MEDPACE

EXPERT INSIGHTS: Q&A ON THE INTEGRATION OF CONTINUOUS GLUCOSE MONITORING (CGM) AND WEARABLES IN CLINICAL TRIALS FOR DIABETES AND OTHER INDICATIONS

Tell us a little bit about your background in clinical development and Continuous Glucose Monitoring (CGM) trials.

Susan Brumm, DNP, APRN, CNP, BC-ADM
Advanced Clinical Practitioner

My interest in diabetes research began over a decade ago in my master's program and continued in my doctoral program. Prior to joining Medpace my work was in translational research which included taking guidelines and translating diabetes research for use in day-to-day clinical practice. The areas I focused on were diabetes education, remote monitoring, and transitional care. Additionally, I am board certified in Advanced Diabetes Management and have past experience as a member of an Institutional Review Board (IRB), where I reviewed diabetes and endocrine protocols. These experiences brought me in close contact with continuous glucose monitors and devices used in diabetes care and sparked my long-time interest. At Medpace, I engage with cross-functional teams participating in Phase I-III research trials across the globe. The last five years have been exciting to be involved in Diabetes/Endocrine/Metabolic clinical trials working on the development of medical therapeutics integrating CGM and devices. Medpace has a team of diabetes nurse practitioners who have 20+ years of clinical experience with Type 1 diabetes patients (T1D), CGMs, and insulin pumps. We collaborate with a team of Endocrinologists, Business Development Executives, Medpace Core Lab (MCL), and operational and regulatory experts to seamlessly execute clinical trials for therapies in diabetes and other disorders using CGMs and wearable devices. Our global team is motivated to integrate early in a trial to ensure timeliness and successful execution.

Dipali Gupta, MS
Associate Director, Core Laboratory

My interest in glucose data management and its integrated application in a clinical trial started almost 10 years ago, while being part of a core lab specialized in developing connected devices solutions for multiple modalities of wearables and digital health technology solutions for clinical trials across multiple therapeutic areas. As a team, we have catered to unique requirements on data collection modalities, complex monitoring and reporting expectations, and data exports to meet safety or efficacy endpoints in a study. In fact, the entire spectrum of glucose monitoring devices and its applications, e.g., a Self-Monitoring of Blood Glucose (SMBG) device, a continuous glucose monitoring device, integrating CGM data with electronic Patient Reported Outcomes (ePRO)/ eDiary, or even application of CGM in a programmed insulin pump holistically hold a significant share of the wearable and digital health market.

My journey in handling CGM solutions has almost overlapped with the evolution of a new generation of CGM devices and its application in clinical trial development solutions over the past few years. A clinical trial using CGM solutions typically requires good planning of standardized device provisioning per study design with appropriate data collection mechanism, meet logistics requirements, programming its configuration including blinding, the alerts and notifications, monitoring the compliance, data integration and reporting, data export per study requirements, etc. In past few years, I have had an opportunity to be involved in every aspect of this solution, in collaboration with the endocrinologists, Advanced Clinical Practitioners, Business Development Executives, clinical operations experts, and data management teams. With extensive expertise at Medpace in multiple therapeutic areas

and experience handling operational challenges, this team is confident to partner with stakeholders to design an appropriate CGM solution for all kinds of CGM device provisioning and its data integration requirements.

Tell us a little about the integration of the Clinical Research Organization (CRO), Core Lab, Sponsor, and Patient in CGM trials.

It is important to integrate the CRO, Core Lab, and the Sponsor early to have collaboration across different stakeholders in CGM trials. Regulatory and operational insight and experience brings different functional areas together to enhance integration in the clinical trial. Collaboration is crucial to select the hardware, software, and the digital data platform to capture safety and efficacy endpoints. CGM data can be paired with other devices, such as Bluetooth glucometers and Bluetooth ketone meters, to present a picture of the patient's glucose status at a particular date and time. EDiaries can be integrated into Electronic Data Capture (EDC) to document the time and date of carbohydrates eaten, insulin dosed, and Level 3 hypoglycemia signs and symptoms.

The FDA has recognized the importance of CGMs in clinical trials. In its draft guidance, *Diabetes Mellitus: Efficacy Endpoints for Clinical Trials Investigating Antidiabetic Drugs and Biological Products* (May 2023)[7], the agency recommends if using hypoglycemia endpoints, Sponsors consult with the agency early in the drug development program on how best to measure primary endpoints and provide justification for why the selected device methodology is appropriate for the assessment of the hypoglycemia-based endpoint(s) within the context of the specific clinical development program. The FDA is available prior to the study start to discuss audit of the data streams. It is recommended that Sponsors use a single CGM device model with accuracy in the hypoglycemia range to ensure consistent technical characteristics and eliminate sensor bias. All subjects should be provided with the same study-provided CGM, even if they use a personal CGM that is identical.[2,7] Patients may be using two CGMs of the same manufacturer, one for research purposes and one for standard of care.

