Integrating Continuous Glucose Monitoring with Electronic Clinical Outcome Assessments in Diabetes Clinical Trials: Research and Rationale

Introduction

The use of real-time continuous glucose monitoring (RT-CGM) as an adjunctive approach to traditional self-monitoring of blood glucose (SMBG) has seen a dramatic expansion in clinical research. In conjunction with standard numerical analysis of blood glucose (BG) levels before, during, and after meals using SMBG, cyclical monitoring with RT-CGM may be an efficacious strategy for procuring a tailored treatment plan for type 1 and type 2 diabetic patients. Research into RT-CGM vs SMBG has shown promising results in terms of glycemic control as well as patient-reported outcomes (PROs), and clinicians are quickly recognizing the importance of CGM as an integrative, complementary method for effective diabetes management.

Administration of clinical outcome assessments (COAs) is a common strategy used by trial researchers to determine patient-perceived benefits and rate of efficacy of device integration. Paper-based questionnaires are the most frequently used mediums to evaluate patient-centered clinical outcomes, including quality of life, perceived benefits and efficacy, and treatment satisfaction. Unfortunately, collection issues from standard paper questionnaires may occur during and following administration, ultimately decreasing the validity of results. Electronic clinical outcome assessments (eCOAs) used to collect electronic patient-reported outcomes (ePROs) may be a more effective method for gathering CGM data in clinical trials while minimizing potential for collection error. eCOAs have been utilized in trials studying patient-oriented outcomes with CGM devices for a few years now, and more researchers are continuing to incorporate electronic assessments into their diabetes trials.

Background

As a diagnostic instrument that can be utilized in the clinical setting, CGM may help patients achieve better clinical outcomes due to the device's in-depth analysis and interpretation of BG. As an accompaniment to SMBG, the use of CGM can assist diabetic patients and their caregivers in detecting extreme fluctuations in glucose levels. Research reveals that diabetic devices that utilize CGM technology result in reduced glycemic excursions.[1] Since CGM provides an accurate and continual observance of glucose levels over time, it can monitor the effects of lifestyle and medication—including dose and timing of insulin injections—and help clinicians adjust treatment modalities accordingly.

The device includes a tiny, wire-like sensor that is inserted underneath the skin, hence the often-used term "subcutaneous continuous glucose monitoring." A small, flexible probe on the sensor is inserted in the interstitial space, surrounded by glucose. The sensor is typically an electroenzymatic sensor which features glucose oxidase, an enzyme that reacts to the patient's BG and provides a real-time measurement of BG concentration. The device provides a stable output of information regarding glucose levels throughout the day as well as the direction and rate of change of these values. Once a patient and his/her physician agrees on CGM, a prescription must be written by the physician in order to obtain a glucose meter. Insurance plans may partially or fully cover the device in some instances, providing a minimal financial burden to patients.[2]

Monitoring Methods

Integration of RT-CGM with current technologies may be an effective method for enhancing patient motivation and promoting a higher patient-driven initiative for controlling BG.[3] FDA-approved mobile applications that connect to specific continuous glucose meters have been developed and allowed for marketing in the United States.[4] The Dexcom G5® Mobile application, for example, is an app that allows patients to monitor their daily glucose levels on their smartphone while receiving custom alerts for potential hypo- and hyperglycemic episodes. These applications also allow remote access to glucose readings for caregivers.

Wireless Pager-Like Monitor

There is currently a small number of FDA-approved CGM systems. Each system provides real-time glucose values every one to five minutes and has an alarm to alert patients, caregivers, and clinicians of hyper- and hypoglycemic events.

Devices with regulatory approval for adjunctive use include:

1. **Medtronic Enlite:** A CGM sensor that monitors BG levels and provides readings every 5 minutes while also delivering alerts to the patient during dramatic shifts in glucose. The device is also commonly used in conjunction with MiniMed 530G insulin pump to deliver timely insulin in case of minor and/or extreme glycemic excursions.
2. **Dexcom G4:** A Bluetooth-enabled sensor that allows for sharing of BG levels to remote iPhone users, including caregivers, family, and physicians. Each sensor lasts a total of one week.
3. **FreeStyle Navigator:** This device offers cyclic and regular glucose monitoring for up to 120 hours, with readings based on fingerstick results. These results help users and their physicians detect trends in BG levels for a more tailored approach to treatment.

