WHITEPAPER

Benefits and Challenges of Continuous Glucose Monitoring (CGM) in Clinical Development



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Continuous glucose monitoring (CGM) has transformed the lives and quality of life for people living with diabetes. CGM devices provide opportunities to revolutionize data collection and facilitate participation in clinical trials. In this whitepaper, Medpace experts describe the unique capabilities of CGM devices, envision the possibilities and explore key considerations for implementing CGM in clinical trials with an eye on regulatory guidance.

Continuous glucose monitoring offers novel capabilities

Thanks to the development of CGM technologies and devices, people living with diabetes no longer have to suffer multiple pin pricks daily to keep track of changes in their blood glucose levels. Not only is the process painful, but it can also be time consuming. Depending on the equipment used and the persons' manual dexterity, checking a capillary blood sample with a glucometer could take several minutes. With CGM, patients can access real-time data to manage their blood glucose levels. Real-time feedback allows people to monitor their blood glucose levels 24/7, providing insights into daily patterns and fluctuations of blood glucose levels in relation to food, physical activity, sleep, illness, or medication.

Healthcare providers can see the ups and downs in blood glucose levels that comprise a patient's HbA1c test results and use the information to fine tune the treatment plan. While HbA1c provides information about a person's average levels of blood glucose over the past 3 months, with CGM, physicians can evaluate patterns and detailed data beyond patient logbooks or HbA1c. Logbooks and self-monitoring of blood glucose only provide a handful of blood glucose readings each day while a CGM device that records blood glucose every 5 minutes will record 288 readings per day.





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According to CDC, more than 37 million people in the United States have diabetes and "in the last 20 years, the number of adults diagnosed with diabetes has more than doubled as the American population has aged and become more overweight or obese."¹ Monitoring blood glucose and staying in one's target range helps people with diabetes prevent complications such as cardiovascular disease, neuropathy, chronic kidney disease and vision loss.²

CGM is safe and convenient for study participants

CGM devices use a tiny wearable sensor inserted under the skin to measure the interstitial glucose level and automatically transmit the readings to a smart device or monitor. Most devices are worn on the upper arm and, depending on the brand, measure interstitial fluid every 5 to 15 minutes. People using a CGM device can set alarms for high and low levels and respond by taking action to control their blood glucose level with food or insulin as needed.

Use of CGM devices reduces the burden for patients interested in participating in clinical trials decreasing the time commitment, the potential disruption to their usual routine, and the need for patients to use a glucometer to collect and record blood glucose levels. According to Ana Pokrajac, MD MSc FRCP, Medical Director at Medpace, "This innovation makes it so much easier for people to participate in clinical trials. Because CGM devices transmit the data automatically, people can 'participate from home' and avoid frequent visits to the study center."

Many studies have shown that CGM benefits individuals with type 1 and type 2 diabetes.³ In one example, the DIAMOND study, researchers found that study subjects using CGM had greater reductions in HbA1c and glycemic variability than the subjects who were using glucometer for glucose monitoring. That study also found that the subjects, who were \geq 60 years old, were able to sustain CGM use for more than 6 months and were highly satisfied with CGM.⁴ Other studies have shown reductions in hypoglycemia and improved time in the target glucose range.⁵

The technology for CGM has been advancing. In 2016, the FDA approved the first CGM system "to allow for replacement of fingerstick blood glucose testing for diabetes treatment decisions in people 2 years of age and older."⁶ By 2018, the FDA had approved the first CGM system for use as part of an integrated system, including automated insulin dosing systems and insulin pumps for diabetes management⁷ and earlier this year, the FDA approved a new version of an implantable CGM system with an implantable fluorescence-based sensor to be worn for up to 180 days.⁸

Ongoing improvements in CGM device convenience: smaller size, lower price and easier insertion are helping to increase adoption.⁹ Depending on the country, age group, access to health services and insurance, about 50% of patients with Type 1 diabetes use CGM to inform diabetes management and this number is growing.^{10, 11} For example, in the United States, use of CGM by people with Type 1 diabetes has grown exponentially, "from 6 percent in 2011 to 12 percent in 2014 to 24 percent in 2016 to 38 percent in 2018"¹² and was nearing 50 percent by 2021.¹³ Use of CGM in people with Type 2 diabetes is less common but is also on the rise.¹⁴