The core lab can play the key role in designing the appropriate workflow for CGM and other glucose monitoring devices and the CGM platform in collaboration with CGM device manufacturers in designing the specs for configurations for data integration. The core lab will validate the workflow per study expectations, develop the integrated post collection data analysis, and reporting to all stakeholders. The core lab also plays a vital role in operational delivery of the study requirements by executing and monitoring the logistical needs, designing appropriate monitoring, developing training plans and materials, providing ongoing site support, implementing data management, and ultimately ensuring a seamless trial execution.

There are different cloud-based platforms for digital data streaming. It is important to communicate at the outset of the trial as to how the data will be integrated and report near real time access to the investigators, monitors, and Sponsors. Oversight of the data should be determined, and technical oversight is recommended to be in place if there is a possibility of a gap in the wear of CGM to mitigate risks of the integrity of the data. Visibility of the data flow and availability of results to the Sponsor, CRO, and investigator is important. Data that is secure, valid, auditable, and meets Good Clinical Practice (GCP) is crucial. Recommending a single sign-on is suggested for privacy and ensuring data traceability, which will allow data management to know the data is coming from the right person in the right context.

What are some of the unique challenges faced in type 1 diabetes (T1D) integrating CGM in clinical trials?

The American Diabetes Association Standards of Care - 2024 states the initiation of CGM should be offered in people with T1D early in the disease, even at the time of diagnosis.[1] The unique challenges facing CGM in clinical trials includes combining CGM as standard of care (SOC) and maintaining FDA Part 11 compliance for glucose data in the research. Patients review their glucose levels on CGM and receive alerts and notifications, which help inform them of high or low glucose levels. This glucose data may be shared with the health care provider (HCP) and designated followers through an app. The glucose data used for the patient's individual care cannot be used in research because it does not comply with Part 11 data transfer requirements.

There are several ways to design and implement a CGM solution in a trial that caters to the trial need and at the same time ensures patient burden is reduced. Medpace collaborates with Sponsors to suggest a workflow which is individualized to the study design. Many alternatives are possible. Using a blinded CGM or unblinded CGM integrated with glucometers, ketone meters, and electronic Patient Reported Outcomes (ePRO) including considerations to adhere to patient's SOC, ensures endpoints are met and supports patient safety. Some solutions make certain the patient does not have to wear two sensors simultaneously while also meeting all trial needs. Ultimately, Medpace works with Sponsors to implement the preferred CGM solution among the many options.

A unique consideration is the different CGM devices in the marketplace which patients will be using for SOC. To adhere to the FDA guidance, all subjects should be provided with the same CGM for the research data. If patients use a personal CGM in addition to a CGM for research, a subject may have to change the model of their personal devices during longer trials due to the rapidly changing device environment, which may be a confounding variable.

CGMs send glucose data at frequent intervals throughout the day. Designing how to monitor and organize this data stream is a collaboration between data management, biostatistics, the medical monitoring team, and the Core Lab. The Core Lab can play a role in defining data collection through a platform provider or through ClinTrak®, Medpace's proprietary, feature-rich, and fully customizable Clinical Trial Management System. Dashboards have visualizations that allow for aggregate of all the device data, including the eDiary, for ease of monitoring. Data transfers can be requested at different time intervals for the Sponsor and CRO per study requirement.

Education on the chosen CGM, glucometer, ketone meter, and eDiary used in the trial is important for all patients, site staff, and study team. Medpace consistently meets this challenge with robust online lessons, Clinical Research Associate (CRA) face-to-face education, patient handbooks and study manuals, continuous education throughout the trial, and close collaboration between the medical, core lab, and operational teams.

The last consideration to mention with using CGM in clinical trials involves detecting gaps in the duration of time wearing CGM devices. This includes making sure there is a working sensor with CGM input. Wearing an overlay patch may mitigate the risk of dislodgement of the sensor.

How does a Core Lab play a key role in CGM trials and what should a Sponsor look for in a partner?

A Sponsor should look for a Core Lab partner who will integrate all the software and hardware systems, and that has the expertise and knowledge to provide guidance on what devices would work best for their endpoints and for patient safety. Our integrated Medpace Core Labs (MCL) provide an end-to-end suite of services to enhance and expedite biopharmaceutical and medical device development, while providing oversight and analysis for essential biometric data. Medpace can integrate the data into the overall study and harmonize it to present strong regulatory cases, ensuring that these components are seamlessly integrated into the complex structure of the overall clinical trial.