Advantages of eCOAs in CGM Trials

Many of today's regulatory guidelines encourage trial sponsors to embrace the use of eCOAs, rather than paper-based methods, for PRO evaluation. While there is concern regarding usability issues in older adults unfamiliar with the technology, more mediums are utilizing simpler methods for successful eCOA administration. Using CGM devices in clinical trials and medical practice offers numerous advantages to patient care, especially for diabetes. Incorporating eCOAs in clinical trials with the intent to assess CGM acceptability and efficacy among patients is also highly beneficial for enhancing treatment satisfaction.

Here are some of the top benefits for using electronic assessments in diabetes trials:

- **Efficient and Timely Capture of Patient-Reported Data**
- **Web-Based Models Can Be Performed Easily at Home**
- **Is a Generally Well-Accepted Medium by Patients**
- **Incurs Less Overall Administrative Cost**

Objective

This white paper is designed to show clinical researchers that eCOAs and ePROs have been successfully incorporated into trials studying CGM in diabetic patients. Researchers in the field of endocrinology and diabetes are progressively integrating CGM devices with eCOAs into clinical trials to gain an overview of CGM supplementary therapy in type 1 and type 2 diabetes management. Research studies evaluating patient acceptance and satisfaction with CGM have been published in the literature for some time,[5] and similar trials are now active and underway.

Paper-based COAs have been used extensively in clinical diabetes research for decades, yet their limitations have become increasingly revealed since the advent of electronic mediums. One advantage of eCOAs over standard COAs in diabetes research is their ability to control the "parking lot effect," a phenomenon in which patients enter subjective data retrospectively or prospectively due to adherence neglect of standard testing protocol. The term comes from the idea that patients, in their forgetting to take the assessment at the appropriate times, enters potential information into the paper COA quickly in their car in the parking lot. This reduces variance in the data and influences the study's overall view of drug, device, or intervention efficacy.[6]

Methods

COAs are imperative for scrutinizing subjective patient outcome measures during CGM treatment, and eCOAs can be a beneficial alternative to paper COAs for circumventing error in data collection. While the study of advanced CGM technology in relation to eCOA collection is minimal, there is still some evidence to suggest the marrying of electronic data collection with diabetes research is beneficial. Clinical trials referenced in this white paper were found using PubMed. Results were filtered to include the most relevant trials that pertained to electronic capture of PROs.

Results

Trials are currently underway assessing PROs and clinical outcomes of CGM; however, there is published research already showing the integration of eCOAs in the evaluation of CGM treatment. This summary is by no means complete, yet it does provide a glimpse into the successful assimilation of electronic mediums vs paper into diabetes research.

Trial One

A study from the *Journal of Diabetes Science and Technology* utilized an Internet survey as a means of procuring ePROs in diabetic patients using CGM to complement diabetes standards of care (n = 162) vs patients using self-monitoring of blood glucose (n = 149).[7] Participants (N = 311) with a median diabetes duration of >15 years responded to the Internet survey, completing items that assessed the glucose monitoring system's convenience, burden, glucose control, interference, cost satisfaction, overall satisfaction, treatment preference, and quality of life (QoL). Diabetes-related worries, psychological wellbeing, and social burden were the main QoL factors evaluated. Differences amongst each group was assessed using analysis of covariance and controlled for respondent characteristics. Using data collected from the electronic questionnaire, real-time CGM patients provided significantly superior ratings than the SMBG group for their monitoring system's glycemic control efficacy, desire to switch, overall satisfaction, and willingness to recommend. The device wasn't without its flaws, however, with the CGM group giving worse ratings for interference with daily activities. Researchers using the eCOA to evaluate health-related QoL (HRQoL) and clinical outcomes in CGM patients concluded that an integrated real-

time CGM system accounts for more benefits of treatment, higher HRQoL, improved glucose management, and greater user preference.

Trial Two

A similar study utilizing eCOAs published in *Diabetes Technology and Therapeutics* examined life-related benefits and disadvantages to using RT-CGM.[8] HRQoL changes were reported in an online questionnaire by diabetes patients using RT-CGM in current treatment strategy. Underlying factors in relation to HRQoL benefits/losses were revealed using an exploratory factor analysis (EFA), and three of those factors emerged: Perceived Control over Diabetes, Interpersonal Support, and Hypoglycemic Safety. HRQoL improvement following RT-CGM initiation was more common for Hypoglycemic Safety and Perceived Control Over Diabetes (85% and 86%, respectively). Independent predictors of perceived benefits were high in satisfaction with device accuracy, usability, and older age. Following evaluation of the electronic assessment, researchers found that perceived efficacy for the device was also high.