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CGM device output metrics provide unique insights for clinical trials

CGM devices produce additional useful metrics beyond HbA1c, such as time in range (TIR), time below range (TBR), and time above range (TAR) while also recording patterns and daily glucose highs and lows. The oscillations in blood glucose levels—glycemic variability—is a meaningful metric and is associated with an increased risk of adverse clinical outcomes.¹⁵

The granularity and accuracy of the data provided by CGM, along with the convenience for researchers and study subjects, make CGM a useful tool to incorporate into research protocols. Since CGM first became available, more than 20 years ago, the systems have become more reliable. One recent analysis found that "average sensor MARD (mean absolute relative difference; a summary accuracy statistic) has decreased from >20 to <10%."¹⁶

Researchers are even expanding the use of CGM in clinical trials beyond Type 1 and Type 2 diabetes to indications such as obesity, hypoglycemia, hyperglycemia, pre-diabetes, hyperinsulinism, insulin resistance and bariatric surgery and its complications. Medpace sees an opportunity to use CGM in the early phase trials of investigational products targeting any organ that plays a role in glucose homeostasis, including the liver, pancreas and muscles, to explore mechanisms of action or provide new ideas on indications for use.

CGM may capture previously hidden effects of an investigational product on variations in glucose levels

Dr. Pokrajac notes, "Glucose levels change throughout the day even in healthy populations. In patients with diabetes, obesity, hypoglycemia, hyperinsulinism, insulin resistance, or those who have had bariatric surgery, monitoring glucose levels and how they fluctuate may be critical to understanding the effect of the investigational product 24/7 rather than depending on a limited number of data points from designated glucose sampling times."

These fluctuations may or may not have been recorded or felt by patients in previous clinical trials where traditional glucometers were used at designated glucose sampling times. CGM ensures that researchers see the effect of the investigational product on glycemic fluctuation, hypoglycemia (especially important in patients with reduced awareness) and hyperglycemia—even during sleep. "The additional data captured by CGM and the ability to follow study subjects as they go about their usual routine can demonstrate a competitive advantage of one product over another," adds Dr. Pokrajac.



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Managing common challenges of CGM in clinical trials

Incorporating CGM into clinical trials presents unique opportunities, but can also pose challenges. Researchers must consider which device will be most suitable for the needs of their specific trial, what endpoints to measure and how best to collect, track, secure and monitor the data while ensuring participant safety and maintaining the patient's usual standard of care. It's important to ensure that the choice of device meets the mission and goals of the clinical trial. Some of these goals include: factoring in the operational considerations necessary to minimize demands on patients and sites throughout the clinical trial while also identifying appropriate endpoints, and optimizing secure data collection.

Educating study participants and personnel

Even though trial participants may be using a CGM device to measure and manage their blood glucose levels before they volunteer to participate in a clinical trial, it's unlikely that all participants would be using the same brand and model. In research, it's necessary for all subjects across all sites to use the same device for uniform data collection, which means that the device being used to capture trial data may be new and unfamiliar to trial participants or investigators. Because these devices may differ from the consumer device a patient is used to, it's important to provide education to study participants as well as training for site personnel to ensure proper utilization and avoid data loss.

"To avoid confounding factors during clinical trial, the standard of care should continue, patients should continue to use their regular glucometers or the CGM devices they were using before the trial," advises Dr. Pokrajac. In addition, study subjects will have a study-specific CGMs for the sole purpose of collecting study data. The study-specific CGM can be completely ignored by the study participant and set to blinded mode. Depending on the type of device and setting, data can be collected remotely.

At the conclusion of the study period, the participant can remove the device and either return it by mail or return it to the study site during a scheduled visit. Making the experience as convenient as possible for the patient and study personnel may help improve patient retention and compliance with the study protocol.