MCL is comprised of a group of dedicated physicians, scientists, technologists, and analysts that provide support for studies that include remote monitoring of CGM, cardiac health, ECG,

Holter, actigraphy, glucometers, and ambulatory blood pressure, using wearable devices, data-cloud integration services, data analytics and reporting. In diabetes trials, patients report exercise through eDiary. Medpace has extensive experience managing numerous global clinical trials spanning all phases of investigational product development, and has experience with remote/home-based recording of physiological biomarkers from patients, aimed at capturing real-life physiological responses, activities, and movement patterns in decentralized clinical trials.

MCL provides a full spectrum of services starting with vendor evaluation and selection with an early collaboration with CRO, Sponsor, and the technology provider with complete oversight throughout the course of the study. With extensive experience and expertise in central device provisioning with appropriate study specific kitting, configurations, logistics and its management, Medpace will ensure all CGM devices and accessories are provisioned with 100% compliance with the device lifecycle.

For a CGM trial, one of the key success factors is providing appropriate training materials for the site and patients. MCL will ensure that the study training material is developed specifically to meet a CGM study requirement. Additionally, in collaboration with CRO and with help of well-defined SOPs, training is provided to the site and patient (via site) such that the CGM device application, data collection, and processing are done with utmost effectiveness.

Furthermore, Medpace also monitors the setup processes, data collection, site support, analyses the collected data for its validity, and ensures the feedback is shared with trial sites on an ongoing basis so that the patient and the site staff are re-trained if necessary.

In addition to validity assessment, MCL manages the study required integrated data analysis for CGM, as well as all other associated diabetes management data points like eDiary, blood glucometer, ketone meter, etc. for each study need. Additionally, develops comprehensive data reporting including standard CGM parameters like Time Above Range (TAR), Time Below Range (TBR), Time In Range (TIR), etc. to facilitate in medical monitoring of the trial.

How have recent breakthroughs in CGM trials and wearables offered new hope for patients?

We recognize how exciting of a time it is in clinical research and the incredible opportunity presented to help patients lead a healthy lifestyle while using marketed devices to reduce the amount of time they have to mentally think about their diabetes care each day.

With recent guidance, a timely consideration is the use of the Automated Insulin Delivery (AID) systems in trials, an insulin pump that automatically delivers insulin based on a CGM communicating to the pump. This is accomplished through a program on a phone or inside the pump using advanced algorithms. The American Diabetes Association (ADA) Standards of Care in Diabetes - 2024 recommends AID systems should be offered for diabetes management to youth and adults with T1D who are capable of using the device safely either by themselves or with a caregiver.[1] Recently, trials have not allowed these subjects into the study due to fear of data not being comparable across arms. In the US, only approximately 20% of people with T1D meet the glycemic goals of HbA1c< 7.0%, recommended from the Diabetes Control and Complications Trial (DCCT), a landmark study in T1D patients (2014)[5]. The DCCT recommended to achieve glycemia as close to the nondiabetic range as safely possible which reduced microvascular and cardiovascular complications of diabetes. There are a large number of T1D patients using AIDs and ethical challenges exist to remove patients from

these devices. To date, there has been one completed Phase III study which enrolled eligible subjects using AIDs.[4] Medpace will continue watching the landscape closely to collaborate with Sponsors on including patients on these insulin pumps.

The FDA has recently approved a new single hormone (insulin) AID system called iLet.[3] This fully automated system is an AID but not a hybrid closed loop system. The iLet makes all the decisions and determines every single dose of insulin based on the sensor data from the Dexcom CGM. The system has three algorithms: basal, correction, and meal. The algorithms determine insulin doses, and the dose is delivered through a pumping system which can communicate to the HCP through a smart phone, app, and data stream to the cloud. The algorithms determine the insulin dose given by the pump every five minutes without the patient entering or changing the insulin to carbohydrate ratio (ICR), carbohydrates eaten, or insulin correction factor (ICF). The patient enters their weight, and the algorithms determine the rest. The only patient input is their weight, what meal and the size of the meal they are eating, and glucose target. The algorithms use glucose data from the last 24 - 48 hours to predict insulin needs.

On April 1, 2024, the UK National Health Service (NHS) began offering hybrid closed loop (HCL) systems to people with T1D in England and Wales. This landmark guidance is one of the most progressive guidelines globally. Based on The National Institute for Health and Care Excellence (NICE) recommendation of 2023 which looked at cost effectiveness, agreed the technology and the science is strong enough for AID devices to be funded by NHS.[6] The UK has a five-year implementation plan. The ADA Standards of Care in Diabetes - 2024 also recommends AID systems to be offered for diabetes management to people with T1D. Moving forward this may be a consideration to include an arm of participants who use AID devices for global T1D trials in the present and the future.

Does Medpace recommend one particular CGM device for clinical trials?

Medpace collaborates with Sponsors to recommend a GCM device for the endpoints and required workflow. MCL is in collaboration with CGM device manufacturers and data platform providers to continually improve current capabilities and to integrate a newer generation of CGM technologies as per trial needs.

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