Trial Three

CGM-enabled insulin pumps can be effective devices in the management of glucose levels. A 2015 study from the *Journal of Diabetes Science and Technology* administered a 50-item online questionnaire to assess clinical outcomes and device satisfaction in type 1 diabetic patients using CGM-enabled insulin pumps.[9] The study, utilizing an electronic medium for data collection, found that treatment satisfaction scores were higher in the groups using the device in their therapy regardless of previous insulin use. It should be noted that treatment satisfaction and adherence typically translates to better glycemic control. Incorporating strategies, like CGM devices, may be an important step in reducing diabetes-related morbidity due to its high patient preference.

Trial Four

A 2009 two-site study from *Diabetes Technology and Therapeutics* evaluated PROs for an integrated CGM and a continuous subcutaneous insulin infusion (CSII) pump system in patients with type 1 diabetes (N = 28).[10] Researchers randomized CSII-naïve adult diabetes patients (mean glycosylated hemoglobin [A1C] = 8.6%) into a control arm (n = 14) consisting of numerous diurnal injections and SMBG or the study arm (n = 14) consisting of CSII with RT-CGM in addition to SMBG. The Insulin Delivery System Rating Questionnaire (IDSRQ) and the parallel Blood Glucose (BG) Monitoring System Rating Questionnaire (BGMSRQ) were administered to participants at the beginning and end of the trial. Additionally, study arm participants also completed the User Acceptance Questionnaires (UAQs) for CSII, DMS, and RT-CGM at the end of the trial.

There was significant A1C control and reduction from trial start to completion in study and control arms (-1.7% and -1.0%, respectively). In the study arm, the BGMSRQ revealed significantly greater benefit in the monitoring system's ability to manage glycemic control as well as less interest among participants in switching to an alternative blood glucose monitoring system. The study arm also showed positive scores for system features. Also, the IDSRQ showed greater ratings for blood glucose monitoring requirements, tolerability, convenience, diabetes concerns, interpersonal challenges, efficacious blood glucose control, and higher satisfaction overall. There were many more positive PROs in the study arm compared to the control, and researchers concluded that the CGM/CSII system was accepted more readily by participants with higher satisfaction.

Trial Five

CGM may also benefit women with gestational diabetes in early pregnancy. A study from the UK published in *Diabetes Medicine* sought to assess self-reported satisfaction and limitations for real-time CGM among women with pregestational diabetes (N = 68).[11] Women with type 1 diabetes (n = 54) and type 2 diabetes (n = 14) were offered CGM for 6 days at a median of 9 gestational weeks. Around 43% (n = 43) women used CGM for at least 5 days. Participants were then provided with a semi-structured questionnaire assessing patient satisfaction. The median HbA1c level for this study was 49 and median diabetes duration was 12 years. Women experienced 2.7 alarms per each 24-hour period, one-third of which was technical and another one-third resulted in sleep disruption. The proportion of women reporting discomfort of the CGM device were small, with 24% (n = 16) reporting irritation during daytime and 18% (n = 12) reporting discomfort during sleep.

Prior the 6 days of intended CGM, 36% (n = 24) patients had their monitoring system removed, and 15% (n = 10) of women reported not wishing to use the system again in pregnancy. Self-reported skin irritation, CGM inaccuracy, and technical problems were reasons for early removal. There were, however, no differences in CGM use, compliance, or inconvenience with regards to diabetes type. Despite these challenges experienced by a small number of participants, 52% (n = 35) reported improved diabetes understanding, and 83% (n = 56) would recommend CGM to other women with gestational diabetes. In conclusion, researchers discovered that real-time CGM was found useful for the majority of pregnant women with gestational diabetes, and CGM intervention was well tolerated regardless of diabetes type.