Selecting the best device for a clinical trial

"The most obvious consideration when selecting a CGM device for use in a clinical trial is technical performance, particularly accuracy in the low glucose ranges. It's also important to consider participant convenience and overall cost," notes Dr. Pokrajac. Devices that don't require sensor scanning, warm-up time, or calibration will facilitate use by study participants.

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For clinical trials, some CGM devices offer special features. For example, devices can be:

- Blinded to participants by default or for the purpose of the trial
- Set up to configure the data to meet the clinical trial's mission
- Programmed with an alarm to protect the safety of study participants

For global trials with sites in the European Union, CGM devices need to have the CE (conformité européenne) mark, which means that the manufacturer affirms the device's conformity with European health, safety and environmental protection standards. Some CGM devices do not have the CE mark.

Turning data from a CGM sensor into useful endpoints

CGM and other remote or wearable biosensors deployed for clinical trials generate a data stream that is potentially continuous, and that must be captured as source data supporting an endpoint for a clinical trial. It is important to protect the integrity of such data streams similar to the way that researchers are used to protecting the integrity of more conventional endpoint data such as blood samples, or imaging data. Tracking and storing the data securely, with identifiers that associate each data stream with the correct patient and time point in the trial, helps ensure the data is useful and compliant. Researchers can monitor the data stream to ensure that the CGM device is transmitting data correctly and that data is being received and recorded accurately. If case values fall into a range that generates concern about the health of a patient, alerts can be generated from the data and appropriate action can be taken.

CGM data streams can be analyzed for trends, peaks, ranges and other parameters of interest as indicators of safety or efficacy of an investigational product. Such results can be displayed graphically or tabulated at specified intervals to allow for convenient presentation to study staff, central readers, or a sponsor. All of these must-have functions to turn data from a CGM sensor into useful endpoints for a clinical trial can be effectively managed by a core laboratory.



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Regulatory guidance for clinical trials utilizing CGM

Interest in the use of CGM in clinical trials is growing. An analysis published in 2021, showed an increase in CGM usage in clinical trials over time. The authors considered "2,032 clinical trials of 40 antihyperglycemic therapies currently on the market with a study start date between January 2000 and December 2019." In 2005, less than 5% of these trials used CGM, by 2019, 12.5% did. The authors concluded that this "is still low given its inclusion in the American Diabetes Association's latest guidelines and known limitations of A1C for assessing ongoing diabetes care."¹⁷

In our own analysis, of information available on ClinicalTrials.gov, we found the number of clinical trials including CGM has quadrupled since 2015 going from 26 trials in 2015 to 101 trials in 2021.

According to Dr. Pokrajac, "CGM output has been used as source of exploratory, secondary and recently, for the assessment of the primary endpoint." The InRange study's primary endpoint was "percentage time spent in glucose range of \geq 70 to \leq 180 mg/dL (\geq 3.9 to \leq 10 mmol/L) at week 12." ¹⁸ However, use of CGM has been a challenging area for regulatory bodies. For example, the Food and Drug Administration has guidance for new drug development in diabetes, but doesn't provide guidance on CGM. While the European Medicines Agency has recently encouraged use of CGM for glucose monitoring in clinical trials.¹⁹

At this year's Advanced Technologies & Treatments for Diabetes Conference, a consensus group was established to provide guidance on use of CGM in clinical research and address issues such as:

- Standardization of CGM data collection reporting, and which devices to use
- Unblinded rtCGM or blinded CGM
- Measurable parameters: TIR, TBR and TAR
- How to power the study based on CGM metrics

This guidance will pave the way for regulatory bodies to pick up the speed with the latest technological developments and even greater use of CGMs in research.

Contact our expert team to learn how we can help.

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Full-service clinical development

Medpace is a scientifically-driven, global, full-service clinical contract research organization (CRO) providing Phase I-IV clinical development services to the biotechnology, pharmaceutical and medical device industries. high-science and disciplined operating approach that leverages local regulatory and deep therapeutic expertise

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