM and SMBG devices into your clinical study as part of our full-service offering.

CONCLUSION

Wearables and other patient-centric portable device CGMs have emerged as a valuable tool in clinical trials, offering insights into glycemic patterns and helping to reduce the risks of adverse events such as hypoglycemia. The ability of CGM to provide real-time and continuous data offers a more comprehensive picture of glycemic control compared to traditional methods. Integration of CGM in clinical trials can enhance data collection, improve patient convenience, and lead to more accurate and meaningful outcomes. It is crucial for regulatory bodies and the research community to recognize the value of CGM and adapt trial protocols accordingly to minimize burden on participants and maximize the potential of this technology in advancing diabetes management.

FULL-SERVICE CLINICAL DEVELOPMENT

Medpace is a scientifically-driven, global, fullservice clinical contract research organization (CRO) providing Phase I-IV clinical development services to the biotechnology, pharmaceutical and medical device industries. Medpace's mission is to accelerate the global development of safe and effective medical therapeutics through its high-science and disciplined operating approach that leverages local regulatory and deep therapeutic expertise across all major areas including oncology, cardiology, metabolic disease, endocrinology, central nervous system and anti-viral and anti-infective.

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