Trial Six

The use of CGM alongside eCOAs are increasingly investigated in the clinical trial environment. Another recent clinical trial from 2015 was performed to evaluate glucose monitoring devices and their impact on quality of life.[12] Researchers of this study developed the Glucose Monitoring System Satisfaction Survey (GMSS) as a validated method to examine CGM treatment satisfaction. Approximately 42 GMSS items were developed in response to in-depth interview sessions among 15 adults with type 1 diabetes or type 2 diabetes and 10 diabetes healthcare professionals. Among patients with type 1 and type 2 diabetes, separate exploratory factor analyses were conducted. Researchers established construct validity with the World Health Organization-5 Well-Being Index, Diabetes Distress Scale, Self-Monitoring of Blood Glucose Obstacles scale, and the Blood Glucose Monitoring System Rating Questionnaire. The analyses of the PROs determined that GMSS, in relation to CGM device satisfaction, is a dependable form of measurement in both diabetes types and provides a thorough assessment of satisfaction in clinical research.

Trial Seven

Another study examined the relationship between PROs and their importance in determining the positive impact of CGM in clinical care.[13] The study assessed psychometric properties of the 22-item Glucose Monitoring Survey (GMS) and the 44-item CGM Satisfaction Scale (CGM-SAT). The GMS rated the blood glucose monitoring system patients (n=447) and parents (n=221) were using (standard home glucose meter +/- CGM) at 6 months and baseline. The 44-item CGM-SAT rated patients' (n = 224) and parents' (n=102) experience with CGM over a 6-month period. Following factor analysis, it was found

that significant correlations of CGM-SAT with CGM use frequency between baseline and 6 months as well as GMS with conventional daily SMBG frequency at baseline supported convergent validity. Therefore, GMS and the CGM-SAT were established as valid measurements of CGM PROs.

Trial Eight

One of the primary endpoints for CGM is its ability to manage glycemic control effectively. One study from *Diabetologia* in 2009 evaluated the use of a patient-led sensor guided pump management on glycemic control and its comparison to standard insulin pump therapy.[14] This open multicenter, parallel, randomized, controlled trial recruited patients with well-controlled type 1 diabetes (N = 55) and randomized these patients to either a study (n = 26) or control group (n = 29) for 3 months. Compared to the control group which used a standard insulin pump, a sensor-guided pump management system was utilized in the intervention group without providing instructive guidelines for construing the device's real-time statistics. To assess and compare outcomes of each group, CGM and HbA1c level analysis were used. Compared to the control group, the intervention arm achieved a mean 0.43% lower HbA1c value at the end of the study. There was no significant difference in CGM-derived time in target, hypoglycemia, and hyperglycemia among the groups. In patients in the intervention group with sensor use ≥70%, HbA1c was 0.51% lower compared with study participants with sensor use <70%. It was gathered that sensor-guided pump management can be employed to improve glycemic control in patients with an established insulin pump therapy regimen.

Conclusion

The use of eCOAs as a means of capturing and interpreting PROs in CGM clinical trials has been proven effective in previous published studies. Although paper mediums are still common, the use of electronic patient-reported data, like Internet surveys and web-based questionnaires, are consistently utilized to improve data collection time and accuracy as well as reduce financial burden for clinical trial sponsors. Electronic-based questionnaires may enhance participants' experience by reducing the reliance on cumbersome paper models. Continuing research utilizing eCOAs for CGM treatment is essential for shaping newer, more effective technology in diabetes management.

Summary

CGM is an effective adjunct to SMBG, and this treatment strategy is seeing an upsurge in clinical investigation. Devices that utilize CGM technology include a tiny subcutaneous wire-like sensor that provides real-time monitoring of BG and may promote a greater initiative among type 1 and type 2 diabetic patients for BG control. This white paper was designed to study the effects of electronic collection of PROs in diabetes trials using CGM in an effort to support further use of eCOAs in future clinical trials. Upon review of current and past studies examining ePROs in relation to CGM, it's evident that electronic means of data collection is highly successful in the research environment. Recent studies evaluating CGM in relation to PROs have utilized eCOAs as a simpler approach for examining HRQoL in diabetic patients. Regulatory guidances are encouraging clinical trial sponsors to incorporate some form of an eCOA into their trials. Despite the minimal concerns of eCOAs, there may be greater benefit to utilizing this approach for patient-reported data capture that outweigh any perceived limitations. These benefits include efficient and timely capture of subjective PROs, an overall positive acceptance by patients, less administrative costs, and ease of use.

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